PHARMACOLOGY IN CLINICAL PRACTICE

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Preface

This book is aimed primarily at medical undergraduates during their clinical years, but it is hoped that it will also be of value to all doctors in clinical practice and to whom drugs are an essential therapeutic tool.

The book is divided into two parts. The objective behind Part I (Chapters 1–9) is to provide a bridge between basic pharmacology and clinical pharmacology. Thus it contains both brief summaries of important areas of basic pharmacology including mechanisms of drug action, drug distribution, metabolism and excretion and slightly more detailed chapters on aspects of pharmacology that are particularly important in clinical practice, such as pharmacokinetics and clinical trials.

The main part of the book, Part II (Chapters 10–42), covers the clinical pharmacology of the most important and widely used groups of drugs in clinical practice. Each drug or group of drugs is considered under the four main headings of *drug action*, *drug fate*, *adverse effects* and *clinical use*, so as to provide students with an invariable frame within which to consider the information concerning any drug.

This book is not intended as a book on therapeutics. Therapeutics is concerned with all aspects of treatment and hence must be concerned with more than drug therapy. However, as drugs are probably the most widely used tool in therapeutics it is hoped that the information on drugs contained in the book will facilitate therapeutic decision-making and benefit thereby the patient.

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Chapter 1

Drug Actions

The study of drugs may be divided into pharmacodynamics, which is the study of drug actions and modes of action, and pharmacokinetics, which is the study of the fate of drugs in the body. In this chapter pharmacodynamic aspects of drugs and their relevance to clinical pharmacology will be discussed.

Pharmacodynamics For drugs that reach their sites of action from the blood stream, there are four steps linking drug administration to drug effect.

1. Transfer of drug from site of absorption to plasma water.
2. Transfer of drug from plasma water to receptor compartment.
3. Drug-receptor interaction.
4. Production of drug effect.

Steps 1 and 2, the transference steps, are the concern of pharmacokinetics and are considered in Chapter 4. Pharmacodynamics therefore starts with a study of drug-receptor interactions.

Drug receptors In most instances, the initial event in the sequence that culminates in a drug-induced effect is the interaction between a drug molecule and a 'receptor' molecule or area located on the surface of the 'target' organ. Exceptions to this rule include chelating agents (Chapter 41) which interact directly with a particular cation and drugs whose actions are a consequence of their physical properties, e.g. bulk laxatives, osmotic diuretics and topical cooling agents. Receptors are macro molecules and in a few instances they have been isolated and their physico-chemical characteristics determined. In most of these the receptor is an enzyme that is stable *in vitro*, e.g. carbonic anhydrase, acetylcholinesterase, monoamine oxidase. Most receptors thus far characterised have been proteins located on cell surfaces, but this is not always the case; e.g. RNA is the receptor for the cytotoxic agent actinomycin D (Chapter 38) and ergesterol, a sterol component of the fungal cell membrane, for the antifungal agent nystatin (Chapter 35).

For drugs whose receptors cannot be isolated, the nature of the drug-receptor relationship has derived from studies using indirect methods such as analysis of the dose-effect relationship and structure-action relationships. On such evidence receptors may be classified in terms of their specificity for drugs. Receptors with a low degree of specificity do not discriminate between optical isomers or between drugs of very similar but not identical structure. They occupy a relatively large area of the surface of the target organ and drug effects are only produced at relatively high drug concentrations. The receptors have a low affinity for the drugs with which they interact and their actions cannot be

antagonised by other drugs that compete for and occupy the same receptors. Examples of drugs whose receptors have a low degree of specificity include local and general anaesthetics (Chapter 12 and the surface-active antibacterial agents, polymyxin and bacitracin (Chapter 35).

Receptors with a high degree of specificity are mostly those that are receptors for chemical transmitter substances, e.g. cholinergic, adrenergic, dopaminergic and 5-hydroxytriptaminergic receptors or receptors for hormones. These discriminate between minor differences in chemical structure and between optical isomers. They occupy a tiny fraction of the cell surface, have a high affinity for specific drugs which are therefore active at very low concentrations.

Dose-effect relationship Most of the concepts derived from studies on the dose-effect relationship have come from studies on the effects of drugs on smooth muscle *in vitro*. Such studies have shown that the dose-effect curve is

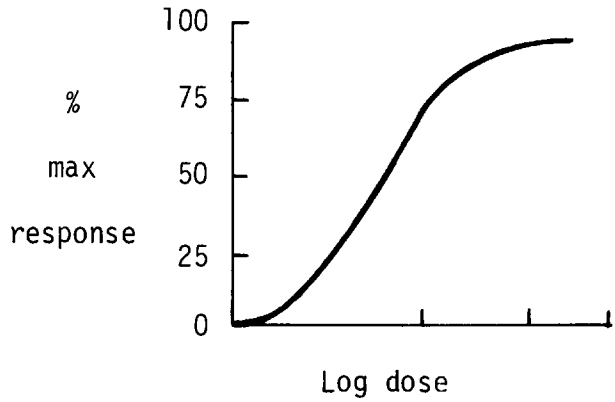

FIG. 1 Log dose-response relationship.

hyperbolic and if the intensity of effect, expressed as a percentage of the maximal response that the drug is capable of eliciting, is plotted against the log of the dose, the curve becomes sigmoid, the points between 25% and 75% maximal response falling along strait line (Fig. 1).

A. J. Clarke (1933) applied the law of mass action to interpret the log dose-effect relationship. He assumed that one drug molecule reacted with one receptor molecule.

$$R + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} RA$$

R = a free receptor; A = a drug molecule; RA = an occupied receptor.

Assuming that the number of drug molecules is far greater than that of receptors, then at equilibrium:

$$P_A = \frac{C_A}{C_A + K_A}$$

P_A = fraction of the total number of receptors occupied,
C_A = concentration of drug A; K_A = dissociation constant (k_2/k_1)

Clarke assumed that receptors did not interact and that a 100% response is only achieved when 100% of receptors is occupied. The theory that the intensity of response to a drug is proportional to the number of receptors occupied by drug molecules is known as the 'occupancy theory'.

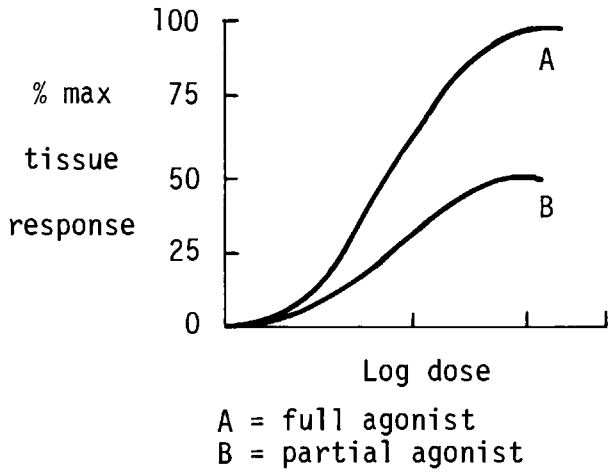

FIG. 2 Comparison of full agonist and partial agonist in log dose-response relationship. A = full agonist; B = partial agonist.

The log dose-response relationship could also be accounted for if particular receptors varied in their affinity for specific drugs and if this variability was normally distributed over the target organ. Studies on isolated receptors have, thus far, failed to show variations in receptor affinity for specific drugs.

The occupancy theory has been modified to account for the fact that different agonists, that are assumed to act on the same receptors, do not always produce the same maximal response. Such differences have been explained on the basis of a hypothetical drug characteristic 'intrinsic activity' or 'efficacy'. Thus drugs with a high degree of 'intrinsic activity' or 'efficacy' are capable of causing the maximal response of which the tissue is capable (full agonists) while drugs with a low degree of 'intrinsic activity' or 'efficacy' cause a less than maximal response at a maximally effective dose (partial agonists) (Fig. 2).

For the most part, drug effects are thought to be the consequence of conformational changes induced in receptor structures. It is notional that partial agonists, when occupying or interacting with a receptor, do not induce the same degree of conformational change in receptor structure as do full agonists.

Antagonists occupy receptors but produce no tissue response. They therefore have negligible 'intrinsic activity' or 'efficacy'. They are described as being 'competitive' if they cause a shift to the right in the dose-response curve, but do not reduce the maximal response to an agonist (Fig. 3).

In the presence of a full agonist, a partial agonist acts as a partial antagonist as it occupies a proportion of receptors and the intensity of response resulting is less than that caused by that proportion of receptors interacting with the full agonist.

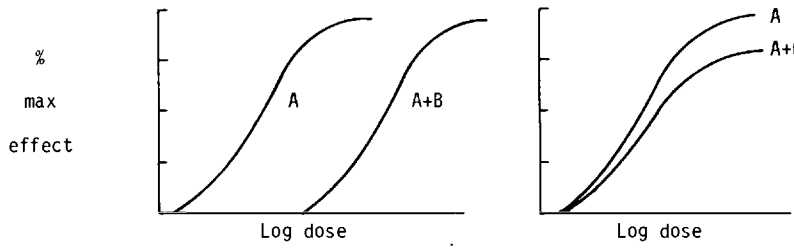

FIG. 3 and 4 Log dose-response curves: A = agonist; B = competitive agonist; C = antagonist that irreversibly binds to receptors and hence inactivates them. C has not caused a shift to the right in the log dose-response curve, indicating that the tissue does not possess spare receptors for A.

If an antagonist binds irreversibly to receptors, then its effect is to reduce the maximal response of the tissue to a given agonist (Fig. 4). However, it has become apparent that many tissues possess 'spare' receptors in that full agonists are capable of producing a maximal response, while interacting with only a small fraction of receptors. In tissues in which there are spare receptors for a given agonist, the agonist may produce a maximal tissue response even in the presence of an irreversible antagonist. The latter then only causes a fall in the maximal response in concentrations sufficient to reduce the numbers of receptors available to below that necessary for the agonist to produce a maximal effect.

An alternative interpretation of drug-receptor interactions is that the intensity of response to a drug is proportional to the rate of drug-receptor interactions, i.e. the number of interactions/unit of time. According to this 'rate theory' the factor that determines the difference between an agonist and antagonist is the dissociation rate constant k_2 (*see* equation 1) which describes the rate a drug leaves its receptor. The greater the rate of dissociation the greater the rate of drug-receptor interaction. Agonists, therefore, have a high rate of dissociation

and antagonists a low rate of dissociation. As yet, there is too little data on the k_2 values of drugs to evaluate the general applicability of this theory.

Production of drug effects The consequence of drug-receptor interaction and the conformational changes in receptors that result depends on the physiological role of receptor molecules and the organs of which they are part.

Most drug receptors are located on cells. This is not always the case since, for instance, the anticoagulant heparin induces conformational changes in a receptor molecule antithrombin III which is free in the plasma. This conformational change increases the affinity of antithrombin III for its substrate thrombin and the plasma concentration of free thrombin falls in consequence. Drugs may affect many aspects of cell function, e.g. membrane permeability to cations, active transport systems, the availability of cyclic nucleotides that modulate intracellular metabolic events, etc. In general, their primary effect is to inhibit or impair biochemical processes. They are more effective at impairing energy requiring (i.e. active) rather than passive processes and if they inhibit a particular metabolic sequence, they are most effective when inhibiting the rate limiting step.

Drug effects on cells cause changes in the function of the organs of which they are a part. These changes may be localised to the organ itself or they may trigger off a physiological response to the change in function of the target organ. For example, the primary effect of the hypotensive drug hydrallazine is vasodilatation of resistance vessels. This causes a fall in peripheral resistance which is sensed by baro-receptors in the aortic arch and carotid body and results in an increase in sympathetic tone, causing an increase in heart rate and cardiac output. The net effect on the BP of hypertensive subjects depends on the balance between these opposing primary and secondary effects.

The actions of drugs therefore may be considered at the molecular level (drug-receptor interactions), the cellular level, the organ or tissue level, and at the level of the whole animal. Clinical pharmacology is concerned with the use of drugs in man in both health and disease, a further consideration being drug actions in particular disease states.

In clinical practice a detailed analysis of drug actions at all levels is frequently unnecessary and attention is focused on actions that may be of benefit (i.e. therapeutic) in particular conditions and actions that may be detrimental (i.e. adverse). In this text, the mode of action of drugs will be described briefly and related, where possible, to what is known of the pathophysiology of the condition for which it is being prescribed.

The relevance of the mode of action of drugs to clinical pharmacology Clinical pharmacology often seems to be concerned with pharmacokinetic aspects of drugs at the expense of pharmacodynamic aspects, whereas knowledge of the latter is just as often of value in the clinical usage of drugs.

Drug-receptor interactions Knowledge of the nature of the binding of drugs to their receptors is essential for the interpretation of pharmacokinetic data. For

drugs that bind reversibly to receptors there is generally a close correlation between the concentration of drug in plasma water and the intensity of drug effect. For drugs that bind irreversibly (covalently) to receptors on the other hand or that induce irreversible changes, the response is often proportional to the peak plasma concentration but thereafter the relationship between plasma concentration and response is poor.

Drug interactions Pharmacodynamic drug interactions can often be predicted from knowledge of the mode of action of drugs that are administered concomitantly (Chapter 9).

Drug potency The potency of a drug refers to two separate characteristics:

1. The more potent a drug, the lower the dose necessary to produce a given effect. The absolute weight of a drug prescribed is only occasionally of relevance in therapeutics. If the dose is large, it may be inconvenient to take and the compliance with drug-taking instructions may fall off; e.g. in tuberculosis, paraminosalicylic acid is prescribed in 10–15 g dose/day. Its bulk is inconvenient and causes a proportion of patients to stop taking it and this encourages the emergence of resistant organisms.

2. The size of the maximal effect. If two drugs produce the same effect, e.g. the diuretics frusemide and bendrofluazide, but the maximal effect of the one (frusemide) is greater than that of the other (bendrofluazide), then the one with the greater effect is described as the more potent, irrespective of the size of their maximally effective doses.

Therapeutic index In animals, the ratio of the dose that is lethal to 50% of a group of animals (LD50) to the dose that produces a given effect in 50% (ED50) is described as the therapeutic index or ratio. In clinical pharmacology there can be no such simple expression relating what is desirable about a drug (therapeutic) to what is undesirable (adverse) for a variety of reasons.

1. A drug effect may be described as 'adverse' in one set of circumstances but therapeutic in another; e.g. the hypotensive effect of L-dopa in parkinsonism is often the dose-limiting adverse effect but it is the 'therapeutic' effect of alpha methyldopa in hypertension.

2. Drugs usually produce a number of effects some of which are therapeutic and some adverse. The dose-response curves for all these effects may differ considerably in slope and shape so that no single ratio can relate what is therapeutic to what is adverse. Furthermore, adverse effects often vary enormously in severity between those on the one hand that decrease the quality of life without serious consequences, e.g. drowsiness, nausea, dizziness, etc., and those on the other that are life-threatening, e.g. bone marrow depression, hepatocellular damage, etc. Knowledge of the relationship of both to the therapeutic dose range is necessary for effective use of drugs.

3. It is seldom possible to construct log-dose response curves in man for therapeutic effects of drugs and this is hardly ever possible for adverse effects.

The relationship between therapeutic and adverse effects of a drug in a

particular condition can only be established with any degree of certainty in clinical trials (Chapter 6) which should provide evidence on the degree of statistically significant benefit to be derived from taking a drug in a particular condition and on the nature, severity and incidence of adverse effects.

Variability in response to drugs The dose necessary to produce a given effect varies considerably between individuals for almost any drug. This inter-individual variation is comprised of–

1. Pharmacokinetic variability, i.e. variations in the ways drugs are handled in the body.
2. Pharmacodynamic variability, i.e. variability in responsiveness of the tissues to a given drug concentration.

In man, pharmacokinetic variability accounts for most of the observed variability (Chapter 4). However, when the plasma drug concentration producing a given intensity of effect is estimated in a number of patients with the same condition, there is usually a four- to ten-fold range of concentrations.

There are at least three sources of pharmacodynamic variability:

1. Differences in tissue responsiveness to a given drug effect between individuals.

2. Differences in the severity of the disease being treated between individuals Many diseases are not individual entities with a unitary aetiology and pathophysiology etc., but are collections of disorders presenting with similar signs and symptoms, e.g. congestive cardiac failure, atrial fibrillation, hypertension, epilepsy etc. It is probable that the dose-response relationship to a given drug will vary between different diseases presenting in similar ways and that the degree of response will vary with the severity of the disease.

3. Interindividual variation The response of an individual to a given concentration of a single drug may vary with time. This may be due to (a) tolerance at the cellular level: tolerance is not seen with all drugs but is most prominent with drugs that affect the CNS, e.g. narcotic analgesics, barbiturates, amphetamine, ethanol; (b) The intensity of symptoms or the severity of a disease being treated may vary with time so that the drug concentration necessary to produce a given effect will also vary.

The considerable variability in the log-dose response relationship in man means that there cannot be a 'therapeutic' dose for a drug. Rather it implies that there is a range of doses over which a drug produces a therapeutic effect in most patients, below which it is ineffective and above which it will probably produce unacceptable adverse effects in a sizeable proportion of patients.

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Chapter 2

Drug Absorption, Disposition and Excretion

One of the principal areas of interest in clinical pharmacology is the understanding of the many factors that relate 'the dose' of a drug that the patient receives to the concentration at its site of action. In this chapter the more important of these factors will be outlined and their relationship to drug pharmacokinetics discussed.

DRUG ABSORPTION

Gastrointestinal tract Absorption of nearly all drugs from any site in the gastrointestinal tract is by passive diffusion. The rate and extent of absorption is determined by the physicochemical characteristics of the drug and by physiological and pathological factors affecting the gastrointestinal tract.

Drug characteristics Most drugs are presented to the gastrointestinal tract as solids and the facility with which they go into solution is a major determinant of the proportion of a dose that is absorbed (drug bioavailability—Chapter 7).

As absorption from the gut is mostly by passive diffusion the more lipid soluble a drug, the more readily it is absorbed from all sites in the GI tract. The degree to which a drug is ionised at different sites in the tract can be calculated from the drug's pKa and the pH of the gut lumen. The partition on either side of the gastrointestinal membrane can be calculated from equations (1) and (2).

$$\text{For acids} \quad \frac{\text{concentration in gut lumen}}{\text{concentration in plasma}} = \frac{1 + \text{anti log (pH lumen} - \text{pK)}}{1 + \text{anti log (pH plasma} - \text{pK)}} \quad (1)$$

$$\text{For bases} \quad \text{"} = \frac{1 + \text{anti log (pK} - \text{pH lumen)}}{1 + \text{anti log (pK} - \text{pH plasma)}} \quad (2)$$

The pH of saliva is 6·0–7·0, of stomach 1–4, of upper small bowel 5·5–6·5, in lower small bowel 6·5–8·0 and in colon and rectum 6·0–7·0. Thus acids that

remain in solution in the unionised form, e.g sulphonamides, acid stable penicillins and aspirin, are partly absorbed from the stomach while basic compounds are concentrated up to 40 times in the stomach compared with plasma, the extent of concentration being limited by stomach blood flow rather than the theoretical partition ratio. In the small intestine, the estimated pH at the mucosal surface (5·3) is lower than that in the lumen and drugs with pKs 3–8·0 are rapidly absorbed. Absorption of drugs that are highly ionised throughout the GI tract, e.g. neostigmine, propantheline and guanethidine is slow and incomplete, the proportion of an oral dose absorbed often varying between individuals.

The binding of drugs in the gastrointestinal lumen decreases the rate and extent of their absorption. Dietary contents often affect drug absorption, the rate at which a drug is absorbed usually being reduced by administration with or shortly after food. One drug may decrease the absorption of another by forming insoluble complexes with it (*see* Drug Interactions).

Physiological factors—blood flow This is the major factor determining the rate of absorption from any site in the bowel. The blood supply in the small bowel is better than that in other sites and as a consequence, drug absorption is most rapid from this site. Absorption from the rectum and colon is also good but in general drug absorption after rectal administration is more variable and hence less predictable than after the oral route.

Motility As the small bowel is the principal site of drug absorption, factors that slow gastric emptying, for example, antimuscarinic agents, tend to slow drug absorption, while factors that expedite gastric emptying, e.g. metoclopramide, increase the rate of drug absorption.

Hepatic blood flow Drugs that are very rapidly metabolised in the first passage through the liver are often ineffective when swallowed, but are active sublingually. This is because the blood draining the buccal cavity does not go straight to the liver and the drugs are therefore more slowly metabolised, e.g. isoprenaline and glyceryl trinitrate (*see* Pharmacokinetics).

Pathological factors There is very little evidence in man demonstrating that disease of the gastrointestinal mucosa, for example gluten sensitive enteropathy or Crohn's disease, appreciably reduces drug absorption. However, in diseases in which the blood supply to the gut is reduced, such as shock and migraine, drug absorption is often substantially reduced.

Injection sites The rate and extent of absorption of drugs from injection sites depends on the solubility of the drug in the solution in which it is injected, its solubility in water, the water content of the tissues and the blood supply to the injection site. Absorption is generally more rapid after i.m. than s.c. administration owing to the better blood supply of muscle. Similarly it is better from the deltoid than the gluteal muscles owing to the better blood supply of the former. Conversely, the absorption may be greatly diminished when the blood supply to

the injection site is reduced, either as a consequence of a generalised reduction in tissue perfusion as in hypovolaemic shock or left ventricular failure, or as a consequence of the inclusion of a vasoconstricting agent such as adrenaline in the injection. Drugs that are poorly soluble in water may precipitate out at injection sites (digoxin, phenytoin, diazepam and chlordiazepoxide are examples), and this greatly delays the absorption of a proportion of the administered dose.

For drugs with very short plasma half-lives, absorption may be delayed in a number of ways. The drug may be administered in a solvent in which it is very soluble and from which it diffuses into the blood stream slowly (e.g. depot preparations of anabolic agents, gonadal steroids and phenothiazines). It may be administered in crystalline form (e.g. lente insulins) when the rate of absorption varies inversely with the size of the crystal. A drug may be administered as an inactive complex (e.g. procaine penicillin) from which it is released only slowly.

DRUG DISTRIBUTION

Plasma protein binding In most situations drugs are carried from their site of absorption to their sites of action via the blood stream in which drug molecules come into contact with all formed elements of the blood, RBCs, WBCs, platelets and the plasma proteins. A proportion of drug molecules become bound to these constituents and by far the most important of these quantitatively is plasma albumin by virtue of its high total surface area and concentration. Only a few drugs are appreciably bound to other proteins, e.g. steroid hormones and thyroxine to alpha globulin; lipid soluble vitamins to alpha and beta globulins.

Albumin is present in the plasma at a concentration of approximately 5×10^{-4}M. It has an isoelectric point at pH 5·0 and so is principally negatively changed at 7·4. It binds both basic and acidic drugs, hydrophobic and electrostatic bonds being operative in binding drug molecules. Drugs are usually bound to one or two high affinity sites and to a number of sites having less affinity. The processes of association and dissociation are very rapid and are measured in milliseconds only. Albumin-drug binding sites have a relatively low specificity so that compounds with a quite different chemical structure, e.g. salicylates and sulphonamides, may share the same binding site (*see* drug interactions).

In pharmacology, interest is focused on the amount of drug that is free in the plasma as it is only this fraction that can diffuse out of the plasma space to sites of action and elimination. The relationship between the total amount of drug in the blood and the proportion that is free depends on the number of drug binding sites, the affinity of these sites for the drug and the total concentration of drug in the blood. The proportion of total drug free in the plasma therefore varies with the total concentration but with most drugs the extent of variation in the therapeutic dose range is not great, so that the percentage of drug that is protein bound can be expressed as a single figure.

There are a large number of drugs that are highly protein bound (Table 1) at therapeutic plasma concentrations. For these drugs it may be possible to

Table 1

Drugs that are more than 90% bound to plasma albumin at therapeutic plasma concentrations

Flucloxacillin	Propranolol
Cloxacillin	Diazoxide
Doxycycline	Digoxin
Sulphadimethoxine	Tolbutamide
Nalidixic acid	Chlorpropamide
Warfarin	Tolazamide
Phenylbutazone	Diazepam
Oxyphenbutazone	Chlordiazepoxide
Sulphinpyrazone	Amitriptyline
Indomethacin	Imipramine
Probenecid	Nortriptyline
Frusemide	Desiprimine
Burimamide	Chlorpromazine
Ethacrynic acid	Phenytoin
Chlorothiazide	Carbenoxalone
Methotrexate	(Clofibrate)

saturate binding sites and then, by increasing the total plasma concentration, to cause a disproportionate increase in free drug. For example, phenylbutazone is 98% protein bound at plasma concentrations of 40–60 μg/ml such as are achieved after 600 mg/24 hours which is the upper limit of the conventional dose range. If the dose is increased three times, the % protein binding falls to 80%, i.e. the amount of free drug has increased tenfold. This may account for the increase in the instance of bone marrow depression that occurs with daily doses of phenylbutazone greater than 600 mg/24 hours. Similarly, the displacement of one drug by another from a plasma albumin binding site is also only likely to cause an appreciable increase in free drug if the displaced drug is highly protein bound (*see* Chapter 9).

The capillary membrane Drugs leave the plasma space by diffusing across the capillary membrane which has the characteristics of a lipoid membrane. In contrast to other membranes, however, there are relatively large pores in capillary membranes that allow unrestricted diffusion of water-soluble drugs of MW up to 5000 and relatively unrestricted diffusion up to 69 000. Thus, all drugs other than those that are proteins (e.g. asparaginase MW = 90–130 000) can readily diffuse into the extracellular space. The protein-bound fraction of drugs cannot diffuse out of the plasma space and hence is not available to receptors sites outside this space or for sites of metabolism or glomerular filtration. The capillaries of the hepatic sinusoids and to a lesser extent, those of the gastrointestinal tract, have larger pores than elsewhere and this may account

in part for the fact that some highly protein-bound drugs can be taken up rapidly by the liver.

For drugs that are cleared from the plasma by active uptake mechanisms, the rate of uptake is little influenced by the extent to which the drug is protein-bound. Thus highly protein-bound drugs such as propranolol and the dye bromosulpthalein (over 95% protein-bound) that is used in liver function tests, are very rapidly cleared by the liver and drugs such as cloxacillin, frusemide and chlorothiazide are very rapidly secreted by the renal tubules. The effect of drug protein binding on pharmacokinetics is most evident for drugs that reach sites of metabolism by passive diffusion or that are excreted mostly by glomerular filtration. For such drugs, the duration of action increases with the degree of protein binding and in several families of drugs in which there are variable degrees of protein binding between cogeners, e.g. the thiazide diuretics, tetracyclines and sulphonamides, this relationship holds. A further pharmacokinetic point is that for drugs that are highly protein bound, most of the drug in the body remains in the blood stream and the apparent volume of distribution therefore is small and underestimates the extent to which the free drug diffuses into the tissues.

Blood-brain barrier The capillaries of the brain and meninges are less permeable to water-soluble compounds than those elsewhere by virtue of glial foot processes that invest them. This capillary-meninges diffusion barrier is known as the 'blood-brain barrier' and it has the characteristics of cell membranes, in that it behaves like a lipoid barrier. Thus it is only permeable to free drug and to unionised species and the permeability of the barrier increases with the lipid solubility of the compound. The concentration of drug in the CSF is similar to that in brain tissue and the CSF/plasma concentration ratio when the plasma concentration is kept constant is 1/20–30 for highly polar compounds such as benzylpenicillin or quaternary ammonium compounds. For non-polar compounds, the ratio is determined by the plasma protein binding as there is no protein in the CSF, e.g. phenytoin is 90% protein bound in the plasma and the CSF/plasma ratio is thus 1/10.

There is evidence that some organic anions and cations, including benzylpenicillin and quaternary ammonium compounds, are actively transported into and out of the CSF, but this is probably unimportant quantitatively at therapeutic doses. Passive diffusion into the brain and CSF is facilitated by damage to the meninges as in meningitis (*see* penicillin, Chapter 35).

Diffusion into the eye is similar to that into the CSF, the blood-vitreous barrier acting as a lipoid diffusion barrier. However, most compounds leave the aqueous and the vitreous humours at a rate greater than can be accounted for by passive diffusion.

Tissue distribution and tissue binding The rate at which free drug diffuses out of the plasma space is determined principally by tissue blood flow. Thus, the drug concentration reaching the highly perfused tissues such as the heart, brain,

liver, lungs and kidneys are generally higher than those that are less highly perfused such as resting muscle, bone and fatty tissue.

Drugs diffuse into cells principally by passive diffusion so that ionised species remain in the extracellular space. The pH of the intracellular water is approximately 7·0 and is thus more acid than extracellular water. Partially ionised bases therefore reach a concentration inside cells greater than that in the extracellular space as they are more highly ionised in the more acid intracellular water. This 'trapping' of basic ions inside cells largely accounts for the apparent volumes of distribution of bases being greater than that of total body water (0·6 l/kg), e.g. practolol 1·6 l/kg, pethidine 1·5 l/kg, procainamide 1·74.

Tissue binding occurs as the result of chemical bonds formed between drug and tissue components. In a few instances drugs form irreversible covalent links with tissues, e.g. alkylating agents and organophosphorous anticholinesterase agents. However, in most instances the drug-tissue bonds are readily reversible. Highly lipid-soluble drugs such as the barbiturate thiopentone become concentrated in fatty tissue on account of hydrophobic bonds between drug and tissue but in most instances, the nature of the bonding between drug and tissue is not established. Examples of drugs that are highly bound to tissues include cardiac glycosides, quinine and quinidine and the 4- and 8-aminoquinolines, the phenothiazines and tricyclic antidepressants. All these drugs have apparent volumes of distribution many times greater than 1 l/kg, e.g. desiprimine 42 l/kg, nortriptyline 27 l/kg, but they are not selectively concentrated at sites of action. The pharmacokinetic implications of a high degree of tissue binding, i.e. a large Vd are discussed under pharmacokinetics (Chapter 4).

DRUG EXCRETION

Drugs may be excreted either as unchanged drug or as metabolites in the urine, faeces, exhaled air, sweat, tears and milk. Of these, excretion in the urine is far the most important for the majority of drugs. The amount of drug excreted in the sweat and tears is trivial and will not be considered here.

Renal excretion Drugs reach the lumen of the renal tubule by glomerular filtration only or by glomerular filtration and tubular secretion. They leave the lumen principally by passive reabsorption and occasionally by active reabsorption.

The glomerular filtrate is an ultra-filtrate of plasma. The capillaries of the glomerulus are similar to those elsewhere allowing unimpeded diffusion of drugs with a MW 5000 or less and partially impede diffusion for those between 5–69 000. Therefore virtually all drugs that are not protein-bound appear in the glomerular filtrate. The glomerular filtrate is of the order of 120 l/day but the daily urine volume is usually only 1–2% this volume. For compounds like insulin or cyanocobalin (B_{12}) that are filtered by the glomerulus but not actively secreted or reabsorbed, the concentration in the urine (u) is 50–100 times that in the plasma (p). Thus there is a tendency to concentrate drugs in the renal tubule and hence to promote their passive diffusion across the renal tubule back into

the plasma. For highly lipid soluble compounds such as pentobarbitone, warfarin and diazepam, the u/p ratio remains close to unity along the length of the tubule. As a consequence, the renal clearance of these drugs is very low. Indeed if the renal route were the only route of their elimination and they could not be metabolised, the half-lives of such drugs would be measured in tens of years rather than a few hours.

Passive reabsorption of drugs across the renal tubule adheres to the principles affecting passive diffusion. Apart from the reabsorption of salt and water which tend to favour drug reabsorption, by far the most important factor affecting drug reabsorption is urinary pH as the pH range for urine (4·4–8·0) is much larger than at any other sites in the body. There is therefore a 3–5000 fold range in the extent to which weak acids and weak bases may be ionised in the urine. As urinary pH can be deviated in an acid direction very much further from the plasma pH of 7·4 than it can in a basic direction, the maximal renal clearance rate for bases is usually much greater than that for acids unless the latter are actively secreted by the renal tubules. Thus, whereas the maximal renal clearance rate for salicylate (pK 3·0) is about 40 ml/min at urine pH of 8·0 and a urine flow rate of 10 ml/min, that for the base bethanidine (pK 10·6) is over 600 ml/min at a urine pH of 4·4 at the same urine flow rate.

Active secretory mechanisms exist for both acidic and basic drugs. Ninety per cent or more of the para-aminohipuric acid (PAH) in the renal artery is cleared from the plasma in one passage through the kidney and as a consequence of this, the agent is used to determine renal blood flow. Active tubular secretion occurs in the proximal tubule and is known to occur for uric acid, salicylates, sulphonamides, the benzothiadiazine diuretics, phenylbutazone, the penicillins and cephalosporins. Acid conjugates of drugs, the glucuronides and sulphates, are also actively secreted by the proximal tubule. Probenecid, phenylbutazone and sulphinpyrazone block this active secretory pathway and increase the half lives of the drugs secreted by it, for example benzylpenicillin.

Many bases are also known to be actively secreted by the renal tubules including catecholamines, dopamine, quaternary ammonium compounds such as hexamethonium and neostigmine and other amines, e.g. hydralazine, morphine, procaine and quinine. There are no drugs used in clinical practice that block the active secretion of bases.

Active reabsorption, which occurs in the proximal tubule for uric acid, is rarely encountered for drugs, although oxpurinol, the metabolite of allopurinol, is probably reabsorbed by the same mechanism as urate.

Biliary excretion The other important route of drug excretion is the faeces. After oral administration unabsorbed drug remains in the faeces, but for drugs that are absorbed, excretion in the faeces is the result of biliary excretion. Drugs are cleared from the plasma by the hepatocyte and from thence are excreted into the bile as either unchanged drug or metabolite. The principle factors determining the extent to which a drug is excreted via this route are the drug's molecular weight and polarity. In man, the extent to which a drug is excreted in the bile

rises sharply when the molecular weight of the drug or metabolite exceeds 500. As the MW of most drugs is well below this figure, the biliary route of excretion is usually less important than the urinary route. The facility with which a drug is excreted in the bile also increases with its polarity. It seems probable that all drugs and their metabolites obtain access to the bile but only the large highly polar compounds are not reabsorbed during passage down the bile canaliculi. Thus metabolism, especially conjugation reactions which, by addition of highly polar and bulky residues such as glucuronic acid and glutathione (pKa's 3–4) tend to facilitate biliary (as well as urinary) excretion. Protein binding has little effect on the biliary excretion of drugs as highly protein bound components can be rapidly excreted in the bile (*see* above). Many compounds are excreted by both routes and in the presence of renal failure, the biliary route of excretion becomes progressively more important, preventing the drug accumulating in the plasma to the same degree as creatinine. Some drugs known to be partly excreted in the bile are shown in Table 2.

Enterohepatic circulation This is a process whereby phase II metabolites (i.e. conjugates) or drugs excreted in the faeces, are hydrolysed to less polar compounds and reabsorbed into the circulation to be excreted into the bile once more on reaching the liver. Bilirubin is subject to such an enterohepatic circulation and is recycled approximately ten times before being excreted. The most prevalent enzyme in the bowel responsible for the hydrolysis of drug conjugates is beta glucuronidase and the bowel flora is the main source of this enzyme. The consequence of the enterohepatic circulation of drugs on their pharmacokinetics is to delay their excretion and hence lengthen their half-lives as the drug molecules undergoing enterohepatic circulation are not available for metabolism or renal excretion.

Other Routes

The lungs are the principal route of excretion of volatile and gaseous anaesthetics, ethanol, paraldehyde and volatile food constituents (*see* Chapter 12).

Milk Milk consists of a fat suspension in an aqueous medium containing protein, mostly as casein, lactose and inorganic salts. The pH of human milk is 7·0 and the 24 hour volume once lactation has been established 300–1000 ml. Drugs reach the milk by passive diffusion from the plasma, active transport having been documented for very few substances. As only the unionised component diffuses into milk, and as it is acid relative to plasma, the concentration for fairly strong acids such as benzylpenicillin and salicylate will be low, and for weak bases and acids with pKas close to that of 7·4 will be similar to that in the blood. Relatively strong bases will be concentrated in the milk, e.g. amphetamines, ephedrine, erythromycin, heroin, etc.

Whether or not a drug is present in the milk is most relevant to the neonates of mothers on chronic medication, e.g. with phenobarbitone for cortical epilepsy or for those that are drug addicts. The milk/plasma ratio for phenobar-

Table 2
Drugs partly excreted in the bile

Drug group	*Drug*
Antibacterial agents	Ampicillin
	Cloxacillin
	Methecillin
	Nafcillin
	Erythromycin
	Rifampicin
Cytotoxic agents	Vinca alkaloids
	Actinomycin D
	Bleomycin
	Daunorubicin
	Doxorubicin
Analgesics	Morphine
Diuretics	Chlorothiazide
Major tranquillisers	Thioridazine
	Trifluoperazine
	Prochlorperazine
	Chlorpromazine
Minor tranquillisers	Glutethimide
Antidepressants	Amitriptyline
Cathartics	Phenolphthalein
Sulphonamides	Succinlysulphathiazole
	Phthalylsulphathiazole
	Succinlysulphathiazole
Hormones	L-Thyroxine
	Progesterone
	Oestrone
	Testosterone
	Norethynodrel
	Stilboestrol
	Corticosterone
Cardiac glycosides	Ouabain
	Digoxin
	Lanatoside-C
Miscellaneous	Carbenoxalone
	Coumarin
	Orphenadrine

bitone is approximately 0·5 so that if the maternal plasma level is 10 mg/l and the child consumes 500 ml of maternal milk/24 hours and weighs 5 kg, the 24 hour 'dose' of phenobarbitone for the child is 0·5 mg/kg, approximately one third to one half the average adult dose. But as a neonate's capacity to both metabolise and excrete drugs is not as great as that of the adult, it is likely that

the plasma levels of drug on such a 'dose' will be similar to that of the mother. It is obviously advisable therefore, for neonates of mothers on chronic medication to be bottle fed.

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Chapter 3

Drug Metabolism

Most drugs are xenobiotics, that is they are compounds foreign to the metabolic environs of man, obvious exception to this rule being vitamins, minerals such as iron and calcium salts, and hormones. Many xenobiotics are harmful to living tissues and the ability to excrete them is a necessary requirement for species survival. While aquatic species can excrete xenobiotics by simple diffusion into the surrounding water, terrestrial species such as man excrete xenobiotics mostly in the urine, but a basic requirement for renal excretion is that the compound must have a low lipid solubility. The development of a metabolic means of converting potentially toxic chemicals to a form in which they are excretable is an essential adaptation to terrestrial existence.

There are very few drugs that are not metabolised at all before being excreted. Examples are ether, quaternary compounds such as hexamethonium, and the guanidinium hypotensive agent bethanidine. The great majority of drugs either (a) undergo spontaneous changes not mediated by enzymes, including drugs that are readily hydrolysed like the acid labile penicillins, and the alkylating agent mustine or (b) undergo metabolic transformation by enzyme systems. Most drugs fall into the latter category and undergo enzyme mediated biotransformations before being excreted in urine or bile.

Sites of Drug Metabolism

The liver Drugs that are metabolised by enzymes mostly undergo biotransformation in the liver, which, from the toxicological point of view, is strategically situated between the site of drug absorption and the systemic circulation.

The subcellular sites of drug metabolism in the hepatocyte are:

1. Microsomes The microsomal fraction of liver cell homogenates, obtained by differential centrifugation, contains fragments of the smooth endoplasmic reticulum and situated on the smooth endoplasmic reticulum are enzymes responsible for most phase 1 biotransformations (*see* below) including the mixed function oxidases and those for glucuronic acid conjugation.

2. Mitochondria Monoamine oxidases and enzymes mediating drug acetylation are located on mitochondria.

3. Cytoplasm The soluble fraction of differential centrifugation contains cytoplasmic enzymes that mediate alcohol oxidation, aldehyde oxidation and reduction, and those mediating the phase 2 reactions of methylation, sulphate conjugation and mercapturic acid formation.

Extra hepatic sites The plasma contains esterases with a high affinity for

butyrycholine (BuChE) that mediate the hydrolysis of the neuromuscular blocking agent suxamethonium and local anaesthetic esters such as procaine and the short acting intravenous anaesthetic agent propanidid. Esterases, present in the tissues, also contribute to the rapid metabolism of these drugs. Amidases are also located in plasma and tissues which hydrolyse the long-acting local anaesthetics such as lignocaine. The plasma also contains catechol-O-methyl transferase, an important enzyme in the biotransformation of catecholamines (*see* Chapter 11).

The kidney Vitamin D_3 is hydroxylated to 25-hydroxy vitamin D_3 by hepatic microsomal enzymes and to its most active form 1,25-dihydroxy vitamin D_3 by the kidney (*see* Chapter 34).

Gut microflora Gut microflora hydrolyse many conjugated compounds including bilirubin and many drugs, which facilitates the enterohepatic circulation of these compounds. The microflora may also metabolise unconjugated drugs, e.g. salicylazosulphapyridine, a drug used to decrease the incidence of relapses of ulcerative colitis. It is metabolised in the colon to the major metabolite sulphapyridine, which is excreted in the urine, and aminosalicyclic acid, which is excreted in the faeces (Chapter 30). The anti-inflammatory activity of the aminosalicylate may account for this drug's therapeutic effect, while many of its adverse effects have been attributed to the sulphapyridine.

Gut mucosa Gut mucosa contains monoamine oxidases, amino acid decarboxylases and enzymes for sulphate conjugation, which contribute to the metabolic transformation of monoamines such as tyramine, L-dopa and isoprenaline.

Types of Biotransformation

Most drugs undergo metabolism by two phases.

Phase 1 reactions These reactions are classified as oxidations, reductions and hydrolyses during which polar groups —OH, —NH_2, COOH and —SH groups are added to the molecule. The products of phase 1 reactions are therefore usually more polar than the parent compounds and are also in a chemical form in which they can readily participate in phase 2 reactions. Examples of phase 1 reactions are shown in Table 1.

Drug oxidation As drug oxidation is the rate-limiting step in the metabolism of a very large number of drug and some endogenous substrates such as steroid hormones, it is the single most important drug metabolising reaction and as such has been studied extensively both *in vivo* and *in vitro*.

There are a number of enzymes responsible for drug oxidation that are known as the mixed function oxidases. Drugs reach these enzymes on the smooth endoplasmic reticulum by diffusion from the plasma and are first bound to the reduced form of a cytochrome, cytochrome P450. The cytochrome P450 is then reduced indirectly by NADPH by an electro-transfer sequence that involves a flavo-protein and an unidentified carrier in the electron transfer. The reduced cytochrome-drug complex reacts with molecular oxygen to yield oxidised drug

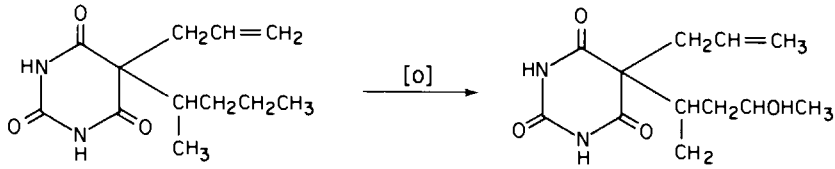
Table 1

Phase 1 Biotransformations

Oxidation

Aliphatic hydroxylation

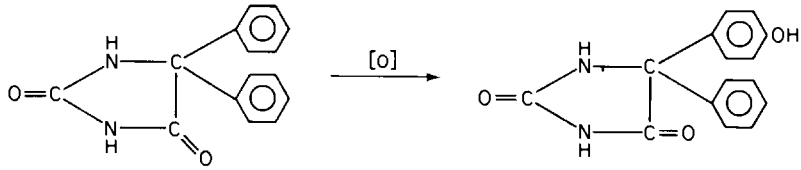
e.g.



Quinalbarbitone — Hydroxyquinalbarbitone

Aromatic hydroxylation

e.g.



Diphenylhydantoin — Parahydroxydiphenylhydantoin

	e.g. of substrate
N—oxidation	impramine
S—oxidation	chlorpromazine
Epoxidation	quinalbarbitone
Dealkylation	phenacetin
Deamination	amphetamine
Desulphuration	thiopentone

Reduction

Nitro reduction

e.g.

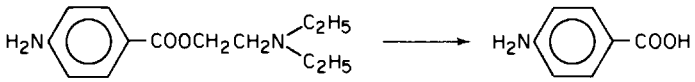
Chloramphenicol — Reduction product

Azo reduction

Dehalogenation — e.g. of substrate protosil halothane

Hydrolysis

e.g. Esters



procaine — PABA + $HOCH_2CH_2N(C_2H_5)_2$ diethylaminoethanol

Amides e.g. lignocaine

and oxidised cytochrome P450. This sequence is shown in Fig. 1 and the rate-limiting step is reduction of cytochrome P450.

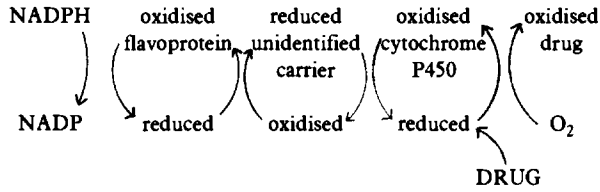
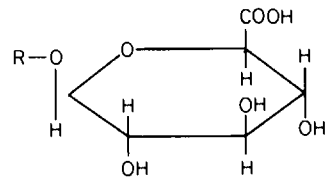


FIG. 1 Sequence of electron transfer in oxidation of drugs by smooth endoplasmic reticulum (microsomal) enzymes.

Many drugs compete for the mixed function oxidases if administered at the same time and as drug oxidation is frequently the rate-limiting step in drug metabolism, competitive inhibition at this site may cause clinically important changes in the pharmacokinetics of one or both competing drugs. Similarly, these enzymes are increased in quantity by enzyme inducing agents so that drug interactions at liver microsomal enzyme sites may cause a decrease or an increase in the rate at which drugs are metabolised (*see* Chapter 9).

Phase 2 reactions Phase 2 reactions are syntheses or conjugations in which the drug, either as the unchanged compound or as a phase 1 metabolite, is usually made more polar by the addition of a highly polar group. The types of conjugation reactions are shown in Table 2.

Table 2
Phase 2 Reactions

Reaction	*Conjugate*
Glucuronidation	
Acetylation	R—CO CH_3
Methylation	R—CH_3
Mercapturic acid formation	R—SCH_2 CH (COOH) NHCO CH_3
Sulphate conjugation	R—SO_3H
Amino acid conjugation	R—glycine, glutamine

Glucuronic acid conjugation is probably the most important phase 2 reaction in man as a wide range of drugs undergo this form of transformation including phenols, alcohols, amino acids and sulphydryl groups. Uridine diphosphate glucuronic acid (UDPGA) is the glucuronic acid donor and the syntheses are mediated by transferase enzymes present in the smooth endoplasmic reticulum of hepatocytes.

Sulphate formation occurs with alcohols, phenols, aromatic amines and sterols, acetylation with primary amines such as sulphonamides and hydrazines, when acetyl coenzyme A is the acetyl donor. Amino acid conjugations occur mostly with carboxylic acid (e.g. salicyclic acids) and acetyl coenzyme A is involved in an intermediary stage. Glycine and glutamine are the most commonly used amino acids.

Factors Affecting Drug Metabolism in Man

Genetic There are major differences in routes of drug metabolism between different species and in rates of metabolism between different strains within any given species. Likewise, in man, there are large differences in the rates of drug metabolism between races (e.g. acetylator phenotypes) and between individuals of a given single race. Genetic factors are the principle determinants of the rates of drug metabolism (*see* Pharmacogenetics, Chapter 5).

Age Drug-metabolising enzymes develop *in utero* and studies in animals and man have demonstrated that the fetus metabolises drugs less rapidly than the mother. Drug-metabolising systems develop rapidly during the first three months of life, by which time they metabolise most drugs at rates similar to those of adults. Children in general metabolise many drugs more rapidly than adults and in old age there is a further small decline in drug-metabolising capacity (Chapter 42).

Route of administration For drugs that are rapidly metabolised in the plasma, gastrointestinal tract or liver, the route of administration will be a major determinant of the rate of drug metabolism. Drugs that are rapidly metabolised in the plasma, insulin and heparin, for example, may be given as depot preparations when the rate of release from the depot determines the duration of action of the drug by controlling the rate at which drug reaches its sites of action and metabolism. For drugs such as lignocaine, glyceryl trinitrate and isoprenaline that are very rapidly metabolised in the first passage through the gastrointestinal mucosa and liver, the rate of drug metabolism is reduced by circumventing the hepatic portal system by administering the drug i.m. or s.c. or sublingually. For drugs that are slowly metabolised, the route of administration has little effect on the rate of metabolism.

Protein binding The extent to which a drug is protein bound is of little importance in determining the rate at which most drugs are metabolised as it only causes significant reduction in the rate of metabolism in drugs that are over 90% bound.

Plasma drug concentration Most drugs are cleared from the plasma by metabolism at rates that adhere to first-order kinetics, i.e. the amount of drug metabolised per unit of time will fall with a fall in the plasma drug concentration. A few drugs, e.g. ethanol, are cleared by a process that adheres to zero-order kinetics, i.e. the amount of drug metabolised per unit of time is constant and independent of the plasma concentration. Some drugs that are cleared from the plasma by a first-order process at lower doses, are cleared by a zero-order process at higher doses, e.g. phenytoin and aspirin.

Enzyme inhibitors and inducers Drug metabolising enzymes may be inhibited by drugs, e.g. disulphiram (antabuse) or monoamine oxidase inhibitors. These inhibitors are non-selective and slow the rate of metabolism of a wide range of drugs. Drugs that share the same metabolic pathway, if administered concurrently, may reduce the rate at which one or both drugs are metabolised. Conversely, there are a number of drugs, e.g. phenobarbitone and food contaminants, e.g. organochlorides, that are capable of increasing the compliment of hepatic microsomal enzymes and hence increase the rate at which many drugs are metabolised (*see* Chapter 9). Cigarette smoke also contains enzyme-inducing substances, and smokers metabolise some drugs more rapidly than non-smokers. Likewise, food cooked over charcoal contains enzyme-inducing substances.

Disease

The liver In view of the central importance of the liver in drug metabolism, it is to be expected that drug metabolism, like that of bilirubin, would be reduced in liver disease. A reduction in the rate of metabolism of a number of drugs has been observed in patients with liver disease, e.g. phenobarbitone, prednisone, isoniazid, tolbutamide, lignocaine and antipyrine, but the reduction only occurs when liver cell failure is severe. The increased sensitivity of patients in liver cell failure to the actions of CNS depressant drugs is due principally to an increased responsiveness to their pharmacodynamic effects rather than to a reduction in the rate of their metabolism.

The kidney In severe renal failure, there is a reduction in the rate of synthesis of 1,25-dihydroxy vitamin D_3, due to reduced hydroxylation by the kidney of the precursor, 25-hydroxy vitamin D_3. Osteomalacia may develop in consequence and be resistant to vitamin D_3 itself but responsive to its active metabolite 1,25 dihydroxy vitamin D_3.

Thyroid disease The rate of metabolism of antipyrine is increased in hyperthyroid patients and reduced in hypothyroid patients. However, there is not sufficient evidence about the effect of thyroid hormone on other drugs to make this a general rule.

Consequences of Drug Metabolism on Drug Fate

The possible sequence of events leading to drug excretion is shown in Fig. 2.

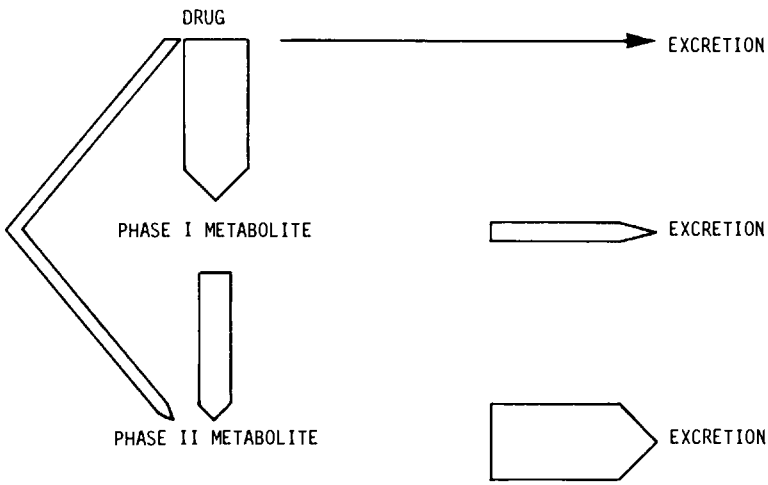


FIG. 2 The fate of drugs

In most instances excretion refers to urinary excretion. The facility with which a drug is excreted in the bile is also increased by increasing its polarity, although there are other factors, such as molecular weight and extent to which it undergoes enterohepatic circulation, that determine whether it is excreted in faeces or urine.

Drugs that are highly polar, such as quaternary ammonium compounds, barbitone and most antibacterial agents, are excreted unchanged in the urine. Most drugs are excreted in the urine, partly as phase 1 metabolites and partly as phase 2 metabolites and as drugs are usually complex chemicals, they give rise to several metabolites. Sometimes the number of metabolites is very large—over 60 metabolites of chlorpromazine have been identified in human urine—and for many of the more complex chemicals and for potent drugs present in tissues in low concentrations, details on metabolism are not available.

Consequences of Drug Metabolism on Drug Action

In the majority of cases, metabolic transformations reduce the duration of action of drugs, not only by converting them to a form in which they can be rapidly excreted, but also to a form that has little, if any, of the biological activity of the parent drug. This led to the concept that metabolic transformations were 'detoxicating reactions'. However, this is not always the case as there are a large number of drugs that form active metabolites and some of these are shown in Table 3.

Metabolites may also contribute to the adverse effects of drugs. For instance, one of the minor metabolites of phenacetin, p-phenetidin, which is readily oxidised to a metabolite that is itself an oxidising agent, causes the methaemag-

Table 3

Some drugs that form active metabolites that contribute to the drug's therapeutic effect

Parent drug	*Active metabolite*
Diazepam	Oxazepam
Chloralhydrate	Trichlorethanol
Primidone	Phenobarbitone
Trimethadione	Dimethyloxazolidindione
Phenylbutazone	Oxyphenbutazone
Phenacetin	Paracetamol
Impramine	Desmethylimipramine
L-dopa	L-dopamine
Propranolol	4-hydroxypropranolol
Prontosil	Sulphanilamide
Cortisone	Cortisol
Prednisone	Prednisolone
Lignocaine	Monoethylglycinexylidide
Procainamide	N-acetylprocainamide
Primaquine	5–6 quinoline-quinone
Proguanil	Triazine
Cyclophosphamide	Phosphoramide mustard

lobinaemia and haemolysis that may occur after a large dose of phenacetin. Acetaldehyde may be responsible for some of the deleterious effects of chronic ethanol ingestion, the hepatic necrosis caused by paracetamol overdosage has also been attributed to a minor metabolite. The major pathways of paracetamol metabolism are conjugation with glucuronic acid or sulphate, but a small proportion (less than 2% of the total therapeutic dose) forms a highly reactive metabolite that may be an epoxide or N-hydroxy-N-acetyl-p-hydroxyaniline (NHAPA) (Fig. 3) which, in the therapeutic dose range, is rapidly conjugated with glutathione. After an overdose, the hepatic glutathione falls and when this is reduced by 85% or more, the reactive metabolite reacts with hepatic macromolecules and causes hepatic necrosis.

The role of metabolites of other drugs in the causation of other adverse effects of drugs is not established, but it is possible they contribute to many of these, including cell necrosis, allergic reactions, blood dyscrasias, mutagenic, carcinogenic and teratogenic effects of drugs. However, reactive metabolites are hard to identify in the plasma as they have short half-lives by virtue of their reactivity and are hence present in the plasma in very low concentrations.

Practical Considerations

The practical value of knowledge of drug metabolism is principally in the relationship between drug metabolism and drug pharmacokinetics. There are

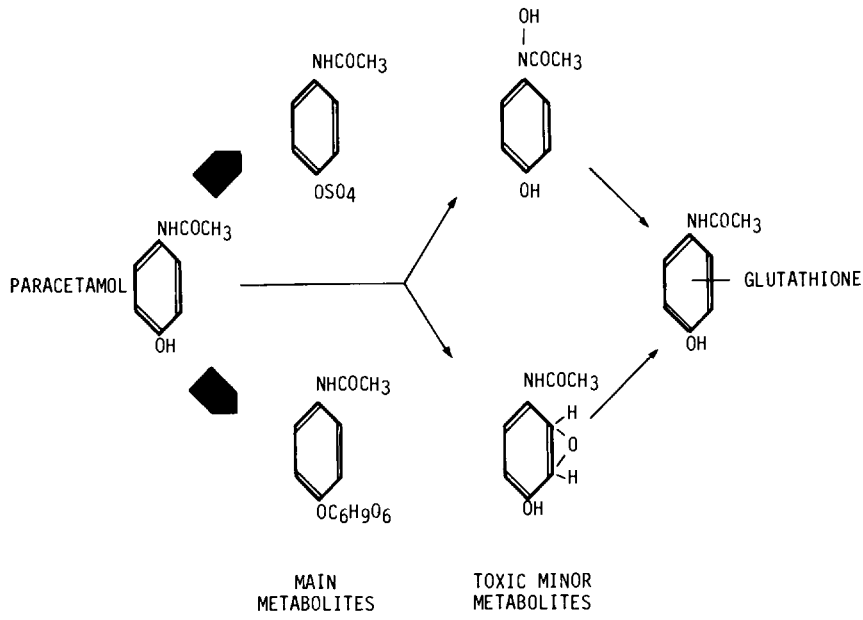


FIG. 3 Paracetamol metabolism.

certain general points that may be useful in drug usage if the drug in question is removed from the body chiefly by hepatic metabolism.

1. There will be approximately a tenfold or greater range in the plasma $t_{\frac{1}{2}}$ of such drugs in the population and in the plasma concentrations achieved after chronic administration of a given dose.
2. Parent drug will not accumulate in renal failure, but metabolites may do so.
3. In severe liver cell failure there may be a fall in the rate of drug metabolism.
4. The rate of metabolism by the liver of a given drug may be inhibited or enhanced by other drugs that are also metabolised by the liver.
5. If there is a poor correlation between the drug plasma concentration and drug effects it is possible that the drug may form an active metabolite or metabolites.

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Chapter 4

Pharmacokinetics

Pharmacokinetics is the study of the rates at which the various physical and chemical processes to which drugs are subjected in the body occur and of the relationship of these to the speed of onset, the intensity and the duration of drug effects. The study of the passage of drugs through the body was established on a sound theoretical basis by Teorell in 1937 and was given the name pharmacokinetics by Dost in 1953. Knowledge of this aspect of clinical pharmacology is essential for the accurate prediction of drug responses and, if properly applied, will enhance the therapeutic and diminish the adverse effects of drugs.

In this chapter, only the basic principles of pharmacokinetics are considered without any mathematical detail. Those interested are referred to the source references for discussion of the theoretical basis to the subject.

Drug plasma concentration The rate of onset, intensity and duration of drug effects are determined by the drug concentration at its site or sites of action. In most instances however, it is impossible to obtain a direct measurement of this and the time course of a drug in the body is determined using drug plasma concentrations. The assumption implicit in such studies is that the time course of drug concentration at its sites of action is determined by that in the plasma. This is a reasonable assumption for many drugs but not for those that are very highly bound by plasma proteins or by the tissues, for drugs that do not diffuse readily across cell membranes or that form active metabolites or for those that cause irreversible changes in target organs. For drugs with these characteristics, the time course of the drug in the plasma may correlate poorly with that at site or sites of action and pharmacokinetic data derived from studies on plasma concentrations must be interpreted with caution.

The drug concentration is measured in plasma rather than whole blood as most drugs are partially bound to plasma proteins, and are therefore present in a higher concentration in plasma than in whole blood. It is also easier to measure drug in plasma than in whole blood using most methods of drug determination. Pharmacokinetic studies can be carried out on urine and saliva but as these are determined in part by the plasma concentration but are subject to more variables, they are generally less informative than plasma concentrations and will not be considered here.

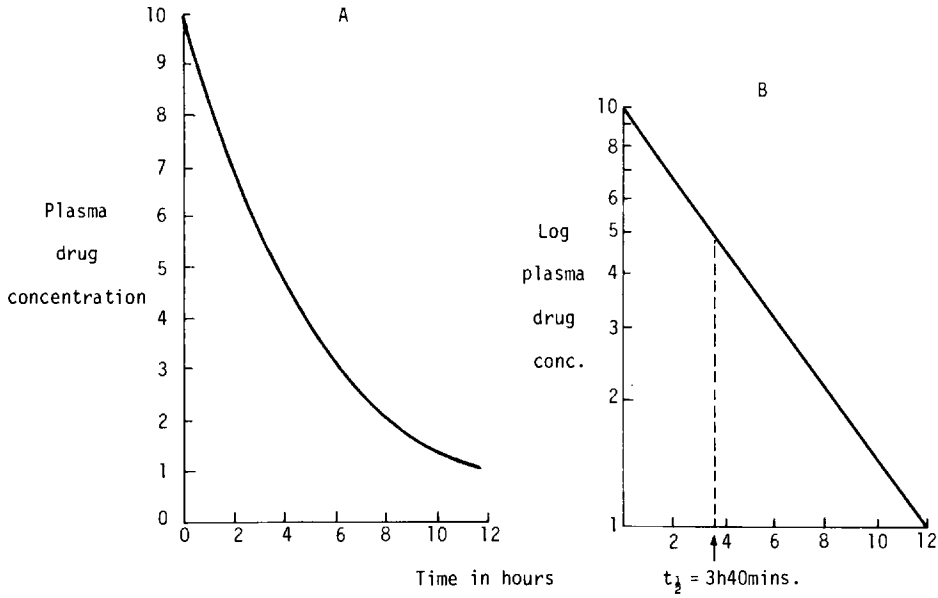
Pharmacokinetic models During its passage through the body, the dose of a drug is subjected to many simultaneous processes, so that a proportion is being absorbed, a proportion bound to plasma proteins, a proportion is undergoing metabolism, etc. The speed of these processes determines the time course of the

drug plasma concentration-time curve. Most pharmacokinetic studies start by studying the time course of the plasma concentration after a single dose i.v. bolus injection, thus eliminating one variable, drug absorption. The data is then interpreted by reference to pharmacokinetic models which are mathematical models of varying complexity that simulate the observed time course. The simplest of these is the one compartment open model and as this is the most useful in clinical practice it will be considered in some detail, only brief reference being made to more complex models.

One compartment open model This assumes that after i.v. bolus injection, all the drug in the body is distributed instantaneously in a single homogenous compartment from which it is continuously removed by a concentration dependent (first order) process or processes. In such a model, the drug concentration in the single compartment falls exponentially in one phase (Fig. 1a) and when the log of the concentration is plotted against time, the points fall along a straight line (Fig. 1b) described by the equation:

$$ke = \frac{\ln Co/Ct}{t} \quad (1)$$

ke = coefficient of elimination
Co = drug concentration at time 0 (t_0)
Ct = drug concentration at time t



FIGS. 1a and 1b Single compartment open model—fall in drug plasma concentration plotted on a linear scale (1a) and a log linear scale (1b)

By convention, the rate of decline in the plasma concentration is denoted by the $t_{\frac{1}{2}}$ (or drug half-life) which is the time taken for Co to fall by half.

At the $t_{\frac{1}{2}}$, ln Co/Ct = 0·693 (the natural log of 2)

Therefore
$$ke = \frac{0{\cdot}693}{t_{\frac{1}{2}}} \tag{2}$$

and
$$t_{\frac{1}{2}} = \frac{0{\cdot}693}{ke} \tag{3}$$

In practice, the $t_{\frac{1}{2}}$ rather than ke is used most commonly to describe first order processes. The half-life of drug elimination from the plasma, when applying a one compartment open model, is of great importance in pharmacokinetics and will be discussed in further detail below.

The apparent volume of distribution (Vd) is the second important pharmacokinetic parameter. It is a proportionality constant relating the total amount of drug in the body to the drug concentration in the plasma. It is not an anatomical compartment but a notional or 'apparent' compartment of sufficient volume to contain all the drug in the tissues at a concentration identical to that in the plasma. It is obtained from knowledge of the dose absorbed and the concentration in plasma at zero time, the latter being obtained by extrapolation.

Thus
$$Vd = \frac{\text{dose absorbed (g)}}{\text{Co(g/l)}} \tag{4}$$

The Vd is expressed in litres, irrespective of the patient's weight or in l/kg by dividing by the weight.

Drug distribution in the tissues is in fact seldom uniform, but the Vd does give some insight into a drug's disposition. Thus, for drugs that are highly bound to plasma albumin, e.g. warfarin, frusemide and L-thyroxine, the Vd is similiar to the albumin space 4–7 l, indicating that most of the dose stays in the plasma space. Highly charged compounds such as quaternary ammonium compounds and salicylate, have Vds similar to the extra cellular space (12–16 l), while drugs that readily diffuse across cell membranes and yet are not bound to tissues, have Vds similar to that of total body water (30–50 l) (e.g. antipyrine, phenytoin and theophyline). Weak bases tend to be concentrated in the more acid intracellular space and hence have a Vd greater than that of total body water (1–3 l/kg), e.g. trimethoprim, beta blockers, pethidine and lignocaine. Drugs that are highly bound to the tissues, such as digoxin, tricyclic antidepressants and phenothiazines, have Vds of several hundred litres.

Two compartment open model After i.v. bolus injection, the drug plasma concentration declines, not in one but in two phases, an initial rapid phase being followed by a slow phase (Fig. 2).

The model used to interpret such a graph is the two compartment open model shown in Fig. 3.

In this model, drug is injected into a central compartment (volume V_1) which

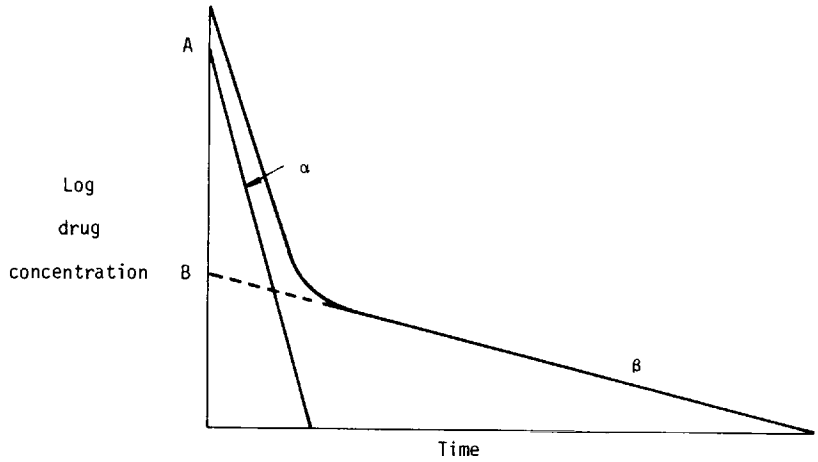


FIG. 2 Decline in the log drug plasma concentration against time after i.v. bolus injection. For explanation see text.

is in communication with a peripheral compartment (volume V_2) and the flux between the compartments is determined by the rate constants k_{12} and k_{21} and the concentration difference between them. Elimination occurs only from the central compartment and is irreversible, the rate being determined by the elimination rate constant ke.

The compartments in the model are of course mathematical and not anatomical entities. The biological explanation of the biphasic nature of Fig. 2 is that the drug is injected into the central compartment which consists of the blood and extracellular space of highly perfused organs such as the heart, liver, lung and kidney. The rapid fall during the alpha or distribution phase is due to drug diffusing out of the blood stream into the less well perfused tissues, muscle, bone, fat, etc., and at the intercept of the rapid alpha phase and the slow beta phase, drug in the two compartments is in equilibrium. During the slow beta phase, drug is eliminate from the body by processes such as metabolism and renal and biliary excretion, that are much slower processes than drug distribution.

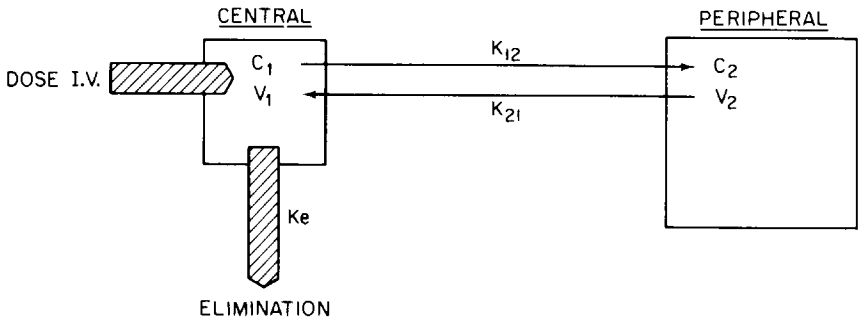


FIG. 3 Two compartment open model.

The two compartment open model is described by the equation

$$C_l = Ae^{-\alpha t} + Be^{-\beta t} \tag{5}$$

The values of A, B, alpha and beta are obtained from Fig. 2. The slope of the beta phase is extrapolated to zero time to give the intercept term beta. The biphasic curve is then resolved into two individual exponential lines by the process of curve stripping whereby the values along the extrapolated line (dotted line in Fig. 2) are subtracted from the observed values during the alpha phase and the resultant values plotted to give a second line with an intercept value A and a slope of alpha.

From knowledge of A, B, alpha and beta it is possible to obtain the values of the pharmacokinetic parameters ke, k_{12}, k_{21} and V_1, V_2 and Vd by application of the following formulae

$$ke = \frac{A + B}{\frac{A}{\alpha} + \frac{B}{\beta}} \tag{6}$$

$$k_{21} = \frac{\alpha\beta}{ke} \tag{7}$$

$$k_{12} = \frac{AB}{(A + B)^2} \qquad \frac{(\beta - \alpha)^2}{k_{21}} \tag{8}$$

$$V_1 = \frac{Dose}{A + B} \tag{9}$$

$$Vd = \frac{Dose}{\beta \text{ (area under the plasma concentration curve from } t_o - t_{oo})} \tag{10}$$

$$V_2 = Vd - V_1 \tag{11}$$

Despite the fact that the pharmacokinetics of most drugs adhere to the two compartment open model, as the distribution phase is usually very short compared to that of elimination, it can be ignored. This allows the application of the one compartment open model in which $ke = \beta$. The apparent volume of distribution can then more simply be obtained using the intercept term B (Fig. 2) as Co

$$Vd = \frac{Dose}{B} \tag{12}$$

Clearance The whole body clearance of a drug is the volume of plasma 'cleared' of the drug per minute, regardless of the means by which it is 'cleared' or removed from the plasma. Like the $t_{\frac{1}{2}}$ and Vd, clearance is an important pharmacokinetic parameter. Applying the one compartment open model it is derived from the ke and Vd

$$\text{Whole body clearance} = ke \times Vd \text{ l/min} \tag{13}$$

Most drugs are cleared from the body by the processes of metabolism and excretion so that

$$ke = k_m + k_R \tag{14}$$

k_m = rate constant of drug metabolism
k_R = rate constant of renal excretion

If a drug can be measured in the plasma and the urine, then its renal clearance (C_R) can be determined in the usual way if the plasma concentration remains constant during the period of measurement.

$$C_R = \frac{UV}{Css} \tag{15}$$

UV = amount of drug excreted in the urine/unit of time
Css = drug plasma concentration at steady state
Then applying (13)

$$k_R = \frac{C_R}{Vd}$$

the contribution of metabolism to drug clearance can be obtained

$$k_m = ke - \frac{C_R}{Vd} \tag{16}$$

For drugs that are removed from the plasma solely by renal excretion, if there is a fixed relationship between drug clearance and creatinine clearance, it is possible to design a dose schedule on the basis of the creatinine clearance. Such schedules have been most usefully applied to the administration of aminoglycoside antibacterial agents, e.g. gentamicin, to patients with impaired renal function.

The Css is the concentration of drug in the plasma at steady state or equilibrium, when the rate of absorption into the plasma is equal to the rate of elimination from the plasma. The amount of drug cleared from the plasma with time is equal to

$$Css \times ke \times Vd \tag{17}$$

Conversely, if a drug is given by continuous infusion for sufficient time to achieve a steady state (i.e. $5 \times t_{\frac{1}{2}}$), then the amount of drug being infused Q, is equal to the amount of drug being cleared from the plasma (17). Therefore, from knowledge of ke and Vd, it is possible to predict Css for any value of Q

$$Css = \frac{Q}{ke \times Vd} \tag{18}$$

For multiple doses Q = fD/DI when
D = dose
f = the fraction of the dose that reaches the systemic circulation
DI = the dose interval

Therefore

$$Css = \frac{fD}{DI} \cdot \frac{t_{\frac{1}{2}}}{0{\cdot}693} \cdot \frac{1}{Vd} \qquad (19)$$

From (19) it can be seen that the steady-state drug plasma concentration achieved after chronic dosing varies directly with the size of the dose, the fraction of it that is absorbed into the systemic circulation and the $t_{\frac{1}{2}}$ and inversely with the dose interval and apparent volume of distribution.

Absorption Absorption from the gut or depot site is a first-order process determined by the concentration gradient between gut lumen, or depot site, and the plasma and by the facility with which the drug diffuses from these sites into the plasma. In clinical pharmacology it is not usually possible to measure the amount of unabsorbed drug at any one time and the rate and extent of absorption is therefore determined from drug plasma and urine concentration measurements.

The proportion of a dose of a drug that reaches the systemic circulation is determined by the extent to which it is absorbed and, after oral administration, by the extent to which it is metabolised during its first passage through the liver (first-pass effect).

Rate of absorption For drugs with no first-pass effect, the rate of absorption after oral administration is determined by the time to peak plasma concentration. The more rapid the rate, the sooner and the higher the peak. As absorption is usually a first-order process, the rate can be expressed in terms of the absorption half-life. In general, absorption is a much more rapid process than elimination (Table 1).

Table 1
Absorption and elimination half-lives (mins) of three commonly used drugs

	Absorption	*Elimination*
Aspirin	15–20	240
Theophylline	70–80	180–900
Digoxin	15–45	2400

The rate of absorption is generally only important as a determinant of plasma concentration after single dose administration as, after multiple doses, it is the slower rate of excretion that determines the plasma concentration.

Proportion absorbed For drugs that are not metabolised in one passage through the liver, the proportion of an oral dose absorbed is equal to the drugs bioavailability and it is determined by comparing the area under the drug plasma concentration vs. time curve (AUC) after an oral dose with that after an i.v. bolus injection of the same dose (Chapter 4). For drugs with a first-pass effect, this can usually only be done using isotopically labelled drugs. The proportion of a dose that

is absorbed is of considerable importance as it is one of the factors that determines the steady-state plasma concentration (Css—*see* Eq. 19) and hence drug concentration at receptor sites after both single and multiple doses.

Most highly lipid soluble compounds such as most hypnotics, minor and major tranquillisers, are completely absorbed whereas less than 50% of an oral dose of highly ionised drug, such as quaternary ammonium compounds, is absorbed and negligible amounts of insoluble compounds, such as disodium chromoglycate, are absorbed.

First-pass metabolism After oral administration drugs are absorbed into the hepatic portal vein where they achieve a concentration higher than at any other part of the circulation. If a high proportion of drug in the hepatic portal vein is metabolised during its first passage through the liver (first-pass effect), the proportion of the dose that reaches the systemic circulation unchanged and hence the peak height and the area under the plasma drug concentration-time curve, will be determined by its rate of hepatic metabolism and not by its absorption kinetics. This first-pass effect determines the bioavailability of a number of commonly used drugs, e.g. isoprenaline, glyceryl trinitrate, propranolol, debrisoquine. For such drugs, higher peak plasma concentrations and longer half-lives for any dose can be achieved by using alternate routes of administrations (e.g. sublingual, s.c., i.m., i.v.) when the blood draining the absorption sites does not go straight to the liver.

Distribution As can be seen from Fig. 2, the distribution or α phase of the plasma concentration-time curve of a drug is very much more rapid than the elimination phase and for most drugs is completed in 10–20 minutes. The process takes considerably longer, 2–6 hours, for drugs that are extensively bound to the tissues, like digoxin and chlorpromazine. As drug distribution occurs more rapidly than absorption from the gut or depot sites, the distribution phase is not evident when drugs are administered by routes other than the intravenous.

Elimination As has already been stated, drug elimination adheres to first-order kinetics in most instances. This is due to the fact that the processes involved in drug elimination, enzyme mediated metabolism, glomerular filtration, tubular secretion etc., are all drug concentration dependent. Knowledge of the $t_{\frac{1}{2}}$ enables certain predictions to be made.

1. The time that must elapse before a drug is almost completely eliminated can be predicted from the $t_{\frac{1}{2}}$.

In 1 $t_{\frac{1}{2}}$ 50·0% is eliminated
2 $t_{\frac{1}{2}}$s 75·0% is eliminated
3 $t_{\frac{1}{2}}$s 87·5% is eliminated
4 $t_{\frac{1}{2}}$s 93·8% is eliminated
5 $t_{\frac{1}{2}}$s 96·9% is eliminated
6 $t_{\frac{1}{2}}$s 98·4% is eliminated

i.e. it takes five half-lives after the achievement of peak plasma concentration for 95% of a dose to be eliminated.

2. The optimal dose interval can often be determined from the $t_{\frac{1}{2}}$ if the therapeutic range of plasma concentration is known. For example, if it was thought desirable that the plasma concentration of a drug should not fall more than 20% between doses, what is the maximal dose interval for a subject in whom the drug has a $t_{\frac{1}{2}}$ of 24 hours?

$$ke = \frac{0{\cdot}693}{24 \times 60} = 0{\cdot}00048 \text{ min}^{-1}$$

Therefore applying (1)

$$\ln \frac{1{\cdot}0}{0{\cdot}8} = 0{\cdot}00048 \times t$$

Therefore

$$t = \frac{0{\cdot}223}{0{\cdot}00048}$$

$$= 465 \text{ min}$$

i.e. an appropriate dose interval would be 8 hours.

3. If the $t_{\frac{1}{2}}$ does not vary with changes in plasma concentration, then plasma log drug concentration vs. time plots are parallel when plotted starting from different plasma concentrations.

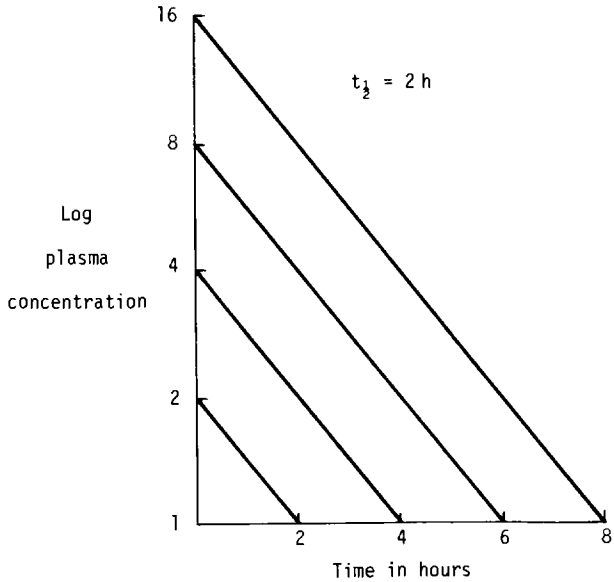


FIG. 4 Log drug concentration vs. time. For drugs whose $t_{\frac{1}{2}}$ does not vary with plasma concentration, to increase the duration of a given effect by 1 half-life it is necessary to increase the peak plasma concentration by a factor of 2.

This shows that to increase the duration of drug effect by one half-life, it is necessary to increase the peak plasma concentration by a factor of 2 and to increase the duration by two half-lives, the peak concentration must increase 4 times, etc. Conversely, if the peak plasma concentration is doubled, the duration of effect is increased by one half-life.

Continuous infusion and multiple doses If a drug is administered by continuous infusion, a fixed amount is usually administered per unit of time, e.g. 1 mg/min. The kinetics of such a process is described as zero-order. The drug plasma concentration vs. time curve when there is a zero-order drug delivery process and a first-order elimination process is shown in Fig. 5.

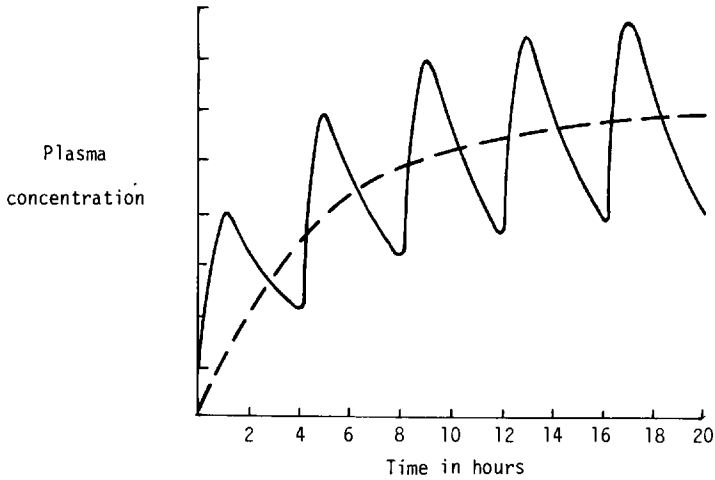


FIG. 5 Continuous infusion with zero-order input and a first-order elmination. The broken line represents the plasma concentration of a drug with an elimination $t_{\frac{1}{2}}$ of 3h, given by continuous i.v. infusion. The unbroken line is the same drug given orally at a dose interval of 3h (i.e. dose interval = elimination $t_{\frac{1}{2}}$).

The same situation obtains when a drug is given orally, or by another route, in repeated doses. As chronic oral administration is the most frequent mode of drug administration, the understanding of the kinetics of this system is important clinically.

It can be seen from the figures that the drug concentration increases rapidly initially, but slows down progressively until a plateau is reached. This occurs as the processes of drug elimination, being concentration dependent, remove increasingly more of the drug as the drug plasma concentration increases until, at the plateau, the rate of elimination is equal to that of infusion. The rate of accumulation therefore is determined by the rate of elimination and a half-time of accumulation is equal to the half-time of elimination. From this it follows that the drug plasma concentration reaches to within 5% of the plateau

value in 5 half-lives (see above). Similarly, if the rate of infusion is changed or the oral dose is changed, the new steady state will not be achieved for approximately 5 half-lives. If there is a change in the rate of drug elimination, for example an impairment of renal function, which results in an increase in the $t_{\frac{1}{2}}$, then the drug will accumulate reaching a plateau value over 5 of the new half-lives.

Drugs with long half-lives It may be desirable to obtain a therapeutic plasma concentration rapidly when using a drug with a long $t_{\frac{1}{2}}$ (e.g. digoxin $t_{\frac{1}{2}}$ = 40 hours). This is achieved by means of a loading dose which is usually several times that of the maintenance dose. If the loading dose is administered in a single dose, the peak plasma concentration may exceed the minimal concentration necessary to cause adverse effects. Under these circumstances, the loading dose is split up into several smaller doses as is the established custom of digitalisation.

Drugs with short half-lives Drugs that are very rapidly eliminated from the blood, e.g. insulin, heparin, sodium nitroprusside, do not achieve a plateau value if given intermittently, using conventional dose intervals (4–24 hours) as they are completely eliminated between doses. To obtain a steady plasma concentration for these drugs, therefore, it is necessary to administer the drugs by continuous infusion or by a slow release depot preparation.

The relationship of drug plasma concentration to drug effect A necessary requirement for the application of knowledge of pharmacokinetics is to know what the relationship is between the drug plasma concentration and drug effect. In this context the drug implies the active component, which is not always the parent drug. On the basis of this relationship, drugs may be grouped into three broad types, shown in Fig. 6.

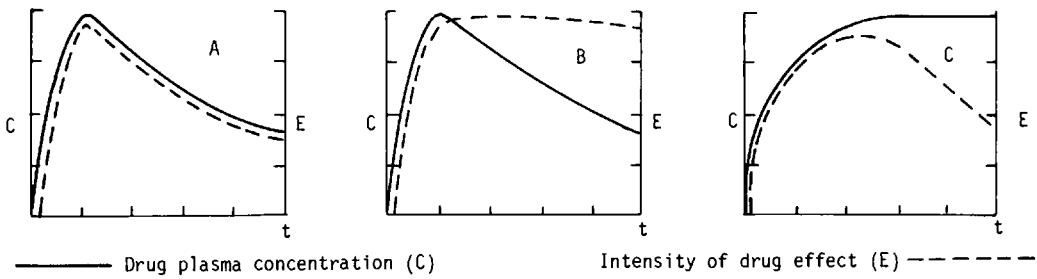


FIG. 6 Relationship of drug plasma concentration to drug effect.
A. the intensity of the drug effect varies with the drug plasma concentration. Type I drug.
B: the intensity of the drug effect does not decline with the drug plasma concentration. The effect of the drug outlasts the presence of the drug in the body. Type II drug.
C: the intensity of the drug effect declines despite the maintenance of a steady-state drug plasma concentration Type III drug.

Type I In this class, there is a close correlation between the drug effect and drug plasma concentration and this relationship persists indefinitely. Included in this class are a large number of drugs whose therapeutic effects correlate closely with the plasma concentration:

e.g. local and general anaesthetics
antipyretic analgesics
anticonvulsants
antidysrhythmic agents
cholinergic and adrenergic receptor antagonists

Type II In this class, the drug effect outlasts the physical presence of the drug itself. This occurs when the drug produces an irreversible change in the tissues, e.g. cytotoxic agents, cytotoxic antibacterial agents; or when a drug irreversibly inhibits an enzyme, e.g. organophosphate anticholinesterase agents and monoamine oxidase inhibitors; or produces a change that can only slowly be reversed, e.g. noradrenaline depletion from sympathetic nerve terminals by reserpine.

Type III With drugs of this class, tolerance to the drug effect develops with time, e.g. barbiturates and many other CNS depressants, narcotic analgesics and amphetamines.

The relationship between drug effect and plasma concentration must also be considered in relationship to the adverse effects of drugs. Thus, while most side effects have a type I relationship to the plasma concentration, most of the serious adverse effects, e.g. blood dyscrasias, hepatotoxic and nephrotoxic effects, have a type II relationship.

The use of pharmacokinetic data Pharmacokinetic data is most useful for type I drugs in deciding on an appropriate dose, dose interval and means of drug administration and some of these points have been illustrated above.

In the treatment of drug poisoning, the feasibility of methods designed to increase drug elimination is decided on pharmacokinetic data. For example, forced diuresis or dialysis is unlikely to expedite drug excretion sufficiently to benefit the patient if the drug has a very large volume of distribution, e.g. tricyclic antidepressants and phenothiazines, if it is highly protein bound, e.g. benzodiazepines, or when k_R is much smaller than k_m, e.g. for barbiturates other than phenobarbitone and barbitone (Chapter 40).

In monitoring drug effects after chronic administration, the time that must elapse before the maximal effect of a given dose develops is determined by the drug half-life (*see* above). The feasibility of using drug plasma concentrations in monitoring drug therapy is also decided on the basis of pharmacokinetic considerations (*see* below).

Practical limitations to the use of pharmacokinetic data The major limitations to the use of pharmacokinetic data in clinical practice are as follows:

I. VARIABILITY BETWEEN INDIVIDUALS

(a) Elimination There are large interindividual differences in the half-lives of

drugs that are cleared principally by metabolism (*see* below), the range varying between a fourfold difference between fast and slow metabolisers of such drugs as theophylline, diazoxide, phenylbutazone and antipyrine to a 10–20 fold difference for drugs such as bishydroxycoumarin, propranolol and nortriptyline.

For drugs that are eliminated mostly as unchanged drug in the urine, the range of interindividual differences in ke is usually smaller in patients with normal renal function, although for weak bases and acids whose pKa's are close to the urine pH range of 4·4–8·0 the rate of excretion will change appreciably with changes in urine pH.

(b) Vd There are differences in the Vd of drugs between individuals, but this seldom varies more than twofold.

(c) Drug responsiveness If the drug plasma concentration is maintained at a constant value, there are quite large interindividual differences in response to a given drug. The reasons for variability in response to a given concentration of a drug are not always clear, but it is in part due to variability between individuals in the disease being treated and partly to variability in responsiveness of the tissues to the drug.

2. INADEQUACY OF PHARMACOKINETIC MODELS The single compartment open model, in which the drug concentration decays exponentially, does not always apply. Some drugs, e.g. ethanol, are metabolised at zero-order kinetics as are several drugs in high therapeutic doses or after overdosage. Phenytoin is metabolised at zero-order kinetics by many patients as doses greater than 200–300 mg/day so that any increase in daily dose over this range will cause a disproportionate rise in plasma concentration (*see* Chapter 17, Fig. 1).

There are a number of drugs, e.g. oral anticoagulants, phenylbutazone, phenytoin, methotrexate, probenecid, salicylate, streptomycin and rifampicin, whose plasma concentration declines exponentially but for whom the rate of decline slows progessively the higher the plasma concentration. This effect is probably due to substrate inhibition of metabolising enzymes or to a limited supply of the molecule with which the drug is conjugated. For instance after high doses of salicyclate, the supply of glycine is such that it limits the rate of conjugation and hence rate of drug excretion. Drugs that are eliminated very slowly, e.g. colloidal gold, go on accumulating in the tissues throughout therapy and are excreted for very long periods after stopping therapy.

3. ALTERATION OF PHARMACOKINETIC PARAMETERS BY DISEASE

Gastrointestinal tract There have been few studies on the effect of gastrointestinal disorders on drug absorption but for most drugs studied, the effect on absorption is small (Chapter 2).

Renal disease For drugs excreted principally unchanged in the urine, the $t_{\frac{1}{2}}$

increases with an increase in renal failure so that if the drug is administered in the same dose and at the same dose interval, the steady-state plasma concentration will also increase in proportion to the half-life. Some examples of drug half-lives in normal patients and in those with oliguria or anuria are shown in Table 2.

Table 2
Drug half-lives in renal failure

Drug	*Normals (h)*	*Oliguria or anuria (h)*
Penicillin G	0·50	7–25
Ampicillin	1·15	6·5
Cephaloridine	0·5	25
Cephalothin	0·5	11–18
Cephalexin	1·0	25
Tetracycline	8·5	85–100
Doxycycline	25	25
Chloramphenicol	2·5	2·5
Streptomycin	2·5	50–100
Gentamicin	2·5	35
Lincomycin	4·5	11
Rifampicin	3·0	3·0
Sulphamethoxazole	10	10
Digoxin	40	85
Strophanthin G	14	60
Digitoxin	170	230

The preponderance of antibacterial agents in the table stresses the importance of renal excretion in the elimination of many of these drugs. This contrasts with most other groups of drugs in which metabolism is the more important factor in determining the rate of drug elimination.

Liver disease The liver has considerable reserves with respect to drug metabolism. With most drugs thus far studied their half-lives only increase when liver damage is severe, e.g. in patients who have experienced at least one episode of hepatic encephalopathy. The increase in drug half-life is even then seldom greater than twofold. There are occasional exceptions to this rule, e.g. in one study the $t_{\frac{1}{2}}$ of lignocaine and antipyrine was found to be 13 times that of normal control values in a woman with chronic liver disease.

Cardiovascular disease In patients in cardiovascular shock who have as a consequence poor tissue perfusion, the Vd of drugs is often reduced. For drugs that are extensively metabolised by the liver, e.g. lignocaine and propranolol, the rate of drug clearance is dependent on liver blood flow. In hypotensive states, this fall and the $t_{\frac{1}{2}}$ of these drugs increases proportionally.

5. ALTERATION OF PHARMACOKINETIC PARAMETERS BY OTHER DRUGS Drug interactions at sites of absorption, protein binding, metabolism, tissue uptake and excretion may effect the pharmacokinetics of one or both drugs (*see* Chapter 9).

The use of drug plasma concentration determinations The variability between patients in pharmacokinetic parameters and in responsiveness to drug effects renders the concept of a generally acceptable 'therapeutic dose' invalid.

For all drugs, the most effective way of establishing a therapeutic dose in an individual patient is to increase the dose until a therapeutic response is achieved. This is possible when the therapeutic effect is readily established clinically, as with relief of pain, the induction of sleep, or when the response to a drug is measurable on an interval or ordinal scale, e.g. prothrombin time for warfarin, mmHg for hypotensive agents, pulse rate for digoxin in atrial fibrillation. For many drugs, however, it is not possible to monitor drug effects precisely and correct dosage is established either by increasing the dose until toxic symptoms are evident (e.g. tinnitus occurs with aspirin at plasma concentrations above the therapeutic range) and then reducing the dose. Alternatively, the dose is established on the basis of clinical trials.

An alternate approach is to establish the plasma concentration at which a drug produces a given therapeutic effect and then to sample the plasma at intervals during therapy to see that the concentration remains close to this value. This method of monitoring drug therapy is most useful for type I drugs and for those that can readily be determined in plasma. Established values for the range of concentrations at which a number of drugs produce a therapeutic effect are shown in Table 3.

The drug serum or plasma concentration necessary to produce a certain therapeutic effect varies between individuals, as has been discussed above, so that values shown in Table 3 must not be interpreted too rigidly. The table illustrates how most drugs are effective in the 1–10μg/ml range, but some, e.g. digoxin, are effective at one thousandth this concentration. For those drugs in which a range of therapeutic concentration has been established, the range is usually smaller than that of the range of drug half-lives.

Clinical situations in which the monitoring of drug plasma concentration is most useful are:

1. When monitoring of the drug effect is difficult, as in the prophylactic administration of an anticonvulsant or antidysrhythmic agent in patients who are unreliable or who are poor witnesses or in whom the fit or dysrhythmia frequency is low.

Conversely, in patients in whom the dose is established on the basis of the drug effect, the determination of the drug plasma concentration at which such an effect is achieved may be of future clinical value.

2. When the drug has a narrow therapeutic index, e.g. digoxin, gentamicin, lithium, procainamide, monitoring the drug plasma level will reduce the liability of overdose effects.

Table 3

Therapeutic serum concentration of some commonly used drugs

Drug	*Drug conc in serum/ml*		*Effect*
aspirin	50–100	μg	analgesia
	350–400	μg	anti-inflammatory
paracetamol	10–20	μg	analgesia
phenylbutazone	40–60	μg	anti-inflammatory
pethidine	0·6–0·75	μg	analgesia
propoxyphene	0·1–0·2	μg	analgesia
digoxin	0·5–3·0	ng	antidysrhythmic positive inotropic
procainamide	4–8	μg	antidysrhythmic
lignocaine	1–2	μg	antidysrhythmic
quinidine	3–6	μg	antidysrhythmic
phenytoin	10–20	μg	anticonvulsant antidysrhythmic
phenobarbitone	10–60	μg	anticonvulsant
carbamazepine	2–10	μg	anticonvulsant
amitriptyline	0·3–0·9	μg	antidepressant
imipramine	2–6	μg	antidepressant
desipramine	0·6–1·4	μg	antidepressant
nortriptyline	0·05–0·2	μg	antidepressant
amylobarbitone	5	μg	hypnotic
chloralhydrate	5–10	μg	hypnotic
methaqualone	2–5	μg	hypnotic
thiopentone	30	μg	anaesthesia
chlordiazepoxide	1–2	μg	sedation
diazepam	0·–0·5	μg	sedation
chlorpromazine	0·5–0·7	μg	sedation
lithium	1–2	nmol/l	sedation
theophylline	10–20	μg	bronchodilator
propranolol	0·1	μg	beta blockade
warfarin	0·6–3·1	μg	anticoagulant
chlorpropamide	30–140	μg	hypoglycaemia
chlorpheniramine	0·008–0·016	μg	antihistamine
gentamicin	4 or less	μg	bacteriocidal
quinacrine	0·005–0·05	μg	antimalarial

3. In renal failure, when it is necessary to use a drug that is mostly excreted unchanged in the urine, e.g. those drugs in Table 2 whose half-lives are appreciably increased in renal failure.

Drug concentration determinations in plasma, urine or saliva may be of use in circumstances other than in drug monitoring:

1. To establish whether a clinical condition is or is not due to an adverse effect, e.g. in patients on digoxin who are admitted with a supraventricular tachycardia which could be due to too little or too much digoxin. If the digoxin plasma concentration is 0·5 nmol/l or less it is most unlikely to be due to a digoxin overdose.
2. In the management of drug-overdosage (Chapter 40).
3. To establish whether the patient is complying with the doctor's instructions on drug taking, i.e. to check patient compliance.

Patient compliance Poor patient compliance is the single most important factor accounting for a poor response to drug therapy including both an inadequate therapeutic response and a high incidence of adverse effects.

A number of factors have been identified as influencing patient compliance. These include:

The disease Poor compliance is more frequent in symptomless conditions (e.g. hypertension) in chronic conditions (e.g. in TB requiring 12–24 months therapy) and when drugs are taken prophylactically (e.g. in malaria, potassium therapy in association with diuretics). It is also more frequent when symptoms reoccur a long time after stopping therapy (e.g. schizophrenia).

The treatment The greater the number of tablets prescribed, the more frequent and the more complicated the dosage regime, the worse the compliance. If the tablets are difficult or unpleasant to take compliance is often reduced. Adverse effects are also a frequent cause of poor compliance, although some studies have shown that trivial side effects often enhance compliance.

The patient Failure to understand instructions on drug taking may occur as a result of old age or extreme youth, intellectual inadequacy or psychiatric illness or dementia. Paranoid and hypochondriacal personalities and those with hostile feelings towards the doctor are all less liable to comply than other personality types.

The doctor An optimistic attitude towards the outcome of therapy and a caring attitude with respect to both the beneficial and adverse effects of drug treatment enhance compliance. Obviously careful explanation of what is required of the patient in taking the drug is also important.

The most effective and simple method to check compliance is to know the number of tablets for each preparation a patient requires between visits to the clinic and to count the pills remaining each visit. Alternatively, the determination of drug concentration in plasma or urine in circumstances when poor compliance is suspected can be useful in adjusting drug regimes.

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Chapter 5

Pharmacogenetics

Interindividual differences in response to drugs are determined by a combination of physiological factors (e.g. age, sex), pathological factors (e.g. liver and renal disease), environmental factors (e.g. other drugs, smoking, diet), and genetic factors. How important each of these groups of factors is, varies from drug to drug and from individual to individual, but in most instances genetic factors are of greatest importance. Pharmacogenetics is the science concerned with those differences in response to drugs that are under hereditary control.

Methods of study The extent to which genetic factors determine drug responsiveness is investigated by means of population, family and twin studies.

Population studies involve administering usually a fixed dose of a drug to a large number of individuals and then measuring either the response to the drug or some pharmacokinetic characteristic such as the plasma $t_{\frac{1}{2}}$ or plasma concentration at a fixed time after drug administration. From this data a frequency distribution curve is constructed.

Figure 1 shows the two most common patterns of frequency distribution. A, a single hump response is known as a unimodal response with Gaussian or continuous distribution. This is the more common of the two patterns and indicates that the response is under the control of a number of genes, or polygenetic control. B, a bimodal response displays discontinuous variation. This implies that the response is controlled by a single gene that is present in the population in two forms, i.e. such a pattern in the frequency distribution implies genetic polymorphism. The rarer trimodal pattern also indicates genetic polymorphism, in which there is a phenotype for each of the three possible genotypes. Assuming a single variant gene, the heterozygotes are discernible as the middle hump between those homozygous for the normal and those homozygous for the variant gene.

The study of frequency distribution of a drug response may be misleading as environmental factors are also important determinants of drug responses. Furthermore, a unimodal frequency distribution may conceal genetic heterogenicity. More precise information on the genetic component determining responsiveness to drugs can be obtained from twin studies. In such studies, a particular variable (e.g. drug plasma half-life) is compared in a pair of uniovular (identical) twins with that of a pair of binovular (fraternal) twins, the assumption being that environmental factors will be similar for each pair of twins. Then an estimate of the genetic component can be obtained from the following formula:

Variance within pairs of fraternal twins–variance within pairs of identical twins

Variance within pairs of fraternal twins

Values near to 1 indicate a high degree of genetic control and those with values near to zero a negligible genetic component.

Family studies establish whether inheritance of a drug response follows a Mendelian dominant, recessive or sex-linked pattern. When variation in a response does not adhere to a classical pattern of inheritance, insight into the genetic component determining the response can be obtained by studying drug responses in parents and children. The 'heritability' of a drug response is obtained from the regression coefficient of the graph of the mid-parent response plotted against the mean offspring response and the higher the value the greater the genetic component.

Genetically transmitted variations arise from mutations of DNA through which structural alterations occur in a protein that directly affects drug

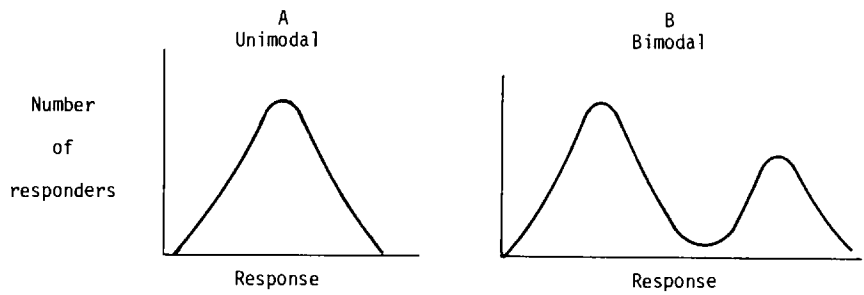

FIG. 1 Frequency distribution patterns in response to a drug: a single dose of a drug is administered to a large number of subjects and the extent of the response is determined. The numbers of subjects giving similar grades of response are plotted out. For explanation of unimodal distribution and bimodal distribution see text.

absorption, metabolism, distribution and excretion or drug-receptor interactions. Such polymorphisms, therefore, may give rise to variations in a drug's pharmacokinetic or pharmacodynamic characteristics. Of the established examples of pharmacokinetic polymorphisms, all affect drug metabolism.

Pharmacokinetic polymorphism

1. Genetic polymorphism affecting phase 1 reactions

The first example of a genetic polymorphism that affected the rate of metabolism of a drug involved the short-acting muscle relaxant suxamethonium (succinyl dicholine). This ester, which is used in induction anaesthesia, is rapidly hydrolysed by butyrylcholinesterase (BuChE), present in the plasma and tissues, to succinylmonocholine and eventually to succinic acid and choline.

The usual duration of action of a single i.v. dose (10–30mg) is 3 to 4 minutes and is determined by the rapid rate of hydrolysis, but in a small number of patients, paralysis lasts for 3 to 4 hours as the rate of suxamethonium hydrolysis is much slower than normal.

The incidence of this atypical response to suxamethonium is very low (1/3000 in the population) and is genetically determined, being inherited as an autosomal recessive trait. The mechanism of the prolonged response (suxamethonium apnoea) is that the BuChE of such patients has a much lower affinity for suxamethonium and other substrates than the normal BuChE. It also has an altered affinity for various inhibitors, e.g. the normal BuChE is inhibited 75–80% by 10 μ M dibucaine (cinchocaine), using benzylcholine as the substrate, whereas the atypical BuChE is inhibited 20% or less. Although heterozygotes have sufficient normal BuChE to metabolise therapeutic doses of suxamethonium at normal rates, the extent to which their plasma BuChE is inhibited by dibucaine (dibucaine number) is intermediate between the normal and the atypical enzyme. More detailed analysis of the biochemical characteristics and protein chemistry of BuChE has revealed that there are a number of genetic variants to atypical BuChE and in some subjects no enzyme is detectable.

The low incidence of suxamethonium sensitivity, makes it impractical to measure the plasma BuChE in all patients before administering suxamethonium and a previous history of an abnormal response is the only reliable clinical method of determining a patient's sensitivity. As BuChE is stable in whole blood, it is possible to treat a prolonged response, apart from artificial ventilation, by administering a blood transfusion, but in practice it is usually thought safer to keep the patient on a respirator until muscle strength returns.

Suxamethonium is metabolised in the plasma and tissues. However, the great majority of drugs undergo phase 1 metabolism in the liver, most of these being oxidative reactions. Genetic polymorphism affecting the liver's carbon oxidative capacity has been clearly demonstrated for a number of drugs, the first of these being debrisoquine.

Debrisoquine is a guanidinium hypotensive agent (*see* Chapter 23) that undergoes carbon oxidation in the liver to form a number of phase 1 metabolites, of which the most important is 4-hydroxy-debrisoquine. When the ratio unchanged debrisoquine/4-hydroxy-debrisoquine in an 8 hour collection of urine is determined in the population, there is a bimodal frequency distribution, 91% of the population rapidly metabolising the drug and having ratios of 0·1–5, while the remaining 9% have ratios of 20–300. Family studies have shown that in this instance, poor metabolisers are homozygous for the variant gene, which is an autosmal recessive allele. Heterozygotes (who represent 40% of the population) are lumped in with subjects homozygous for the autosomal dominant gene for extensive metabolism.

Extensive metabolisers of debrisoquine metabolise most of an oral dose during the first passage of the drug through the liver. As poor metabolisers are

not capable of doing this, they are much more responsive to single oral doses of the drug than are extensive metabolisers.

Poor metabolisers of debrisoquine are also poor metabolisers of other drugs undergoing phase 1 metabolism, e.g. phenacetin, phenytoin and guanoxan, and it is possible that genetic polymorphism for debrisoquine metabolism may represent a polymorphism for a number of other drugs.

2. Genetic polymorphism affecting phase 2 reactions

Acetylator types The rate limiting step in the elimination of the antituberculous drug isoniazid is acetylation, which occurs in the liver. The frequency distribution of isoniazid half-lives shows a bimodal pattern, the mean plasma half-life of subjects who rapidly acetylate isoniazid being one-third that of the mean value for slow acetylators. Rapid acetylation is inherited as an autosomal dominant trait, slow acetylation as an autosomal recessive trait. The distribution of fast and slow acetylators in the population varies between races. 80 to 90% of Chinese, Japanese and Eskimos, approximately 50% of European and American whites, and only 25 to 45% of Jews are fast acetylators.

If tuberculous patients are treated with isoniazid without regard for their acetylator type, fast acetylators respond less well than slow acetylators, but the latter develop adverse effects, such as a peripheral neuropathy, more frequently. Phenelzine, hydrallazine, various sulphonamides, including sulphapyridine, sulphadimidine and sulphamethazine also show polymorphic acetylation. Adverse effects to phenelzine occur most commonly in slow acetylators. Hypertensive patients who are slow acetylators require lower doses of hydrallazine than do fast acetylators, but the systemic lupus erythematosus-like syndrome that may develop in some patients after chronic administration of this drug is much more frequent in slow acetylators. Sulphamethazine may be used to establish the acetylator type of a patient to be treated with isoniazid, phenelzine or hydrallazine.

Unimodal frequency distribution

The frequency distribution of the rates of metabolism for most drugs is unimodal, but the range is large. For example, there is a fortyfold range of steady-state plasma concentrations achieved after chronic administration of a single dose of the tricyclic antidepressants desipramine and nortriptyline. A similar range is found with most drugs that are cleared from the plasma mostly by metabolism if a large population is investigated.

This type of variation has three possible explanations. Firstly, the population under study is genetically similar with respect to the genes controlling rates of metabolism. Secondly, the trait being measured is controlled by genes at multiple loci (polygenic) and thirdly, the observed variation is the result of insensitivity of the method used to separate inherently different populations from one another.

Twin and family studies have established that the major component determin-

ing variation in rates of metabolism of many drugs, e.g. phenytoin, tolbutamide, phenylbutazone, nortriptyline, halothane and ethanol is genetic and this probably holds for all drugs that are extensively metabolised.

Pharmacodynamic polymorphism

Some patients respond in an abnormal way to a drug when the drug plasma concentration is in the normal therapeutic range, and there are a number of instances in which the abnormal response is the result of a genetically determined defect. In general, it is much more difficult to determine the extent to which genetic factors determine variability in the pharmacodynamic effect of drugs, as studies necessary to do this require prior knowledge of a drug's pharmacokinetics in each individual under study.

Glucose-6-phosphate dehydrogenase deficiency Glucose-6-phosphate dehydrogenase (G-6-PD) in Rbcs generates reduced nicotinamide adenine dinucleotide phosphate (NADPH) and if this enzyme is deficient, the reducing capacity of the cell falls, especially the reduced glutathione content. Drugs that have a high redox potential or, more commonly, those that form metabolites with a high redox potential, oxidise the haemoglobin in cells with a low reducing capacity to met- and sulphaemoglobin and also denature protein components of cell membranes. Both changes render Rbcs more susceptible to mechanical trauma. Table 1 shows some commonly used drugs of this type.

Table 1

Drugs that may induce haemolysis in G-6-PD deficiency

Primaquine	Nalidixic acid
Pamaquine	Streptomycin
Chloroquine	Para-aminosalicylic acid
Quinine	Isoniazid
Pyrimethamine	Sulphonamides
	Sulphones
Antipyrine	
Paracetamol	Quinidine
Phenacetin	Probenecid
	Vitamin K (water soluble forms)
Benzylpenicillin	Glyceryltrinitrate
Chloramphenicol	
Nitrofurantoin	

The clinical consequences of administering the drugs in Table 1 to G-6-PD deficient patients is that they develop a haemolytic anaemia. As G-6-PD complement falls exponentially during the life course of Rbcs, the older cells are more susceptible to oxidant drugs and usually only these haemolyse, the

disorder running a self-limiting course of about a week. Drugs are not the only factors to precipitate haemolysis in these patients. Attacks may occur spontaneously after infections or after ingestion of oxidants in the diet, e.g. fava beans.

G-6-PD deficiency is inherited as a sex-linked trait with intermediate dominance. Males develop clinical manifestations of the defect more often than females and affected females hand on the defect to half their sons on average. There are a number of genetic variants of G-6-PD deficiency causing different abnormalities of the enzyme.

Over 100 million people in the world have G-6-PD deficiency and there are wide differences in the extent to which it is present in various races, being highest among Kurdish Jews (70%) and not recorded at all in Eskimos. The incidence amongst Europeans and white Americans is about 4% but is 20% amongst American negroes. As with other types of haemolytic anaemia, its incidence is particularly high in malarious areas and the defect appears to confer some degree of protection against the malaria parasite.

Malignant hyperpyrexia This is a condition that may be precipitated by exposure to inhalation anaesthetics or any muscle relaxant. Within minutes of exposure the patient develops a tachycardia and fever, with or without prodromal muscle rigidity, hyperventilation, sweating, mottling of the skin or flushing and cyanosis. The pyrexia may become severe, hypoxaemia, hyperkalaemia, a metabolic acidosis and other biochemical abnormalities develop and commonly the patient dies. This predisposition to develop hyperpyrexia is inherited as an autosomal dominant trait and is rare. It is associated with a variety of familial myopathies that may or may not be clinically evident at the time that the patient receives an anaesthetic and often, but not invariably, these patients have a raised serium creatine phosphokinase concentration.

Studies on muscle biopsy specimens taken from patients susceptible to malignant hyperpyrexia show that there is impaired binding of calcium to the membranes of the sarcoplasmic reticulum and sarcolemma of affected muscles, so that excessive amounts of calcium are released into the myoplasm by halothane and suxamethonium, which triggers off a variety of catabolic processes. The major steps in treatment of the condition are to lower the body temperature, to correct the acidosis and metabolic abnormalities and to administer high doses of procaine (0·5–1·0 mg/kg/min) or procainamide, which lowers the myoplasmic calcium by facilitating its transport into the sarcoplasmic reticulum. Lignocaine and cardiac glycosides have an opposite effect and are contra-indicated. The response to therapy is usually very poor.

Porphyria Attacks of both intermittent porphyria, presenting with abdominal pain, a peripheral neuropathy, a psychosis or hypertension, and porphyria cutanea tarda, presenting with photosensitive skin lesions, may be precipitated by certain drugs (Table 2).

Both types of porphyria are inherited as autosomal dominant traits and the biochemical defect common to each is an increase in the concentration of

δ-aminolaevulic acid synthetase, the enzyme that expedites the condensation of glycing with succinyl-coenzyme A to form delta amino laevulic acid (δ-ALA). This is the rate limiting step in haem synthesis and with an increase in δ-ALA synthetase there is an increase in the porphyrin precursors of haem. Both types of porphyria are rare, the intermittent form occurring in 1·5/100 000 in Australia and Sweden, and porphyria cutanea tarda, which is most prevalent in South Africa where it affects 1/100 of the Afrikaners.

Table 2

Some drugs that may precipitate attacks of porphyria

Barbiturates	Sulphonamides
Meprobamate	Tolbutamide
Glutethimide	Dichloralphenazone
Griseofulvin	Aminopyrine
Methyldopa	Stilboestrol
	Oral Contraceptives

The common feature of the drugs in Table 2 that can precipitate porphyria is that they all may induce liver microsomal enzymes and it may be that they precipitate porphyria by inducing δ-ALA synthetase.

Others

Warfarin resistance A small number of patients have been found that have a genetically determined resistance to warfarin and coumarin anticoagulants and usually require a maintenance dose 20 times the normal dose. Such patients eliminate warfarin at a normal rate but are very sensitive to the effects of vitamin K. Warfarin resistance is inherited as an autosomal dominant trait and is probably due to an increased affinity for vitamin K by the sites in the liver where vitamin K dependent clotting factors are synthesised.

Glaucoma In certain patients, the topical application of steroids to the eye may cause a rise in intra-ocular pressure. The predisposition to this effect is inherited as an autosomal recessive trait, but heterozygotes also develop a rise in intra-ocular pressure after topical steroids, the extent being less than with homozygotes.

The implications of polymorphisms

The kidneys' capacity to excrete drugs is readily discerned from conventional renal function tests, and there are only small variations in, for example, the creatinine clearance, between subjects with normal renal function. By contrast, as we have already seen, there are very large differences in the rates at which different individuals with normal livers metabolise drugs, and these are determined genetically. Moreover, there are no means available of determining these differences from conventional liver function tests.

It follows, therefore, that for drugs that are cleared from the plasma by metabolism, the dose should be established for each patient empirically, being adjusted in accordance with a measurable response. For drugs whose response is not readily measurable, ideally the dosage should be determined according to the drug's plasma concentration, although, as yet, facilities for such measurements are only available for a few drugs.

Genetic polymorphisms may determine susceptibility to the adverse effects of drugs, as in the case of glucose-6-phosphate dehydrogenase deficiency. The extent to which other serious adverse effects, other than drug overdosage occurring when drugs are prescribed in the normal dose range, are attributable to genetic polymorphisms, has not been established.

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Chapter 6

The Discovery and Introduction of New Drugs

The desire for new and better drugs and medicines has been a constant feature of human behaviour since the earliest times and references to the use of drugs, some of which are still in use today including ephedrine, cannabis, iron salts and castor oil, are contained in the earliest written documents of China and Egypt. Ethanol was known to many cultures in prehistoric times, while the alkaloids of opium, belladonna, squill and ergot and the metals arsenic and antimony were being used in medicine by the Greeks before the birth of Christ.

The rate of introduction of new drugs has been largely dependent on advances in man's knowledge of the world and of advances in science, especially in chemistry. Thus, very few drugs of lasting value were introduced in the first millenium A.D. although these did include colchicine, picritoxin and senna. With the discovery of America in the 15th century, there was an influx into Europe of a large number of new herbal remedies and poisons from both north and south of the continent which included tobacco, quinine (Cinchona bark), cascara and ipecacuanha. The therapeutic value of digitalis was discovered in the latter half of the 18th century. At the same time the principles at the foundation of modern chemistry were being established under the leadership of Lavoisier. The first anaesthetics, nitrous oxide and ether, were synthesised at this time, although their use in anaesthesia was delayed until the middle of the 19th century.

The rate of new drug discoveries gathered pace in the 19th century, largely as a result of advances in chemistry and with burgeoning interest in pharmacology. New drugs included the synthetic compounds chloralhydrate and some barbiturates, salicylic acid, phenacetin and antipyrine, quinidine, chloroform and ethylene and the nitrates. Several naturally occurring compounds were also discovered including the first hormone (thyroid), physostigmine, pilocarpine and cocaine.

The number of drugs introduced in the first 70 years of the 20th century greatly exceeds that of all previous times right up to the end of the 19th century and includes all antibacterial agents, all cytotoxic agents, most vitamins, many hormones, drugs capable of modifying mood, for controlling blood clotting, for modifying the function of endocrine glands and the inflammatory response and many more besides. Pharmacology has flowered as an independent science and the means of assessing drug effects in man, 'the clinical trial' (*see* below), has been established on a scientific footing.

There are two sources of drugs, natural sources including drugs derived from plants, animals, micro-organisms and minerals and those derived as a result of chemical synthesis. The former accounts for all drugs up to the end of the 18th century while the great majority of new drugs being introduced at the present time are synthetic compounds.

Methods in drug discovery There are usually many factors operative in the discovery of a new drug and luck, as in all discoveries, is an essential component. In the discovery of a number of drugs, including digitalis and penicillin, much has been made of the good fortune of Withering and Fleming in having the chance to make their original observations. But astute observation of the chance event that is seminal in discovery, and a system of ideas that enables the observer to register the novelty of his or her observations, are essential for the conversion of a chance event into a lucky event.

There are a number of methods that are widely used in the search for new drugs or for new uses of established drugs.

1. Screening This is a process whereby the pharmacological activity of chemicals or extracts from biological material are assessed on a number of pharmacological preparations, the nature of preparations used depending on the type of activity anticipated. Screening methods were first used by Erlich in the search for a chemotherapeutic agent effective against *Treponema pallidum*, the pathogen responsible for syphilis. He screened a large number of organo-arsenical compounds and his studies culminated in the discovery of arsphenamine which was the first effective antitreponemal agent. More recently, screening methods have been most widely used in the search for new antibacterial agents and cytotoxic agents. For instance, it has been estimated that in the USA alone from 1945 to 1967, 88 550 agents were screened for cytotoxic activity of which only 12 were eventually used clinically in the treatment of malignant disease. Screening methods are also widely used in the routine work up of any putative new drug (*see* Table 2).

2. Investigation of drug side effects The observation and investigation of side effects of drugs has been a most fecund source of new drugs and of new uses for established agents or agents under trial. The sedative effects of chlorpromazine were first observed when it was being used as an antihistamine. The mood elevating effects of iproniazid were first observed while it was undergoing clinical trials as an antituberculous agent, its ability to inhibit monoaminoxidases only being discovered later. The anti-Parkinsonian activity of amantadine was discovered during a clinical trial of the drug as a prophylactic agent against influenza.

The usual course of events starts with the observation of a side effect. A series of tests are carried out to relate the particular side effect to a particular chemical structure, i.e. to establish the structure-activity relationship, and the chemical structure is modified where possible to maximise the particular effect. The consequence of this sequence of events is that families of chemically related

drugs emerge that differ pharmacologically in their spectrum of effects. The sulphonamides have been the most fruitful source of new drugs in this respect (Table 1).

Table 1
Drug groups derived from the sulphonamides

Action	*Group*	*Examples*
Diuretics	benzothiadiazines	hydrochlorothiazide
	monosulphamyl diuretics	frusemide
Hypotensive agent		diazoxide
Carbonic anhydrase inhibitor		acetazolamide
Antithyroid	thioureas	carbimazole
Hypoglycaemic agents	sulphonyl urea	tolbutamide
Anticonvulsant		sulthiame
Antituberculous drug		thiacetazone

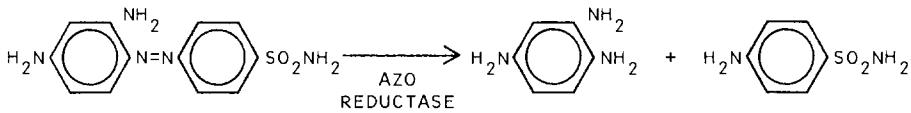
Modification of the chemical structure of benzylpenicillin has resulted in the development of agents that differ from benzylpenicillin in being acid stable and therefore orally active (phenoxymethylpenicillin, ampicillin and cloxacillin); in having a broader spectrum of antibacterial activity (ampicillin, carbenicillin) and in being penicillinase resistant (methicillin, cloxacillin).

Families of drugs may be derived by chemical modification of a basic chemical structure. The drugs resulting from such modifications are closely related both chemically and pharmacologically to the parent compound, but differ either in potency or in pharmacokinetic characteristics or in both. Such changes have given rise to large families of drugs that are closely related pharmacologically, e.g. thiazides, antihistamines, antimuscarinic agents, barbiturates, benzodiazepines, phenothiazines, beta-blocking agents and many others.

3. Logical research sequence An increase in the knowledge of pharmacology and related basic medical sciences has resulted in an increasing number of new drugs being derived from research into specific areas, often without there being the objective of discovering a new drug. An obvious example in the application of basic knowledge of pharmacology to therapeutics was the use of physostigmine in the treatment of myasthenia gravis by Mary Walker in 1935. The theory current at that time was that myasthenia gravis was due to a curare-like compound present in the circulation and as it was also known that physostigmine antagonised the actions of curare, it seemed logical to Mary Walker to investigate the therapeutic efficacy of physostigmine in this condition. The beneficial effects of physostigmine on the first patient treated by Dr Walker were dramatic and although theories on the pathogenesis of myasthenia gravis have altered with time, anticholinesterase agents are still the bedrock of drug treatment. The therapeutic benefit of L-dopa in Parkinson's disease derived from research in a number of related areas which included transmitter

substances in the CNS, especially the basal ganglia; the mechanism whereby reserpine causes parkinsonism; the nature of the chemical lesion in patients with Parkinson's disease and eventually clinical trials of L-dopa in parkinsonian patients. On a longer time scale, the plethora of selective adrenergic receptor agonists and antagonists for alpha and beta receptors, has resulted from growth in knowledge of the sympathetic nervous system. Another example of basic medical research programmes yielding new drugs, is that of Hichins and colleagues whose researches into the biosynthesis of nucleoproteins and folate metabolism have yielded the xanthine oxidase inhibitor and prophylactic agent for gout, allopurinol, the cytotoxic agents 6-mercaptopurine and azathioprine, the folate dehydrogenase inhibitors, pyrimethamine, a prophylactic agent in malaria and the antibacterial agent trimethoprim.

Drug metabolism Studies on the metabolism and pharmacokinetics of drugs have revealed that metabolites of many drugs have appreciable pharmacological activity, sometimes exceeding that of the parent compound (Chapter 4). The first important observation of this nature was that of Tréfoüels, Nitti and Bovet that sulphanilamide was the active component of the first sulphonamide prontosil, and that prontosil was converted to sulphanilamide in the body.



PRONTOSIL SULPHANILAMIDE

Paracetamol is the major metabolite of phenacetin and while the analgesic activity of phenacetin was established in the 19th century, it was not until the 1960s that paracetamol was first used as an analgesic in its own right. Other examples of drugs that were originally discovered to be active metabolites are oxyphenbutazone, oxazepam and desmethylimipramine.

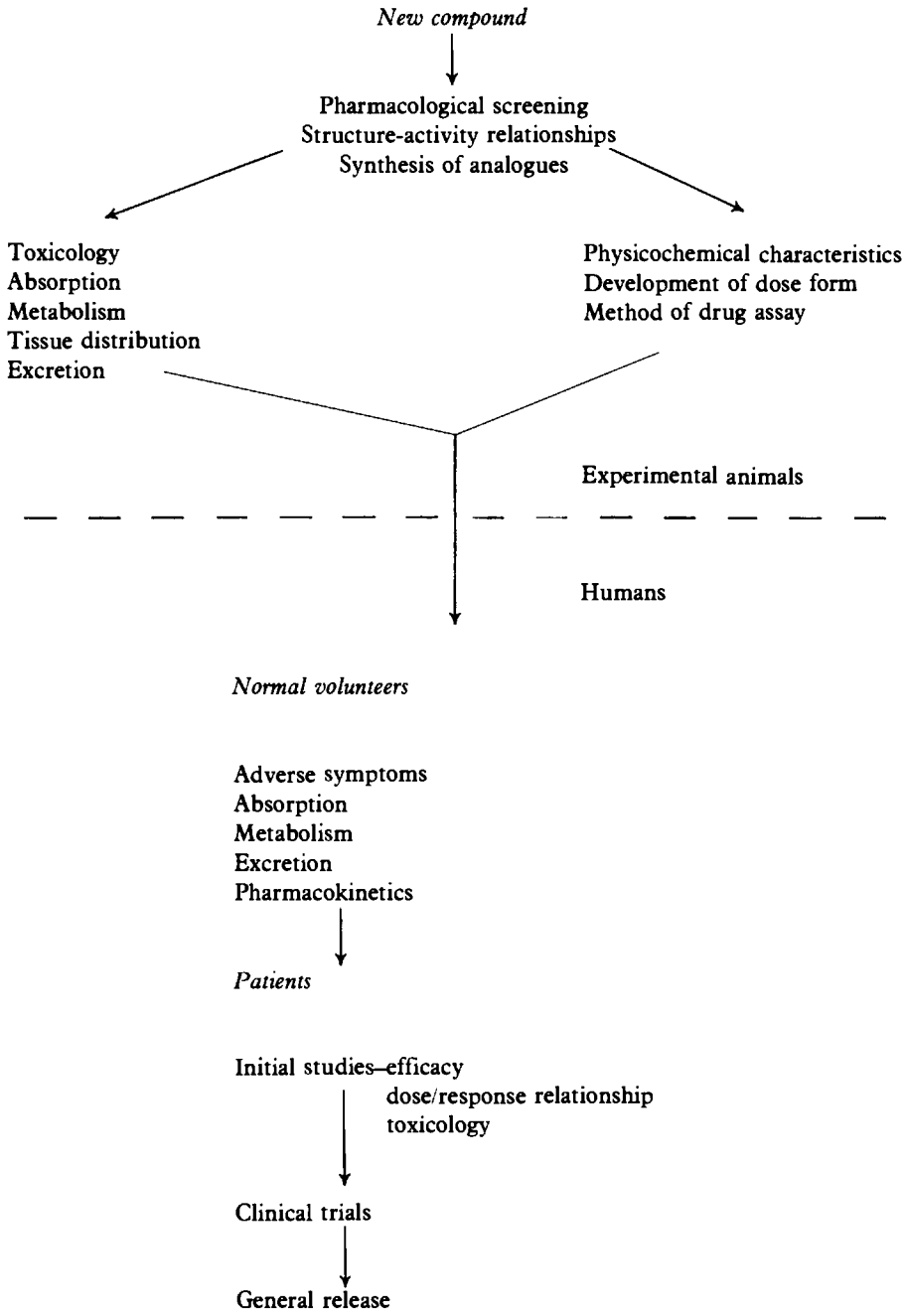
Stages in the development of a new drug The stages in the development of a new drug from its initial synthesis or purification are summarised in Table 2.

The toxicological studies and those on metabolism are carried out on a number of species as there is no species that is always similar to man. The toxicological studies include establishing the LD50 and studies for possible mutagenic, teratogenic and carcinogenic effects. Where appropriate, studies on the drug's abuse liability are also undertaken.

Before a drug is studied for its effects in patients, a submission is made to the Committee on the Safety of Medicines. Following the thalidomide disaster in the early 1960s when, owing to the teratogenic activity of the minor tranquilliser thalidomide, approximately 8000 children were born with major limb deformities, consumer protection committees were set up by governments around the

Table 2

Stages in the development of a new drug



world in an attempt to prevent such a disaster recurring and to guarantee that drugs are adequately tested for all foreseeable toxic effects before being used in patients. In the USA the Food and Drug Administration (FDA) is a government agency that regulates the introduction of new drugs. It was in operation at the time that thalidomide was introduced into Europe, and it did not allow thalidomide to be marketed in the USA. In the UK the Dunlop Committee was set up, originally under the chairmanship of Sir Derek Dunlop, and this was changed in 1970 to the Committee on the Safety of Medicines. Unlike the FDA, this committee does not have powers to prevent a drug from being marketed, but there is a voluntary agreement between the government and the pharmaceutical industry that all new drugs and drug combinations should be submitted to the committee before release onto the market. The committee vets the preclinical studies and decides whether or not studies in patient may be undertaken. It also regulates the studies in patients at each stage in development. As yet, the medicolegal implications of an unforeseen adverse reaction developing to a new drug that had not been screened by the Committee on the Safety of Medicines, has encouraged the fullest co-operation between the committee and the pharmaceutical industry.

THE EVALUATION OF DRUG EFFECTS

Introduction The traditional method of evaluating a therapeutic procedure is for the individual doctor to compare the course of a disease before and after administering treatment to a patient or to compare the course of a disease in a treated patient with that in an untreated patient. In both instances a comparison is made, but it is made in retrospect and hence relies on the accuracy of the doctor's memory. Furthermore, the comparison may be a poor one for a variety of reasons. For instance, when the response to a given treatment is evaluated in the same patient, the stage of the disease, the general health of the patient, the patient's mood etc., may all be different during the untreated and treated periods. When the response to a treatment is evaluated in two different patients, the comparison may be poor by virtue of differences between the patients in age, weight, race, stage of disease etc., all of which may influence the course of the disease. Moreover, as most patients wish to benefit from treatment and most doctors to benefit their patients, both are biased in their evaluation of treatments, tending to exaggerate their therapeutic efficacy.

The traditional form of evaluating a therapeutic procedure has proved effective in conditions with a predictable natural history and where therapy is highly effective. Thus no elaborate study was necessary to demonstrate the effectiveness of insulin in the treatment of diabetic coma or of penicillin in the treatment of staphylococcal septicaemia. However, many therapies are not so obviously effective and the less obvious the effect of a drug, the more difficult it is for the individual doctor to evaluate it in individual patients. Many drugs are introduced because of their ability to restore to the normal range a particular physiological variable, e.g. blood sugar, urate etc. Such effects can often be readily demonstrated in individual patients and hence are usually evident to

individual doctors. However, the therapeutic effectiveness of drugs depends on the balance between therapeutic effectiveness and adverse drug effects and to evaluate either of these in the treatment and prevention of disease, e.g. hypoglycaemic agents in diabetes, uricosuric agents in gout, is beyond the capability of individual doctors using conventional techniques.

The need for more effective ways of evaluating treatments evolved with the increase in drugs and other forms of therapy in the latter part of the 19th and throughout the 20th century. It was accentuated by the increasing use of the controlled experiment in other branches of natural science as the most effective means of acquiring knowledge. Although experiments to evaluate the effectiveness of certain remedies were carried out earlier than the 20th century, e.g. the demonstration by Lind in 1600 of the effectiveness of oranges and lemons in the prevention of scurvy, it is only in the last 50 years that the science of evaluating the effectiveness of therapeutic procedures has been developed, a development that was given great impetus in the United Kingdom by the setting up of a Therapeutic Trials Committee by the Medical Research Council in 1931.

CLINICAL TRIALS

Clinical trials are clinical experiments designed to evaluate the effectiveness of one or more therapeutic procedures. A similar approach is adopted in the conduct of any clinical trial designed to evaluate a therapeutic procedure, but in this chapter only drug trials will be considered. In common with all experiments, clinical trials are designed to give reproducible results. They always compare two or more treatments, although one may be 'no treatment' and they are carried out prospectively so that account may be taken of all known factors likely to influence the comparison.

The principle difference between clinical trials and experiments on laboratory animals is that in the laboratory, standardisation of procedure and test animals is relatively easy by using animals of the same sex, age, weight, strain etc., whereas patients are much more heterogeneous. Furthermore, as outlined above, there is often a large subjective element influencing response to treatment as assessed by both doctor and patient and this tends to bias observations and impair the comparison. The clinical trial is designed to minimise the influence of both these potential sources of bias.

The practical details in the execution of a clinical trial vary enormously depending on the nature of the trial. Only factors common to all trials will be considered here.

Objectives The aim of a clinical trial is to provide unbiased, quantitative information concerning the effects of therapeutic procedures, i.e. the size of therapeutic benefit and the cost of that degree of benefit in terms of adverse effects. Trial design therefore starts with a question, e.g. does the hypotensive drug X lower the BP in hypertensive patients more effectively and with as few adverse effects as drug Y? Do drugs A, B or C alter the natural history of

rheumatoid arthritis? What is the frequency of adverse effects to each of these drugs?

In general, the more clear-cut the question the more clear-cut will be the answer.

The comparison Essential to the evaluation of the effects of a given drug is the setting up of adequate controls so that the effect of the drug can be assessed independently of all known factors likely to affect the outcome. Thus in 'controlled' clinical trials the effects of the drug being evaluated on one group of patients (treated group) is compared with a control group who receive either an inert compound (placebo) or an alternative drug.

Trial design

Matched groups This is the most common form of trial design in which patients entering the trial are allocated to a treatment or control group. It is desirable that the patients in these two groups should be equal in number and similar in all respects likely to effect response to treatment. The allocation process used in the setting up of matching groups is the process of random allocation. Randomisation can be achieved in a number of ways, e.g. by numbering each patient and then allotting them to one or other group according to a set of random numbers; by use of the patient's date of birth or hospital number, allocating all even numbers to one group and all odd numbers to another group. The random allocation of patients does not ensure that the groups are perfectly matched (or 'balanced') but it does ensure that any differences between them are due to chance only. It also means that the comparison of treatments will not be invalidated by the conscious or unconscious selection of a particular kind of patient for a particular form of treatment and it guarantees the validity of statistical tests of significance applied to the results.

It may be that there are certain variables known to be of major prognostic importance, and therefore in a particular disease likely to influence the outcome of therapy, e.g. the severity of the disease itself in chronic conditions such as Parkinson's disease, diabetes mellitus or hypertension; the cell type in acute leukaemmias and other tumours. Rather than leaving to chance the balancing of groups with respect to these variables, it may be desirable to classify patients according to them at the outset and then to allocate randomly the members of each subgroup to the various treatment groups. This process is known as 'random stratification' and its aim is to improve the comparability of the treatment and control groups.

The success of the randomisation process is evaluated in retrospect by comparing the two groups according to as many variables as are thought likely to influence response to treatment. If the randomisation process has been successful the two groups should be similiar. An example of this is shown in Table 3.

This shows the data on hypertensive patients in a placebo group and a treated

Table 3

Patient data from the Vetrans Administration Trial on the efficacy of hypotensive agents in moderate hypertension

Characteristic	*Measurement data*			
	Placebo group (N=70)		*Treated group (N=73)*	
	mean	*S.D.*	*mean*	*S.D.*
Age	51·5	10·8	50·0	8·7
Height (in)	69·0	2·6	68·7	2·9
Weight (lbs)	182·9	34·5	185·2	36·7
Duration of known hypertension (yr)	5·4	4·4	5·3	4·7
Average hospital diastolic p (mmHg)	105·8	8·4	106·5	8·4
Average clinic systolic p (mmHg)	186·8	17·4	185·6	15·4
Average clinic diastolic p (mmHg)	121·0	4·7	121·2	5·0
Mean severity grades				
Fundi (hypertensive)	1·2		1·3	
Fundi (sclerotic)	1·3		1·4	
Cardiac	1·2		1·0	
CNS	0·4		0·3	
Renal	0·5		0·3	
Blood glucose (fasting) mg/100 ml	96·8	20·6	97·7	18·9
Blood glucose 2h post prandial	118·0	41·5	116·1	54·3
Cholesterol (mg/100 ml)	251·8	59·5	242·0	51·5

group who received one of two possible hypotensive regimes and it can be seen that the groups were comparable in respect of these data.

The use of randomised groups is suitable for the evaluation of both short and long term effects of drugs and has the advantage that the comparison occurs contemporaneously.

Cross-over design In chronic diseases, each patient may be used as his own control, each receiving the treatments being compared in sequence. As the sequence of treatments may affect the outcome, an equal number of patients start with each of the treatments, the order being allocated in a random fashion. The name of this design refers to patients crossing over from one treatment group to another (*see* Fig. 1).

The cross-over design overcomes problems of matching, but treatments are not compared contemporaneously and, as many chronic diseases such as rheumatoid arthritis, peptic ulcer and multiple sclerosis, are diseases that relapse and remit, the severity of the disorder may not be the same when the response to each treatment is being assessed.

Ethics The doctor's first duty is to safeguard the welfare of his patients, and,

in the realm of therapeutics, this means that he must prevent his patient from receiving harmful remedies and conversely treat him with the best available therapies that he knows. It is only justifiable to allow a patient to participate in a clinical trial designed to compare the effectiveness of two or more treatments, although one may be 'no treatment', if:

1. The doctor does not believe that one form of therapy is more effective than the other or others. It may happen that participating doctors have an opinion on the relative merits of therapies being compared. Their participation in such a trial may be justified, however, if there is collective uncertainty on this matter.
2. In all measures other than the therapy being compared his patient receives the best available treatment.
3. The patient must be informed of the nature of the trial and be allowed to choose whether or not to be included in it.

These considerations are derived principally from the declaration of Helsinki which was produced as the result of a conference on human experimentation

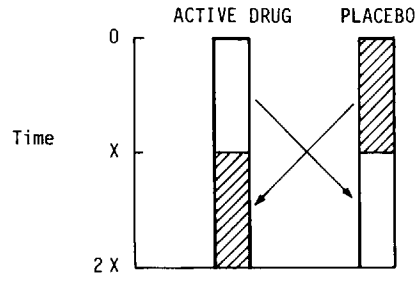


FIG. 1 Cross-over design of a clinical trial. The hatched and unhatched blocks represent two groups of patients. Patients are randomly allocated to the active treatment or placebo group. After a given period of time the treatments are changed, the duration of the second period being the same as the first.

held at Helsinki in 1964 under the auspices of the World Medical Association. The section of the declaration most relevant to the conduct of clinical trials is set out below.

Clinical research combined with professional care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure if, in his judgement, it offers hope of saving life, re-establishing health or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent, after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from

the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

There are no hard and fast rules concerning ethics that apply to all trials so that the ethics of each trial must be considered in the special circumstances that apply to each trial.

The treatments All aspects of therapy other than the drug treatments being compared, such as diet, exercise, physiotherapy, other drug therapy etc., must be the same for the treated and the control group and must be the best available. The drug treatment of the control group may be either:

1. The most effective existing drug for the condition being treated, e.g. in the evaluation of a new antidysrhythmic drug with positive inotropic properties for the treatment of atrial fibrillation, digoxin or digitoxin would be suitable treatment for the control group.

2. *A placebo*—a placebo is a compound with no pharmacological actions. It may be used in clinical trials aimed at demonstrating a particular pharmacological action of a new drug (e.g. hypnotic or analgesic) at a particular dose. It may also be used to demonstrate a therapeutic effect of an established drug whose pharmacological actions are well known. For example, in a trial conducted by the Medical Research Council on the therapeutic benefit of the antihistamine thonzylamine on the severity and duration of symptoms of the common cold, the response to the antihistamine was compared to that of a placebo containing 5 mg quinine sulphate. A placebo was used in this case as there was no known pharmacological means of decreasing the severity and duration of a cold. The results of the trial demonstrated no difference between the antihistamine and the placebo groups.

Alternatively, a placebo may be used in the evaluation of the long term therapeutic benefit of a particular drug effect. An example of this occurred in the trial of hypotensive therapy in hypertensive subjects carried out by the Veterans Administration referred to above. Patients in the treated group received a regular maintenance dose of 100 mg hydrochlorothiazide, 0·2 mg reserpine and 150 mg hydrallazine hydrochloride. There were only two severe complicating events in the 'treated' group during the trial whereas in the placebo group there were 27 such events.

A placebo group should be incorporated in a clinical trial when there is likely to be bias on the part of the patient or the doctor or both in favour of active drug therapy and in conditions with a variable natural history. The response to a placebo in trials is usually substantial. For example, in a trial carried out by the Medical Research Council (1965) on the effects of electroconvulsive therapy (ECT), imipramine, phenelzine and a placebo in patients with depressive

illness, in the physicians overall rating at the end of four weeks of the trial (Table 4), 53% of males and 42% females were judged to have improved on the placebo, a figure higher than that for the monoamine oxidase inhibitor phenelzine in females.

Table 4

Physicians' overall rating of the response to treatment of depresses patients at four weeks weeks

Treatment	*No. of patients*	*% improvement*		*Total improved*
		M	*F*	
ECT	58	71	92	84
Imipramine	58	82	67	70
Phenelzine	50	60	29	38
Placebo	51	53	42	45

The placebo response has two main components. Firstly, response due to suggestion. The administering of any form of therapy including drug administration is a most effective means of suggesting to the patient that they are going to get better. Secondly, response due to spontaneous recovery. Most patients only seek treatment when they have symptoms, and most symptoms, whether they be depression, pain, insomnia, diarrhoea etc., tend to get better spontaneously. Thus, in any trial testing the effect of a drug on a particular symptom, a placebo group is essential to allow for this tendency of most symptoms to recover spontaneously.

Drug administration It is essential to eliminate bias due to preconceptions held by both patient and doctor concerning the relative merits of the drugs being compared. This is done by ensuring that neither patient nor doctor know which drug each patient is receiving. This is known as the 'double-blind' procedure and is usually organised by the department of pharmacy who allocate the appropriate drug to the individual groups. In cross-over studies, it is also necessary to make sure that patients cannot detect differences in drug formulation such as colour, shape and taste, as these may affect response to drugs.

There are instances when a side effect may be peculiar to one drug and be detectable to the patient, doctor or both, e.g. drowsiness, bradycardia, diarrhoea, which invalidates the double-blind procedure. On some occasions it may be desirable for the doctor in charge of a patient to know which drug the patient is receiving if one of the drugs is known to have particularly hazardous side effects alone or when interacting with other drugs. The trial then becomes 'single-blind' as only the patient is unware of which drug he is receiving. An example of this situation occurred during a trial on the secondary prevention of

ischaemic heart disease, using the hypolipidaemic agent clofibrate, carried out by a research committee of the Scottish Society of Physicians (1971). Many patients were treated with oral anticoagulants during the trial and in view of the known ability of clofibrate to enhance the anticoagulant effect of these drugs, the doctors supervising the patients knew which of the anticoagulated patients were receiving clofibrate and which the placebo.

The double-blind procedure is not always necessary in drug trials. For instance, it is not necessary when the end points of the trial, such as death or X-ray changes, are not influenced by suggestion. It may also be impossible when the dose of active drug is variable, being determined by the effect it produces, e.g. anticoagulants, hypotensive agents, etc. The double-blind procedure is not possible when physical or psychological methods of therapy such as surgery, physiotherapy or psychotherapy, are being evaluated. Thus, it is impossible in these situations to evaluate the influence of suggestion in determining the response and tendency to spontaneous recovery can only be evaluated by comparison with past experience or so called historical controls.

Doses In animal pharmacology, drugs are usually compared by constructing a dose-response curve for each drug and plotting the response (R) as a percentage of a maximum response against the logarithm of the dose. The doses that produce a 50% maximal response are then compared. Such an approach is not feasible in clinical pharmacology as it is very seldom that a maximal response can be obtained and the number of observations necessary to obtain even part of such a curve is time consuming and may be dangerous to the patient. Nevertheless, it is important to remember the log-dose-response relationship as it will prevent inferences on the relative potencies of two drugs being drawn from single dose studies.

In clinical trials drugs may be administered in fixed or variable doses. If a fixed dose is used, it is chosen on the basis of existing clinical evidence or from preliminary trials in man and must be in a range that is likely to be effective. Such a dose schedule is suitable for use in trials designed to demonstrate the presence or absence of a given effect. A variable dose regime is one in which the dose requirement is individualised for each patient and can only be used when the drug effect can be readily quantified, e.g. a lowering of blood pressure, blood sugar, uric acid concentration, etc. In using such a schedule, criteria for dose adjustment must be determined in planning the trial.

Measurement of drug effects Drug effects must be assessed as precisely as possible. Those to be monitored and the frequency with which they are to be monitored, must be decided in planning the experiment. Both subjective and objective responses should be sought and where appropriate the double-blind procedure should be adhered to. An example of the number of assessments used in a trial carried out by the Empire Rheumatism Council (ERC) (1955) comparing the relative effectiveness of aspirin and cortisone in the treatment of rheumatoid arthritis is shown in Table 5.

Table 5

Empire Rheumatism Council cortisone—aspirin trial assessments

	Employment	1 Fit for previous job 2 Previous job modified 3 Change to lighter job 4 Unfit for employment
	Function	
(a)	Objective	1 Normal 2 Moderate limitation 3 Serious limitation 4 Helpless
(b)	Subjective	100%, 75%, 50%, 25%, 1%, fit
	Number of joints affected of 68 possible	Any of the following three 1 Tenderness and pain 2 Limitation 3 Swelling
		X-ray of paired joints ESR Westergen mm/h Haemoglobin g/100 ml Complications

These assessments were carried out at 0, 6, 12 months and thereafter 6 monthly for 6 years.

Statistical considerations

Trial design Errors in clinical trials, as in other experiments, are of two types, false positives (or alpha errors) when a difference between two drugs is demonstrated when in reality there is none, and false negatives (or beta errors) when a real difference is not demonstrated by the trial. Alpha errors occur as the result of mismatching. If the random allocation procedure is used then a false positive result arises through chance differences in the composition of the groups. Beta errors most commonly occur as the result of inadequate numbers in the trial.

Numbers The number of patients required in a trial depends on the degree of difference between the drugs being compared and the degree of statistical significance that the investigator requires of any difference found. The difference between drugs prior to a trial can only be guessed from clinical and other data already available on the drugs, so that these data are only a rough guide to patient numbers. The relationship between the numbers required in each group and the hypothetical effectiveness of two treatments is shown in Fig. 2 taken from Clarke and Downie (1966).

It can be seen that the numbers required decrease with the percentage expected to respond to the new treatment and increase with the percentage that respond to the old treatment. The greater the degree of statistical significance between observed differences required by the investigator, the greater the number of patients required in the trial. In general, the more rigorous the trial design, the less the degree of statistical significance required and the smaller the numbers in the trial.

Duration of trial The duration of a trial is determined by the time each individual is studied and by the period of recruitment. This, in turn, depends on the nature of the disease, the duration of the treatment period, the length of

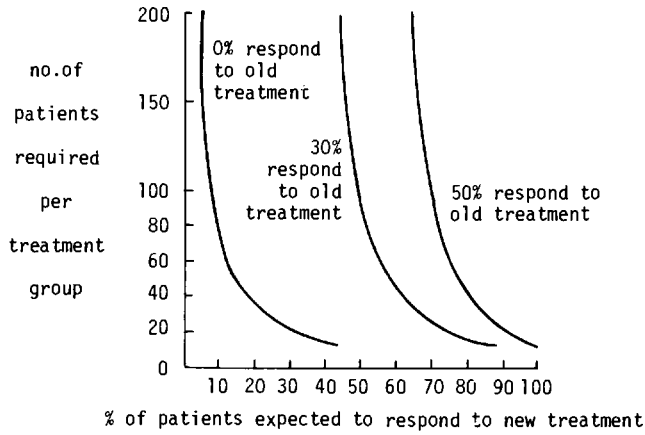


FIG. 2 Number of patients required/treatment group when existing treatment produces 0, 30 and 50% response (From Clark and Downie, 1966).

follow up after stopping treatment and the time it takes to collect an adequate number of patients. In many trials, insufficient patients are available at any single medical centre and then it is necessary to set up a 'multi-centre' trial in which patients and medical staff are drawn from two or more centres. Increasing the number of centres usually involves decreasing the validity of the results as, inevitably, standardisation of procedures is impaired and observer error multiplied. There are often large differences in results from individual centres. This is illustrated in Table 4, from a trial on the influence of various hypoglycaemic agents on the mortality from cardiovascular disease in patients with adult onset diabetes, carried out by 12 university centres in the USA (the University Group Diabetes Program—UGDP). It can be seen that, of the 823 patients in the trial over the eight years ten months of its duration, more deaths occurred in the tolbutamide group (12·7%) than in any other group. However, in four clinics there were no deaths at all in this group, whereas in Cincinnati 31·8% of the tolbutamide treated patients died. Such a study is in effect a series of 'within centre' comparisons, the pooled data giving a mean estimate of differences between treatments.

Table 6

Taken from the trial of hypoglycaemic agents carried out by the UGDP; % dead by clinic from cardiovascular causes

Clinics	*Nos*	*Placebo*	*Tolbutamide 1·5 g/day*	*Standard insulin 10, 12, 14 or 16 U/24 h*	*Variable dose insulin*
Baltimore	87	0·0	4·5	0·0	0·0
Cincinnati	90	8·7	31·8	16·7	19·0
Cleveland	77	0·0	5·6	0·0	5·0
Minneapolis	94	9·1	25·0	8·3	8·3
New York	85	13·6	10·0	0·0	0·0
Williamson	92	4·3	13·6	8·7	12·5
Birmingham	49	0·0	18·2	0·0	0·0
Boston	63	6·7	23·5	6·3	6·7
Chicago	46	9·1	0·0	8·3	9·1
St. Louis	44	0·0	0·0	8·3	0·0
San Juan	52	0·0	0·0	7·7	0·0
Seattle	44	0·0	0·0	9·1	0·0
All clinics	823	4·9	12·7	6·2	5·9

Evaluation of results It is obviously desirable to terminate a trial as soon as a statistically significant difference between treatments is established. In most trials it is not possible to monitor results as they are obtained and the trials are only stopped after a predetermined time or after a predetermined number of patients have completed the trial. Assessing results before such a time is hazardous in that it may introduce bias, e.g. if a trial is stopped arbitarily when the results suggest that a particular form of therapy, favoured by the investigator, is doing better than other treatments.

At the termination of the trial, before evaluating the results, the numbers of patients that have dropped out of the trials and the reasons for dropping out, are recorded. If the reason is due to a drug effect then the patient must be recorded as a failure of therapy for the particular drug. Matching may have been affected by drop-outs and the comparability of the groups must again be checked in retrospect. The result of the trial only relates to the groups as determined by the randomisation process. The larger the number of drop-outs, for whatever reason, the less the validity that can be attached to the results.

The 'null hypothesis' A statistical evaluation of results is undertaken when the double blind code has been broken. The hypothesis that is tested in each trial is the 'null hypothesis' that states that there is no difference between the drugs being compared. If a difference between the mean responses to two or more drugs is recorded, then the probability of this difference being due to chance is

tested by an appropriate test of statistical significance. The choice of significance test depends on the nature of the scale on which the results are recorded. These are of three types:

1. Interval scale—in which drug response is recorded on a numerical scale e.g. mmHg, degrees Centigrade.
2. Nominal scale—in which the drug response is grouped and recorded in words, e.g. good, moderate, poor, nil.
3. Ordinal scale—the response is recorded on an interval or nominal scale for a number of drugs and the drugs are then compared by the construction of a ranking order, e.g. drug A is better than drug B which is better than drug C in achieving a certain therapeutic effect.

In general, interval measurements are handled most easily, either by assessing individual means of each measurement, determining the standard error and evaluating the significance of differences by means of the Student t-test. If there are several sources of variations affecting a drug response, these may be considered at once in an analysis of variance. Reports on trials tend to stress the statistical significance of differences described by the 'P' value. But the results should also show clearly the magnitude of an effect, whether it be therapeutic or adverse and the confidence limits that can be attached to recorded differences, as it is these that the clinician reading the trial will find most useful.

The statistical significance of results recorded on a nominal scale is best evaluated by the chi-squared (χ^2) test, while for those recorded on an ordinal scale, a non-parametric test, e.g. Willcoxon's rank sign test, is used.

Levels of statistical significance If a difference is recorded in the response to two drugs in a trial, the test of statistical significance indicates how frequently such a result could be due to chance, i.e. supposing that the null hypothesis was actually true, then if the experiment was repeated one hundred times a difference as large as that observed would occur: once/100, $p = 0{\cdot}01$; five times/100, $p = 0{\cdot}05$; ten times/100, $p = 0{\cdot}1$ etc. The level at which a difference is considered to be 'statistically significant' is arbitrarily decided and $p =$ less than $0{\cdot}05$ is the most widely accepted level of significance. However, the required level of significance will vary with the conditions of the trial and in general the less rigorous the trial design and the less meticulous its execution, the greater is the requirement for a high level of statistical significance. The clinical circumstances in which the drug may be used should also influence the required level of statistical significance. Thus, for a safe drug used in a disease with a high morbidity and mortality, a relatively low level of statistical significance is acceptable. Conversely, for a drug that causes serious adverse effects in the teatment of a relatively benign disease, a high level of significance is required.

Sequential analysis An alternative method of collecting and evaluating results is to use a 'sequential' method, of which the most extensively used has been that of sequential analysis. In this method, patients are allocated in pairs to two

treatments and the trial is terminated when sufficient preference for one or other of the treatments has accumulated to satisfy predetermined stopping rules.

Sequential analysis is ideal for trials carried out on potentially lethal diseases in which one drug, or form of treatment, may be better than another so that an early demonstration of this difference can be achieved and lives saved accordingly. An example in which this approach was used was a trial carried out between London, Ibadan and Jamaica in 1960 to demonstrate the efficacy of tetanus antitoxin (200,000 i.u.) in preventing death from tetanus. After only 18 preferences, the treated group had a mortality of 49% compared with 76% for the untreated group, the P value for this difference being less than 0·02. The principal disadvantage of sequential analysis is that if the condition whose treatment is in question is rare, it may be difficult to obtain pairs of patients at any one time.

Limitations of controlled clinical trials There are many problems in therapeutics that are not amenable to evaluation by properly controlled clinical trials. The reasons for this are both financial and technical.

1. Financial Clinical trials are expensive to conduct and the longer the trial lasts, the more expensive it becomes. The factor that most commonly limits the size of a trial is the availability of suitable patients and very few trials have included more than 1000 patients or run for longer than 5 years. This constraint means that clinical trials are unlikely to demonstrate long term effects of drugs, e.g. in a trial to evaluate the effects of the beta blocking drug practolol on the survival of patients following a myocardial infarct, the oculomucocutaneous syndrome, which is now known to occur in a small number of patients after prolonged use of practolol, was not demonstrated in patients in the trial. Similarly, trials do not reliably demonstrate infrequent but potentially lethal adverse effects, either acute or chronic, e.g. bone marrow depression by chloramphenicol, which is reported to occur in 1/2000–1/50 000 treated patients.

2. Technical The essential requirements of clinical trials cannot be satisfied in many clinical circumstances. The lack of adequate controls in the evaluation of physical and psychological methods of therapy have already been mentioned. Many of the treatments used in medical emergencies are not amenable to evaluation by clinical trials because of the difficulty of randomising patient allocation, of adhering to a double blind procedure, of obtaining patient consent etc., for an event that may occur at any time, anywhere in the hospital. Although a high proportion of medical resources are devoted to the care of the very young and those over 65, there are many difficulties in the conduct of clinical trials in these age groups, e.g. the difficulty in obtaining informed consent, of matching patients as many elderly patients suffer from multiple diseases, in patient compliance with therapeutic procedures etc.

Alternative methods of drug evaluation

Historical controls The effects of a drug or any other form of therapy can be compared retrospectively with patients treated previously by the same investigator or with patient groups reported in the literature. The major limitation to such an approach is that the groups compared are seldom comparable and it is difficult to check comparability as not all the prognostic factors likely to influence therapy may be available. Furthermore, whereas in prospective trials unknown factors that may influence treatment are randomly distributed between groups, this may not be the case in uncontrolled trials and no check on this can be made retrospectively. For this and other reasons, the use of historical controls is fraught with difficulties and medical history is full of conclusions drawn from such trials that have been invalidated by properly controlled trials.

Epidemiological studies

The identification of infrequent adverse effects of drugs or adverse effects from chronic drug administration may be made by studies on very large groups of patients. For instance, the Boston Collaborative Drug Surveillance Programme is a means of screening drug usage in a number of hospitals in New England whereby all data on the use of drugs by patients is obtained by nurse monitors. This programme has provided a great deal of evidence regarding the prevalence of adverse drug effects and also provided evidence suggesting that aspirin may be of use in the prevention of myocardial infarction.

Reference to health statistics may reveal correlations between drug usage and disease. For instance, in 1967 Speizer, Doll and Heaf, using the Registrar General's statistics on health, demonstrated a 3·4 fold increase in deaths from asthma in the 5–34 year age group and a 7·2 fold increase in the 10–14 year age group recorded in England and Wales between 1959–1966 which correlated with the introduction and widespread use of pressurised bronchodilator aerosols. Later studies on some of the patients who died with asthma confirmed the close correlation of sudden and unexpected death in asthmatics and the use of isoprenaline aerosols.

Summary

The study of drug effects in man is made complex by the large number of factors that may affect responses to drugs. Most commonly, drug effects are studied in individual patients, but as a comparison of drug effects using this approach is retrospective, the results are only valid when the difference between drugs compared is large and the natural history of the condition being treated predictable.

The most reliable information on drug effects derives from studies on groups of patients in which the effect produced by a given drug is identified from effects due to other factors by the setting up of an adequate control group. In

controlled clinical trials, essential features are that trials must be prospective, that patients are randomly allocated to a control and treated group and that where necessary observer bias is eliminated by adherence to a double blind procedure. If the results disprove the null hypothesis, the probability that such a result could be due to chance is evaluated by appropriate tests of statistical significance.

Studies on very large groups and the use of health statistics may provide information on drug effects, such as chronic adverse effects or infrequent adverse effects, that are not amenable to study by clinical trials.

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Chapter 7

Pharmaceutical Aspects of Clinical Pharmacology

Pharmacy is the science of drug formulation and the preparation of drug dosage forms. In earlier times, when most doctors were their own dispensers, having to prepare their own dosage forms, pharmacy was an essential part of every doctor's training. But, with rapid developments in chemistry and the pharmaceutical industry, drug formulation has been taken over by the pharmaceutical profession and hence dropped out almost entirely from the undergraduate curriculum. Recently, however, there has been a reawakening of interest amongst clinicians in some aspects of pharmacy, mostly as a consequence of the relatively rare but well-publicised episodes of unexpected drug reactions caused by a change in a drug's formulation.

There is a considerable area of overlap of interests between clinical pharmacology and clinical pharmacy (biopharmaceutics) in that both disciplines are interested in the relationship between drug formulation and drug bioavailability. In this chapter drug formulation will be briefly discussed in relation to how it affects drug bioavailability.

Drug formulation Drug formulation involves preparing an amount of active drug (dose) in a form suitable for clinical use. The drug preparation must be storable for quite long periods of time, inoffensive to patients, presented in a form that is easy to administer and readily available for absorption once administered. As most drugs are administered orally, the major problems of drug formulation are concerned with oral preparations and the problems of parenteral preparations will only be briefly mentioned here.

Drug preparation Drugs are mostly stored and administered in solid form, partly as they take up less space as solids and partly because chemicals in general are more stable in the solid than the liquid form. This obtains for drugs in the pharmacy and in the home so that they are best kept in a dry place. The bathroom corner cupboard, that time-honoured place for drug storage, is therefore almost certainly the worst place in the house to keep drugs, at least in respect of drug stability.

The solid drug is usually in the form of a powder and may be of crystalline or non-crystalline form. It may also be in a solvated form, i.e. usually a hydrate, or anhydrous. The powdered or particulate form is usually compressed into a tablet or may be enclosed in a soluble capsule. To facilitate tablet preparation

and ultimate disintegration and dissolution in the gut lumen, various inert additional substances (excipients) are usually added. Fillers or diluents, e.g. calcium phosphate or lactose, increase the bulk of the preparation; binding agents facilitate the preparation of physically stable tablets; wetting agents and disintegrants such as starch are hydrophilic compounds that rapidly absorb water and facilitate tablet disintegration. Surface active agents fulfil the same purpose, while hydrophobic compounds, such as magnesium stearate, although valuable as a lubricant, delay the rate of disintegration and therefore delay absorption. Flavours may be added to improve taste and this is especially important in liquid preparations and in paediatric oral preparations. A film or sugar coating may be used to protect the preparation against moisture or to delay absorption (enteric coating) or the same objective may be achieved by impregnating a non-absorbable matrix (e.g. wax) with drug particles from which the drug is slowly released into the bowel lumen.

Presentation The size of a solid dose oral preparation is limited by the incapacity of patients to swallow tablets over a certain size, and in general the smaller the oral preparation the better. The shape and colour may affect the patient's attitude to taking tablets and taste is especially important if the tablets are chewed or if the drug is taken in the form of a liquid. The presentation of oral preparations is a major factor determining patient compliance, an unattractive or offensive preparation increasing the incidence of defaulting in drug taking.

Parenteral preparations may be stored as solutions contained in ampoules or in solid form to be made up into solution or suspension shortly before use. Some compounds are very unstable in solution and have to be made up only a few minutes before administration, e.g. the nitrogen mustard mustine hydrochloride, the short-acting barbiturate sodium thiopentone. Many parenteral preparations are stable for several hours if added to i.v. infusions, but this is not always the case, e.g. sodium methicillin is hydrolysed at a rate of 40% per 24 hours in normal saline and in 5% dextrose.

Bioavailability The bioavailability of a drug is the percentage of a dose that reaches the systemic circulation after administration via a stated route. The bioavailability of any drug after i.v. administration is 100% and is usually assumed to be close to this value when given i.m. or s.c., although for some highly insoluble drugs, e.g. phenytoin, digoxin, chlordiazepoxide, diazepam, this is not so, as a proportion of a dose precipitates out at the depot site and is then only slowly absorbed. The bioavailability of drugs after oral administration is frequently less than 100% and in view of this, problems regarding drug bioavailability usually refer to the oral administration of drugs.

Measurement The bioavailability of a drug is determined by comparing the area under the drug-plasma concentration vs. time curve after oral administration of a single dose with that obtained when the same dose is given i.v.

$$\text{i.e. drug bioavailability} = \frac{\text{AUC oral}}{\text{AUC i.v.}} \times 100$$

There is no fixed relationship between the rate of drug absorption and its bioavailability so that the peak height and the time to peak height are not relevant to a drug's bioavailability. If all the drug that is absorbed is excreted unchanged in the urine then a similar process can be carried out using the urine concentration versus time curve, but if the drug is metabolised, the metabolites must be measured as well as the parent drug. The bioavailability can also be determined after chronic administration of the drug and there is usually good agreement between the results obtained using a single dose with those achieved after multiple doses.

Factors determining bioavailability—Drug formulation The steps in the fate of oral preparations in the bowel are shown in Fig. 1.

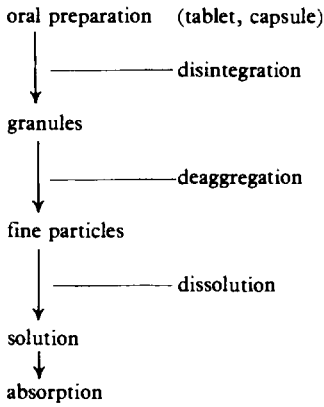

FIG. 1 Steps in the fate of oral preparations in the bowel

The first step in drug absorption from a tablet is disintegration whereby the tablet is broken down into granules. In general both the rate and extent to which a drug is absorbed are greatest when the drug is administered already in solution and decreases in the sequence solution, suspension, capsule, tablet, enteric coated tablet. The rate of absorption increases with the rate of disintegration and the objective in the formulation of most drugs is to produce rapid disintegration. This can be increased by including wetting agents or hydrophilic disintegrating agents in tablets and may be delayed by including hydrophobic agents or by enteric coating the preparation. Failure of a tablet to disintegrate is the cause of the well-established but rare clinical experience of patients passing unchanged oral preparations in their stools. The importance of disintegration in determining drug bioavailability has been recognised by the pharmaceutical

profession for many years and the British Pharmacopoeia Commission and its equivalent body in other countries have laid down *in vitro* minimum requirements for the disintegration time of tablets and capsules, although it is now widely recognised that drug dissolution rates are a more important determinant of bioavailability.

The rate of drug dissolution as determined *in vitro* has been found to be the major factor correlating with the bioavailability of many drugs, e.g. prednisone, tolbutamide, aspirin, spironolactone, ampicillin, griseofulvin and some sulphonamides. The rate of drug dissolution is determined principally by the size of drug particles, the smaller the particles the more rapid the dissolution, so that the rate of absorption can be altered by alteration of the drug particle size. Crystal size and crystal stability and the degree of solvation also affects the rate of dissolution as does the solubility of the drug itself in the aqueous medium into which it is released. Thus, weakly basic drugs readily go into solution in the stomach, while weakly acidic drugs are most soluble in the higher pH values of the small and large intestines.

Inactivation in gut lumen, bowel wall and liver Rapid inactivation in the bowel lumen obviously reduces a drug's bioavailability and this is the main reason why the bioavailability of the acid labile penicillins, benzylpenicillin, methicillin and carbenicillin is no more than 25%. L-dopa is also rapidly inactivated in the stomach and its bioavailability is increased by antacids or by increasing the rate of gastric emptying. The bioavailability of polypeptides such as insulin and oxytocin, administered orally, is negligible on account of rapid breakdown in the gut lumen by proteolytic enzymes.

The bioavailability after oral administration of drugs that are rapidly metabolised during absorption through the gastrointestinal mucosa, e.g. isoprenaline, L-dopa and during the first passage through the liver, e.g. isoprenaline, nitrites and nitrates, lignocaine, gaunethidine, debrisoquine, and propranolol is low, despite the fact that these drugs may be rapidly absorbed from the gut. Differentiation between reduced bioavailability due to poor absorption and that due to rapid (first pass) hepatic metabolism can only be achieved by measuring both parent drug and metabolites in either plasma or urine or, preferably, by using isotopically labelled drugs.

Interactions in gut lumen Drugs may form insoluble and therefore unabsorbable complexes with food constituents or other drugs. In most instances drug bioavailability is reduced when the drug is administered with food, presumably because of complex formation. Drug interactions in the bowel lumen causing a reduction in drug bioavailability are dealt with a Chapter 9.

Drug absorption The bioavailability of a drug varies with the facility with which it passively diffuses across the gastrointestinal mucosa. Drugs that are highly ionised throughout the pH range of the gastrointestinal lumen (1·0–8·0), e.g. strong bases such as quaternary ammonium compounds (e.g. neostigmine,

pyridostigmine) and the aminoglycoside antibacterial agents, (e.g. neomycin) have a low bioavailability as do digoxin and bishydroxycoumarin. For drugs that diffuse slowly across the gastrointestinal mucosa, the bioavailability may be further reduced by changes in bowel function and may vary considerably between different proprietary preparations (*see* below).

Bioequivalence Bioequivalence occurs when the bioavailability of a drug from different formulations is the same. Manufacturers do not always use identical processes and formulae in tablet production of a given drug, so that disintegration and dissolution rates may vary between manufacturers. Such variations often lead to differences in drug bioavailability from tablets of identical stated potency prepared by different manufacturers. This bio-inequivalence has been found to exist in different preparations of a number of drugs including digoxin, tetracyclines, aspirin, phenytoin, theophylline, warfarin and is usually most evident in drugs that are poorly absorbed and in enteric coated preparations. Occasionally a manufacturer may change the production process for a given preparation with a resultant change in the drug's bioavailability between the old and the new dosage forms. The therapeutic significance of the bio-inequivalence of some drug dosage forms is greatest for drugs with a narrow therapeutic index and for drugs whose effects are closely related to their plasma concentration, e.g. warfarin, digoxin, phenytoin, oral hypoglycaemic agents and cytotoxic agents. For many drugs however, the differences in bioavailability between different brands are small and of trivial therapeutic importance.

The bio-inequivalence of different formulations of the same drug has been widely publicised by the pharmaceutical industry as a rational argument in favour of prescribing drugs by their proprietary rather than their approved names. It has prompted both the pharmaceutical industry and government agencies concerned with consumer protection (e.g. the Committee on Safety of Medicines and the Food and Drug Administration) to press for a minimum standard of bioavailability for oral dosage forms to eliminate major differences between products.

Practical measures Measures available to the clinician to reduce variability in drug responsiveness due to variations in drug bioavailability include the following:

1. Administer oral drug preparations on an empty stomach whenever feasible.
2. Consistently use one proprietary product when there are a number with similar pharmacological attributes.
3. Be aware of drugs that are poorly absorbed and those whose bioavailability is most likely to be reduced by gastrointestinal disturbances.
4. Avoid enteric coated preparations where possible and suspect poor bioavailability if the response to such preparations is not as expected.

Drug nomenclature All drugs whose chemical formula is known have chemical names, but these are nearly always long and quite impractical as a means of drug identification for clinicians. Drugs are therefore given 'approved' names and in the United Kingdom these are determined by the nomenclature sub-committee of the British Pharmacopoeia Commission and by equivalent bodies in other countries. Thus the chemical 6-chloro-3, 4-dihydro-1,2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide has the approved name hydrochlorothiazide. The approved name is derived from the chemical name where possible, although this is not always immediately apparent to the clinical observer. Usually there is international agreement on approved names, but this is not always the case, e.g. frusemide in the British Pharmacopoeia is furosemide in the USP.

The proprietor chooses a brand name arbitrarily for a drug and if the drug is novel, the copyright of the drug lasts for 15 years before other pharmaceutical manufacturers can produce the same drug under different proprietary names. Thus the number of proprietary preparations of a given drug multiplies after 15 years and the older the drug, the more proprietary preparations containing it there will be.

Drug combinations also have their own proprietary names and a glance through MIMS (*see* below) will reveal that a very large number of preparations are fixed dose combinations of drugs. Commonly these contain two or more drugs and many contain potentially dangerous compounds, such as barbiturates, without there being any obvious necessity for such additions. It is now necessary for all new drug combinations proposed by manufacturers to be submitted to the Committee on Safety of Medicines or equivalent bodies abroad with evidence of the safety of such combinations. It is hoped that such a surveillance system will eliminate the needless proliferation of useless drug combinations.

Information on drugs Factual information on the pharmacology of drugs can be obtained from a variety of sources including text books. In the United Kingdom, the British National Formulary, which is compiled by a committee representing the pharmaceutical and medical professions, provides information about drugs under their approved names, including a brief description of pharmacological aspects. Proprietary names are mentioned when there are one or two only. Martindale, the Extra Pharmacopoeia, which is available in most dispensaries and medical libraries, is produced under the direction of the Council of the Pharmaceutical Society of Great Britain and contains monographs on a considerable number of both non-proprietary and proprietary preparations. The Extra Pharmacopoeia has more details on the clinical pharmacology of drugs, especially on clinical uses and adverse effects, than does the British National Formulary, as well as abstracts of a large number of published papers. The approved name of a drug contained in a proprietary preparation on the United Kingdom market can be obtained from the Monthly Index of Medical Specialities (MIMS). It is produced monthly, is readily available to doctors and is most useful in the common clinical situation of seeing

patients without documentary evidence of the treatment they are receiving, when the patient knows the proprietary name of the compound.

The method of obtaining information on drugs is summarised in Fig. 2.

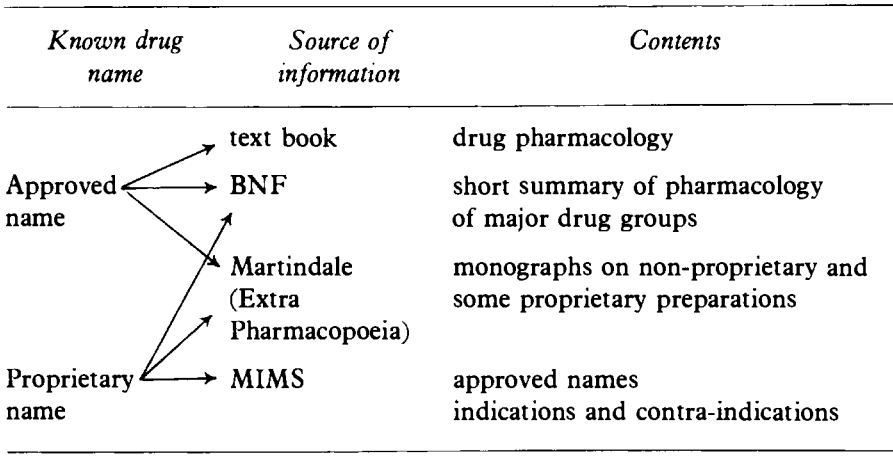

FIG 2 Methods of obtaining information about drugs

Drug prescribing A prescription is a written set of instructions to a pharmaceutical chemist as to the drug or drugs that are to be dispensed for a given patient. It should also contain a set of instructions to the patient whether or not verbal instructions have been given to the patient by the doctor. The information should be written in English, not Latin, and a prescription should contain the following:

Drug—under the approved or proprietary name
Dose
Dose interval
Route
Duration of therapy or quantity of preparation to be dispensed.

In hospital, if a drug is given as a continuous infusion in an intravenous giving set, the nature of the vehicle (normal saline, 5% dextrose etc.) should be specified and the rate at which each unit of volume should be administered, e.g. 1 litre in 12 hours. If a drug is to be given as required by the symptoms (PRN) the times of administration should also be recorded.

Treatment is given to change the natural history of a disease or symptom. Essential in the determination as to whether a given drug has improved or exacerbated a clinical situation is a careful record of the drugs given. Frequently patients are ignorant of the drugs they are receiving and the container in which the drug is dispensed may not contain the name or dose of the drug. As

knowledge of what medicines a patient is receiving is essential in patient management, wherever possible or feasible, a patient should know what drugs he or she is taking and the container should show the drug's name and the dose size, dose interval and date.

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Chapter 8

Adverse Reactions to Drugs

Adverse reactions to drugs are drug effects that are disadvantageous to the patient. The term toxic reactions is commonly used in the same context, but to many, the term implies life-threatening reactions whereas the majority of adverse reactions are of a mild nature, causing disagreeable symptoms only.

The overall incidence of adverse reactions in the community is difficult to estimate. Assessments carried out on hospital in-patients have shown that adverse drug reactions account for up to 5% of all admissions and that 10–20% of in-patients develop an adverse drug reaction during the course of an admission, of which 3% are potentially lethal. As many in-patients suffer from life-threatening disease, often requiring drugs with serious adverse effects, e.g. glucocorticoids, cytotoxic agents, anticoagulants etc., the incidence of adverse effects in out-patients is probably much lower than this. Drugs most commonly implicated in life-threatening adverse effects include cytotoxic agents, anticoagulants, insulin, glucocorticoids, cardiac glycosides, diuretics, anti-inflammatory analgesics and oral contraceptives, as well as normal saline, KCl in both solution and in tablet form, and 5% dextrose.

One of objectives of clinical pharmacology is to decrease the incidence and severity of adverse reactions to drugs without diminishing their therapeutic effectiveness. To achieve such an objective, it is desirable to understand the mechanisms responsible for adverse effects, as the measures necessary in their treatment or prevention differ with the different mechanisms involved.

MECHANISMS OF ADVERSE DRUG REACTIONS

Side effects Drug effects that are dose-related, that occur within the therapeutic dose range and are caused by the same drug action as the therapeutic effect, are termed side effects. The log dose/response curve for side effects are not significantly different from the therapeutic effect (Fig. 1) so it may be impossible to obtain an adequate therapeutic effect without side effects.

Drugs with a wide spectrum of effects commonly cause side effects. Examples are bone marrow depression by cytotoxic drugs, the muscarinic and nicotinic effects of anticholinesterases used in myasthenia gravis and the asthma and left ventricular failure caused by beta-blockers in susceptable patients.

Side effects can be minimised by choosing drugs with a narrow spectrum of effects. Occasionally it may be necessary to administer a second drug to counteract a side effect, such as KCl during thiazide diuretic therapy in patients with congestive cardiac failure to avoid hypokalaemia; an antimuscarinic agent

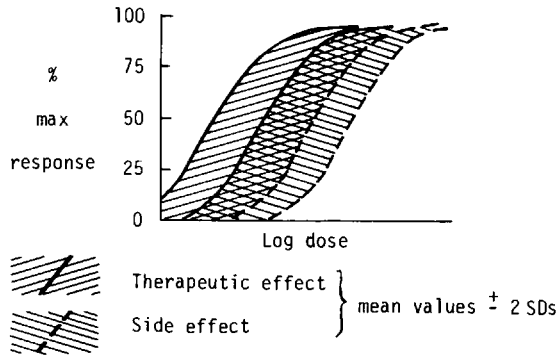
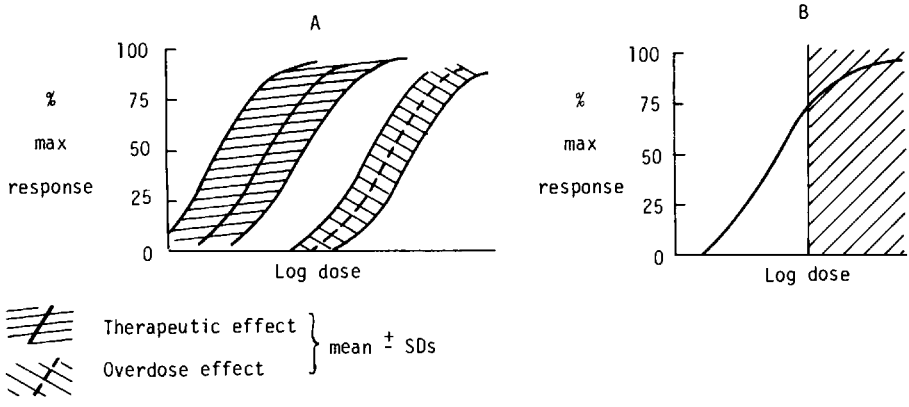


FIG. 1 Log dose-response for therapeutic and side effects.

with doses of a phenothiazine or butyrophenone to counteract parkinsonian side effects.

Overdosage In this chapter, overdose effects are those that occur within the generally accepted therapeutic dose range. (For the treatment of overdosage in voluntary self-poisoning *see* Chapter 40.) Overdose effects may be either an exaggeration of the therapeutic effect (e.g. a prothrombin time 3 times the control value in patients on warfarin) or unrelated effects. The log dose-response relationship of these two overdose effects is shown in Fig. 2.



In this instance, the overdose effect is different in nature from the therapeutic effect. The log dose-response curves are parallel but this need not be the case.

The unshaded area represents therapeutic and sub-therapeutic doses and the shaded area overdose. In this instance, the overdose effect is an exaggeration of the therapeutic effect.

FIG. 2 Overdose

In either case, the overdose effects occur at the higher end of the log dose-response curves. In clinical literature, the relationship between the therapeutic and overdose effect is often described in terms of the steady-state plasma concentrations at which these occur (Fig. 3) although this approach is only applicable to drugs whose therapeutic and overdose effects are closely related to the plasma concentration (i.e. class 1 drugs—*see* Chapter 4), for example anticovulsants and antidysrhythmic agents.

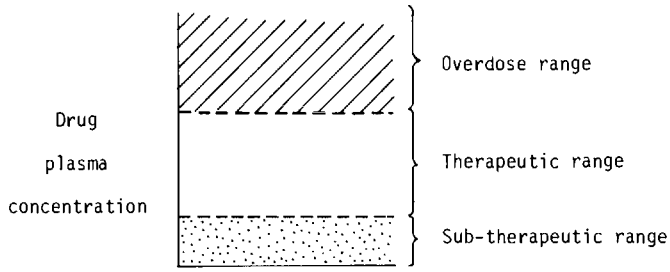


FIG. 3 The therapeutic range of a drug plasma concentration.

In animal pharmacology the relationship of the overdose to therapeutic effect is expressed in the ratio of the LD50/ED50 the 'therapeutic index'. However, as it is seldom possible in clinical pharmacology to obtain an estimate of the ED50 for a drug and never possible to obtain a LD50, there are no hard and fast quantitative guide lines relating the therapeutic and overdose dose ranges.

Overdose effects within the therapeutic dose range may result from:

1. Administration of a relatively large dose on a g/kg basis.
2. Decreased rate of excretion of the active compound in renal failure, e.g. digoxin, aminoglycosides, cephalosporins, tetracyclines.
3. Decreased rate of drug metabolism. This may be genetically determined under the control of a single factor as in suxamethonium sensitivity (*see* Pharmacogenetics, Chapter 5) ot the consequence of liver disease or a drug interaction.
4. Increased sensitivity to drug effects—some patients suffer overdose effects at drug plasma and tissue concentrations within the therapeutic range. Increased susceptibility to drug effects may be determined by genetic or environmental factors. Responsiveness to a drug is determined by a single genetic factor in a small number of instances (Chapter 5). The development of an overdose or altered response to a drug which is determined by a single genetic factor, whether that factor determines the rate of drug metabolism or susceptibility to a given drug effect, is described as a drug idiosyncrasy.

In most instances, however, responsiveness to a drug is determined by a number of genetic factors so that the frequency distribution curve of the response to a given dose of a drug is unimodal.

Those at the extreme right of the dose response curve (shaded area) are especially sensitive to drug effects.

In clinical practice there have been very few studies demonstrating variability in responsiveness to a drug independent of drug pharmacokinetic variables, but what information there is suggests that there is considerable variability between individuals in their responsiveness to drug effects, e.g. in one study on a

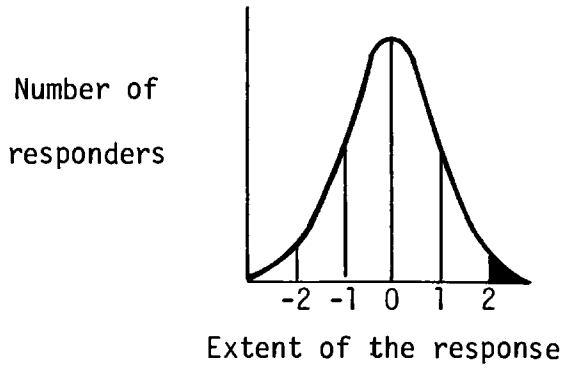


FIG. 4 Frequency distribution curve of the response of a population to a single dose of a drug. The shaded area represents that proportion of the population most sensitive to the drug effect. 0 = mean ± 2 SDs.

number of patients with atrial fibrillation, whose pulse rate was maintained between 60–85 beats/minute, the plasma digoxin concentration varied between 0·3 ng/ml–3·0 ng/ml.

Environmental factors causing an increased susceptibility to drug effects include the patient's age (*see* Chapter 42) and disease, e.g. patients with severe hepato-cellular disease are very susceptible to the CNS depressant drugs such as barbiturates and morphine and to warfarin.

Allergic (hypersensitivity) reactions Adverse reactions mediated by an immune mechanism are described in this chapter as allergic reactions. The term hypersensitivity reactions can also be used in this context but as it is sometimes used to describe an increased susceptibility to drug effects, it will not be used here.

Drugs themselves are mostly too small to be antigenic, exceptions being drugs that are foreign proteins, e.g. streptokinase, asparaginase; or polypeptides, e.g. insulin. They are also relatively unreactive chemically and so do not readily acquire antigenic properties by forming covalent bonds with macromolecules. However, allergic reactions to drugs are common and it seems probable that in most instances the haptenic component of drugs are highly reactive metabolites or contaminants which form covalent links with proteins or occasionally with polysaccharides or nucleotides. This has been clearly demonstrated for penicillin in which the minor metabolite or contaminant penicilloic acid, reacts with lysine

residues in proteins to become antigenic.

Allergic reactions are mediated by circulating immunoglobulins (antibodies) or by sensitisied lymphocytes. Immunoglobulins E, G and M are responsible for most allergic drug reactions and the types of reaction are similar to those due to other allergens and have been classified into four categories:

Type I response Reaginic antibodies (IgE), located on the surface of most cells and basophils, react with circulating antigen releasing pharmacologically active compounds (histamine, kinins, prostaglandins) which are responsible for the clinical syndromes. The most severe response, anaphylaxis, is characterised by hypotension, bronchospasm and laryngeal oedema, urticaria and erythema, cardiac dysrhythmias, diarrhoea and vomiting. If untreated, it is fatal in the majority of cases. Milder responses may cause any one or a combination of these signs. Penicillins have most commonly been implicated as drugs causing Type I responses but other drugs doing so are shown in Table 1.

Type II response In this category the drug, metabolite or contaminant, becomes adsorbed onto the surface of cells, especially the cellular components of the blood, and may react with circulating immunoglobulins (IgG or IgM), activate the complement system and damge the cells to which they are attached. Such a response is responsible for the Coomb's positive haemolytic anaemia caused by penicillins, cephalosporins, PAS, rifampicin, quinine and quinidine. Alpha methyl dopa and mefenamic acid also cause a Coomb's positive haemolytic anaemia, but it is not certain whether they act as haptens in this situation. Type II responses may cause thrombocytopenia, drugs implicated in such a response including quinine and quinindine, sulphonamides (including Co-trimoxazole), thiazides, thioureas, chloramphenicol and meprobamate. They may also cause neutropenia, drugs implicated including phenylbutazone, phenothiazines, sulphonamides, thioureas, sulphonylureas and anticonvulsants. The binding of haptenic drug groups onto the cells of specific organs other than the formed elements of the blood may account for a considerable proportion of the adverse drug reactions causing cell injury described in Table 1, but the types of allergic response causing such responses are not always Type II responses but may also be Type III or Type IV responses.

Type III responses In this type of response, antibody (mostly IgG)—antigen complexes form in the circulation, bind complement and cause damage to the capillary endothelium of various organs. Serum sickness-like reactions are the commonest clinical manifestations and are characterised by fever, arthritis, lymphadenopathy and splenomegaly, oedema, urticarial, purpuric or maculo-papular rashes and occasionally glomerulo nephritis and a peripheral neuropathy. In less severe reactions fever alone may occur or a number of the other signs without fever. Symptoms occur six days or more after the initial drug exposure and they usually resolve within a few days to four weeks after stopping the drug. Drugs that have caused such reactions are shown in Table 1.

Table 1

Some adverse effects of drugs on organ structure and function

Adverse effect	*Drug examples*	
Systemic reactions		
Anaphylaxis	Penicillins	Organomercurials
	Cephalosporins	Local anaesthetics
	Tetracyclines	Dextrans
	Streptomycin	Cyanocobalamin (B_{12})
	PAS	Bromsulphthalein
	Quinine	Heparin
	Quinidine	Aspirin
	Opiates	
Serum sickness	Penicillins	PAS
	Cephalosporins	Thioureas
	Sulphonamides	Phenytoin
	Streptomycin	
Malignant hyperthermia	Succinyldicholine	
	Halothane	
Skin		
Urticaria, Angioneurotic oedema	As for anaphylaxis	
Erythema, Erythema multiforme, Stevens-Johnson syndrome	Penicillins (esp. ampicillin)	Barbiturates
	Sulphonamides	Phenothiazines
	Benzothiadiazines	Phenolphthalein
Erythema nodosum	Sulphonamides	Penicillin
	Sulphones	Iodides
Exfoliative dermatitis	Sodium aurothiomalate (gold)	Sulphonamides
	Organo arsenicals	Trimethadione
		Phenothiazines
Hyperpigmentation	Phenothiazines	Busulphan
Alopecia	Cytotoxic drugs (esp. cyclophosphamide)	Butyrophenones
Blood		
Bone marrow depression, Aplastic anaemia	Cytotoxic drugs	Indomethacin
	Chloramphenicol	Penicillamine
	Sodium aurothiomalate	

Adverse effect	*Drug examples*	
	Suramin	Sulphonamides
	Phenylbutazone	Allopurinol
Neutropenia	Phenylbutazone	Sulphonamides
	Thioureas	Phenothiazines
	Sulphonylureas	Anticonvulsants
Thrombocytopenia	Quinine	Thioureas
	Quinindine	Rifampicin
	Sulphonamides	Chloramphenicol
	Chlorothiazide	Meprobamate
Megaloblastic anaemia	Pyrimethamine	Phenobarbitone
	Methotrexate	Primidone
	Phenytoin	Triampterine
Haemolytic anaemia	*α* Methyl dopa	Nitrofurantoin
	Mephenamic acid	Phenacetin
	Penicillins	Quinine
	Cephalosporins	Quinidine
	Nalidixic acid	PAS
	(*see* Table 1 Chapter 5 for subjects with G6PD deficiency)	
Thrombosis	Oestrogens	
Liver		
Centrilobular necrosis	Chloroform	
Cholestasis	Methyltestosterone	
	Norethandrolone	Erythromycin estolate
	Phenothiazines	Chlorpropamide
Hepatoceullular damage with cellular infiltration	Halothane	Stibophen
	Hydrazine MAOIs	Phenylbutazone
	Pyrazinamide	Indomethacin
	Sulphonamides	Nitrofurantoin
	PAS	Chlordiazepoxide
	Isoniazid	Diazepam
	Rifampicin	*α* Methyl dopa
	Organomercurials	Tetracycline
	Oral contraceptives	
Kidney		
Acute tubular necrosis	Cephaloridine	Probenecid

Adverse effect	*Drug examples*	
	Cephalothin	Organoarsenicals
	Sulphonamides	Tetracyclines
	Aminoglycosides	Penicillins
Nephrotic syndrome	Trimethadione	Primidone
	Phenindione	Penicillamines
Chronic renal failure	As for nephrotic syndrome	
	Phenacetin	
Nephrocalcinosis	Calcium salts + $NaHCO_3$	Vitamin D
Hypokalaemia	Benzothiadiazines	Carbenoxalone
	Frusemide	Organomercurials
	Ethacrinic acid	Mineralocorticoids
Hyperkalaemia	Spironolactone	Triampterine
	Amiloride	KCl
Hyponatraemia	Diuretics	Drugs causing inappropriate ADH secretion (*see* below)
Hypernatraemia	Ethanol	NaCl
	Lithium carbonate	
Nervous system		
Convulsions	CNS stimulants	Ethionamide
	Penicillin	Phenothiazines
	Theophylline	Stibophen
	Lignocaine	Piperazine
	Local anaesthetics	Niridazole
	Reserpine	
Psychoses	Amphetamines	Thiobendazole
	Antimuscarinic agents	Pentazocine
	Phenacemide	Ethanol
	L-Dopa	
	MAOIs	
Depression	Reserpine	
	Clonidine	
	a Methyl dopa	
Encephalopathy	Melarsoprol (Mel B)	
	Melarsonyl (Mel W)	

Adverse effect	*Drug examples*	
Parkinsonism	Phenothiazines Reserpine Diazoxide	Butyrophenones Metoclopramide
Tremor	Sympathomimetic amines Orciprenaline	Salbutamol Terbutaline
Benign intracranial hypertension	Tetracyclines Indomethacin Vitamin A	
Peripheral neuropathy	Nitrofurantoin Isoniazid Vincristine Perhexilene	Chloroquine Organomercurials Methotrexate
Myopathy	Corticosteroids	Colchicine
Muscle weakness	β-blockers	Aminoglycoside antibacterial agents
Eyes		
Amblyopia	Quinine	
Retrobulbar neuritis	Ethambutol Chloramphenicol	Di-iodohydroxyquinoline Tryparsamide
Cataracts	Glucocorticoids	
Glaucoma	Antimuscarinic agents Tricyclic antidepressants	Ephedrine
Retinopathy	Chloroquine	
Ears		
Ototoxicity	Aminoglycoside antibacterial agents Quinine	Frusemide Ethacryinic acid
Cardiovascular system		
Dysrhythmias	β_1-agonists Cardiac glycosides Chloroform Halothane Theophylline	Tricyclic antidepressants L-dopa Anti-dysrhythmic drugs

Adverse effect	*Drug examples*	
Cardiac failure	β-blockers	Quinidine
	Mineralocorticoids	Procainamide
	Phenylbutazone	Duanorubicin
	Osmotic diuretics	Doxorubicin
Hypertension	Mineralocorticoids	Clonidine (withdrawal)
	α-agonists	Ergotamine
	Oral contraceptives	
Hypotension	Hypotensive agents	Pentamidine
	Diuretics	Stibophen
	Procainamide	L-dopa
	Quinidine	glyceryltrinitrate
Raynaud's syndrome	β-blockers	
Polyarteritis	Sulphonamides	
Respiratory system		
Asthma	β-blockers	Phenylbutazone
	Antipyretic analgesics	Indomethacin
Pulmonary fibrosis	Bleomycin	
	Other cytotoxic drugs	
Pulmonary eosinophilia	Nitrofurantoin	
	Sulphonamides	
	PAS	
Gastrointestinal tract		
Peptic ulceration	Salicylates	Phenylbutazone
	Glucocorticoids	Ibuprofen
	Indomethacin	Ethacrinic acid
Small bowel ulceration	KCl	
Steatorrhoea	Cholestyramine	PAS
	Neomycin	Phenindione
Pancreatitis	Vitamin D	Diazoxide
	Corticosteroids	
Endocrine		
Diabetes mellitus	Glucocorticoids	Diazoxide
	Benzothiadiazines	Pentamidine
	Frusemide	

Adverse effect	*Drug examples*	
Hypoglycaemia	Insulin Oral hypoglycaemic agents	β-blockers
Hypothyroidism	Sulphonylureas PAS Phenylbutazone	Thioureas Lithium carbonate
Hyperthyroidism	Lithium carbonate	
ADH secretion	Chlorpropamide Tolbutamide Benzothiadiazines Diazoxide Clofibrate	Metformin Phenformin Vincristine Cyclophosphamide Carbamazepine
Amenorrhoea	Oral contraceptives Cytotoxic agents	Phenothiazines
Gynaecomastia	Spironolactone	Cardiac glycosides
Teeth Staining Enamel hypoplasia	Tetracyclines	
Bones Osteoporosis	Glucocorticoids	
Osteomalacia	Phenobarbitone Phenytoin	Primidone
Aseptic necrosis of bone	Glucocorticoids Phenylbutazone	Indomethacin
Hypercalcaemia	Vitamin D	Calcium salts
Joints and connective tissue Systemic Lupus Erythematosus syndrome	Hydrallazine Procainamide	Phenytoin Practolol
Dry eyes Skin rashes Mucosal ulceration Retroperitoneal fibrosis	Practolol	

Adverse effect	*Drug examples*	
Urino-genital		
Urinary retention	Antimuscarinic agents	Ephedrine
	Tricyclic antidepressants	β-agonists
Urinary incontinence	Anticholinesterases	Muscarinic agents
Impotence Failure of ejaculation	Guanidinium hypotensive agents	
	α Methyl dopa	CNS depressants
	Reserpine	Antimuscarinic agents
Infections		
Increased incidence	Glucocorticoids	Cytotoxic agents
Super-infections	Broad spectrum antibacterial agents	Lincomycin
		Clindamycin
Mutagenic		
Teratogenic	Cytotoxic drugs	
	Phenytoin	
	Androgenic drugs	
Carcinogenic	Cytotoxic drugs	
	Stilboestrol	
Drug dependence		
	Narcotic analgesics	Amphetamine
	Ethanol	Marihuana
	CNS depressants	

Type IV response This response is mediated by lymphocytes and not by immunoglobulins. The lympocytes are sensitised by drug-hapten macromolecule complexes and, reacting with the tissues, cause tissue damage. Contact dermatitis to drugs and other chemicals is commonly mediated through this type of response and occurs most frequently with topically applied antibacterial agents, antifungal drugs, local anaesthetics and antihistamines and occasionally to components of the vehicle in which the drug is applied.

Clinical diagnosis Signs and symptoms similar to those described under the four types of allergic response should alert the clinician to the possibility that these are manifestations of an allergic response to a drug. The characteristic

features of such responses, other than the signs and symptoms, are—

1. There is usually, but not invariably, a prior history of exposure to the drug. Ignorance of previous treatment and the presence of small amounts of the drug in the inhaled air and in food etc., account for most of those who give a negative history.
2. There is no dose-response relationship. Very small doses of drugs have occasionally caused fatal allergic reactions.
3. There is cross-sensitivity between related chemical groups within the same pharmacological class, e.g. between penicillins, sulphonamides, benzothiadizines, aminoglycosides and to a lesser degree between chemically related classes, e.g. penicillins—cephalosporins; sulphonamides—benzothiadizines; sulphonamides—sulphonylureas.
4. The reaction resolves on withdrawal of the drug and recurs on re-exposure.

Individuals vary in the facility with which they develop allergic reactions to drugs, such reactions occurring most frequently in atopic individuals, i.e. those who give a history of asthma, eczema, hay fever or vasomotor rhinitis. Drugs themselves vary in their capacity to induce allergic responses, e.g. allergic reactions to penicillins occur in 1–2% of all patients treated with these agents but have very rarely been recorded for the very much more widely consumed caffeine. The route of administration is also a determinant of the frequency of allergic responses, such responses occurring most frequently when drugs are administered topically and least often after oral administration. Disease may affect the liability to allergic responses to a drug, e.g. the incidence of rashes developing to ampicillin is greatly increased in patients with infectious mononucleosis and other viral infections.

Laboratory investigations There is no universally effective means of determining whether a clinical condition is the result of an allergic response to a drug or of predicting whether a patient will develop such a response on exposure to a given drug. An eosinophilia commonly, but not invariably, occurs with allergic reactions. Provocation tests, in which small amounts of the drug are applied to the patient, usually topically or intradermally, but occasionally intramuscularly or orally, may be effective at evoking an allergic response. However, there are usually a number of false negatives and false positives in such tests and always there is the risk, albeit small, of a severe or fatal anaphylactice response occurring. In the case of penicillin, benzylpenicilloyl—polylysine, a polymer of lysine, is available for topical provocation testing and by the use of a combination of the polymer and benzylpenicillin itself, it is possible to identify over 90% of potential anaphylactic reactors. There are a large number of false positive reactors however, e.g. 10–30% of any adult population who have been treated with a penicillin give a positive response, but only a small percentage of these develop symptoms when treated with a penicillin. In a number of centres, IgE as well as IgG and IgM can be measured in the plasma and the ability of patients' serum to cause lymphocyte transformation *in vitro* may also be of value in assessing Type IV allergic response to drugs.

Prophylaxis and treatment A clinical history of prior exposure to a drug is the single most important determinant of a patient's propensity to develop an allergic response to a drug. In atopic patients and before using drugs such as penicillin, quinine, quinidine or procaine, which are commonly associated with allergic reactions, a careful history of prior drug usage and the consequences is mandatory. As allergic responses occur much less commonly when the oral route is used, this is the route of choice in circumstances in which there is an increased probability of an allergic response. If there is a history of an allergic response, the likelihood of cross-sensitivity to chemical cogeners and other chemically related drugs should be borne in mind.

The treatment of a Type I response (e.g. anaphylaxis) is the immediate administration of 0·5–1·0 mg of adrenaline s.c. (i.m. if there is pronounced peripheral vasoconstriction) as adrenaline antagonises the actions of histamine on vascular smooth muscle and also impairs the release of histamine and other pharmacological mediators from mast cells. For less serious reactions, antihistamines may be sufficient for skin rashes, salbutamol or isoprenaline inhalations for bronchospasm and glucocorticoids for 7–10 days are usually sufficent to eliminate the signs and symptoms of serum sickness reactions. In all cases, the drug responsible should be stopped immediately and never prescribed again except in exceptional circumstances (*see* below) and the patient notified of the name of the drug to which he or she is allergic.

When it is thought essential to continue therapy with a given drug to which an allergic response has developed, desensitisation (hyposensitisation) may be undertaken. Such a process has been quite commonly used in the treatment of tuberculosis before the development of the relative plethora of effective antituberculous agents had occurred, but this is rarely necessary nowadays. As desensitisation procedures always carry the risk of a serious allergic reaction developing, they should only be undertaken when no alternate drug is available.

TYPES OF ADVERSE REACTIONS

Adverse drug reactions may affect any organs of the body and in practice it may be impossible to determine whether an abnormality that occurs during drug therapy is or is not due to an allergic response to the drug. In Table 1 the principal types of adverse drug effects are set out with some examples of the drugs causing them and although the list of effects is by no means comprehensive, it gives some insight to the diversity of such adverse effects.

Functional impairment Symptoms that result from the impairment of organ function, without there being evidence of cellular damage, are easily the most common type of adverse reaction, e.g. nausea, vomiting, diarrhoea and colic, drowsiness, dizziness and headache, breathlessness, malaise etc. Such symptoms are common in the absence of drug therapy and only rarely can be attributed with confidence to a given drug. Such reactions when they are due to drugs are usually

dose related, being side or overdose effects and are reversible if drug therapy is stopped.

Cellular injury Cellular injury may result from either an allergic reaction to a drug, drug metabolite or contaminant or to a direct toxic effect of one of these, and in practice it is usually impossible to say which of these mechanisms is operative. Some examples of drug-induced cellular injury affecting specific organs are set out in Table 1. As the cellular injury may not be reversible, such drug reactions have grave implications for affected patients and for the future use of the responsible drug.

Infections Drugs may increase the liability to infections in a number of ways. Glucocorticoids and cytotoxic agents impair the cellular and humoural defence mechanisms against infections. Antibacterial agents alter the commensal flora of the body and predispose to colonisation by pathogens resistant to the agents being used (super-infections). The use of antibacterial agents at any time favours the multiplication of resistant organisms so that the incidence of resistant organisms in an individual or community increases with the use of these agents.

Mutagenic effects By altering the chemical and physical properties of DNA and RNA, drugs may either kill cells or cause an alteration in the cell's ability to replicate, i.e. in its genetic function. Drugs that most frequently cause such mutagenic effects are cytoxic agents such as the nitrogen-mustards and other alkylating agents. The clinical consequences of such an effect are teratogenic effects if the drugs are administered to the mother in the first trimester of pregnancy (*see* Chapter 29), and carcinogenic effects if these drugs are administered over long periods of time. Cytotoxic drugs also impair both cellular and, at higher, doses, humoural immune mechanisms and this effect may also contribute to their carcinogenic effects.

Social behaviour Adverse drug effects may be manifest not only in an alteration in a subject's sense of well-being and physical health, but also in his or her social behaviour. Addiction to drugs such as ethanol and narcotic-analgesics cause adverse effects chiefly because of the altered social behaviour of addicts. The effects on social behaviour of drugs such as marihuana and benzodiazepines has not yet been evaluated.

Oral contraceptives may have contributed to an increase in sexual promiscuity and an increase in the incidence of venereal disease in young people. The frequency of admission to hospital due to self poisoning with drugs varies directly with the frequency with which drugs that effect the CNS are prescribed.

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Chapter 9

Drug Interactions

In therapeutics the administration of drugs in combination has been the rule rather than the exception to the rule since the earliest times. Thus Galen wrote in the second century AD, 'It is the business of pharmacology to combine drugs in such a manner according to their elementary qualities, heat, cold, moisture and dryness, as shall render them effective in combating or overcoming the conditions in the different diseases'. Medicines recommended by Galen and his pupils had many different components, e.g. theriac, a panacea imposed by Marcus Aurelius on Galen, contained a hundred different ingredients. Later physicians perpetuated these ideas and indeed modern therapeutics, having at its command a very much larger number of drugs than the ancients, continues to use drugs in combination in many circumstances with the objective of achieving a greater therapeutic effect.

In pharmacology the effect that one drug may have on the actions of a second drug on tissue preparations *in vitro* has been a subject of continued interest. The analysis of drug interactions at a tissue level has helped in the understanding of drug-receptor interactions and in the determination of the mode of action of many drugs. Thus the idea that drugs may interact if prescribed at the same time is not new.

Recent interest in drug interactions was initiated by the large number of unexpected drug interactions that occurred shortly after the introduction of the monoamine oxidase inhibitors (MAOIs) as antidepressants. Furthermore, the availability of sensitive chemical methods capable of detecting drugs in therapeutic concentrations in the plasma has made it possible to demonstrate that one drug may alter the pharmacokinetics of another.

It is the purpose of this chapter to outline how and where drugs may interact and to discuss the therapeutic implications of such interactions.

Types of drug interaction

For a drug to have a given effect, it must reach the receptor compartment in an effective concentration. Drug interactions may be divided into those in which one drug alters the pharmacokinetics of a second drug, so affecting the concentration of one or of both in their respective receptor compartments (pharmacokinetic interactions), and drug interactions in which there is no alteration in either drug's pharmacokinetics but there is an altered response to one or both drugs (pharmacodynamic interactions).

Pharmacokinetic interactions

Drugs may interact at several sites before they reach their respective receptor compartments. There are many examples of such interactions documented and they are best considered in terms of the sites at which they occur.

1. IN VITRO Drugs that are mixed in aqueous solution in a syringe or in an infusion apparatus may react causing an alteration in the physicochemical properties of one or both drugs. Many such interactions may occur without a visible change in the solution but the formation of a precipitate or a change in colour of the aqueous solution suggests that such an interaction has occurred. For example, calcium carbonate may precipitate out if calcium chloride and sodium bicarbonate are given together i.v. during cardiac resuscitation. Benzylpenicillin, methycillin and ampicillin are inactivated by several drugs including chlorpromazine, hydrallazine, lincomycin and oxytetracycline.

Such is the frequency of drug interactions in solution that the mixing of drugs in this way should be avoided. If it is desirable to mix two drugs *in vitro*, pharmaceutical advice should be sought before doing so.

2. DRUG ABSORPTION

Gastric and intestinal pH Antacids may decrease the rate of absorption of weakly acidic drugs (e.g. aspirin, warfarin) from the stomach by increasing the degree to which the drugs are ionised in the stomach.

Bowel motility As the small bowel is the site from which drugs are most rapidly absorbed, drugs that delay gastric emptying (e.g. antimuscarinic agents) usually slow drug absorption whereas drugs that expedite gastric emptying (e.g. metoclopramide) increase the rate of drug absorption. Digoxin, which is poorly absorbed from the bowel, is an exception to this rule as its absorption is facilitated by the antimuscarinic agent propantheline.

Insoluble complexes One drug may impair the absorption of another by forming insoluble complexes with it. Thus the chelating agent, desferrioxamine, given by gastric intubation, may reduce the amount of iron absorbed from the bowel in children who have taken an overdose of iron tablets. Activated charcoal taken within 30 minutes of drug ingestion reduces salicylate and paracetamol absorption. Tetracyclines have chelating properties and form insoluble complexes with bivalent and trivalent cations in antacids and in ferrous and ferric salts. Cholestyramine, the anion exchange resin, which binds bile salts in the bowel lumen, may also bind other anions such as warfarin. Liquid paraffin reduces the absorption of lipid soluble drugs and vitamins.

Subcutaneous sites The basic drug procaine forms an insoluble complex with benzylpenicillin and when given together (procaine penicillin) this acts as a depot preparation from which penicillin is released slowly into the circulation. The basic protein protamine forms complexes with insulin and protamine insulins, e.g. isophane insulin, is an effective depot preparation of insulin.

Drug distribution

3. INTERACTIONS IN THE BLOOD

Free drug Chelating agents given parenterally form stable, inactive and readily excretable complexes with cations in the blood, e.g. desferrioxamine and iron. Heparin, whose anticoagulant effect is dependent upon its acidic qualities, is rapidly inactivated by intravenous administration of the arginine-rich basic protein protamine.

Plasma protein bound drug Drug binding sites on plasma albumin have a low degree of specificity, many acidic drugs sharing similar binding sites. If two such drugs are prescribed together the drug with the higher affinity for these sites will reduce the amount by which the other drug is bound. For acidic drugs there seem to be at least two different binding sites, one shared by salicylates, sulphonamides, sulphonylurea hypoglycaemic agents, phenylbutazone, methotrexate and penicillins, the other by barbiturates and probenecid.

Displacement of one drug from albumin binding sites by another drug results in an increase in free drug in the plasma and therefore an enhancement of the drug effect, an increase in its volume of distribution and an increase in the rate of metabolism of the drug and in the amount present in the glomerular filtrate. Such a displacement is only likely to be of clinical importance when the displaced drug has a narrow therapeutic index, when its effect is closely related to its plasma concentration and when the plasma concentration of free drug is appreciably increased. In clinical practice this only occurs when one or both of the drugs is more than 85% protein bound at therapeutic concentrations (*see* Table 1 Chapter 2). Such a situation exists when phenylbutazone, which has a very high affinity for plasma albumin, is prescribed for a patient on warfarin which, at therapeutic concentrations, is over 97% protein bound. This may result in a twofold increase in plasma warfarin predisposing the patient to haemorrhagic side effects, especially from the gastrointestinal tract.

At sites of action Tricyclic antidepressants and phenothiazines antagonise the active transport system for noradrenaline at sympathetic nerve terminals and in adrenergic neurones in the CNS. This carrier mechanism also transports the guanidinium hypotensive agents (guanethidine, debrisoquine, bethanidine) to their site of action inside sympathetic nerve terminals. Tricyclic antidepressants and phenothiazines therefore antagonise the hypotensive effects of these drugs by preventing them reaching their sites of action.

4. DRUG METABOLISM Hepatic drug metabolising enzyme systems have, in general, a low degree of specificity and are shared by many drugs. Drugs may interact at sites of metabolism and cause either an enhancement or reduction in the rate at which one or both drugs are metabolised.

Enzyme induction Certain drugs and chemicals are capable of causing an

increase in the smooth endoplasmic reticulum in liver cells and in the complement of mixed function oxidases located there (*see* Table 1).

Table 1

Drugs and chemicals that induce hepatic microsomal enzymes in man

phenobarbitone	phenylbutazone
other barbiturates	griseofulvin
carbamazepine	rifampicin
phenytoin	organochlorines (e.g. DDT)
glutethimide	
dichloralphenazone	
aspirin, caffeine, and codeine mixture	

Many other drugs have enzyme inducing properties in animals but seldom are these of importance in the concentrations achieved clinically. Furthermore, there are large differences in the enzyme inducing effectiveness of enzyme inducing drugs. Phenobarbitone and rifampicin are the most effective enzyme inducers in clinical practice and phenobarbitone is more effective than other barbiturates at equipotent hypnotic doses. Phenobarbitone has been shown to enhance the metabolism of many drugs being used therapeutically including digitoxin, warfarin, phenytoin, phenylbutazone, corticosteroids and alpha-methyl dopa. The consequence of enzyme induction is usually that for drugs metabolised by liver smooth endoplasmic reticulum enzymes (microsomal enzymes) there is an increase in the rate of metabolism and a fall in the plasma concentration of free drug and hence a reduction in drug effect. The maximal effect is usually a threefold increase in rates of metabolism and this develops over 7–10 days. For drugs that form active metabolites, however (*see* Table 3, Chapter 3), enzyme inducing drugs will cause an enhanced response.

An example of the dangers of this type of interaction occurred when barbiturates were the most commonly used hypnotics. A patient was admitted to hospital with a deep vein thrombosis and was anticoagulated with warfarin. He was also given a barbiturate hypnotic. A maintenance dose of warfarin was eventually established on the basis of the prothrombin time and was higher than the usual dose but not remarkably so. On leaving hospital, the warfarin was maintained at the established dose, but the hypnotic was stopped as the patient was alleged to sleep well at home. As a consequence of stopping the inducing agent, warfarin was metabolised less rapidly and accumulated over 1–2 weeks until a new equilibrium was established which was associated with a greatly prolonged prothrombin time. At this stage the patient developed a massive gastrointestinal haemorrhage.

This sequence has occurred on a number of occasions but is unlikely to occur when benzodiazepine hypnotics are used as these are poor inducing agents in man.

Enzyme inhibition Certain drugs may inhibit hepatic microsomal enzyme systems so decreasing the rate of metabolism of drugs metabolised by them. Some examples of this form of interaction are shown in Table 2.

Table 2

Examples of drugs whose metabolism is inhibited	*Inhibitors responsible*
ethanol	disulphiram
	chlorpropamide
pethidine	monoamine oxidase inhibitors
tolbutamide	chloramphenicol
antipyrine	oral contraceptives
phenytoin	sulthiame
	cimetidine
	disulphiram
	chloramphenicol
	dicourmarol
	isoniazid and PAS
warfarin	ethanol (variable effect as it may enhance warfarin metabolism)
	cimetidine
	phenylbutazone
6-mercaptopurine	allopurinol
paracetamol	salicylates

Enzyme inhibition outside the liver may also increase the duration of action of drugs. Thus monoamine oxidase inhibitors enhance the response to tyramine and dopamine (*see* Chapter 15). Alpha methyldopa hydrazine, a dopa decarboxylase inhibitor, prolongs the half-life of DOPA (*see* Chapter 16).

The consequence of this type of interaction is an accumulation in the plasma of the drug whose metabolism is inhibited until a new equilibrium is established, at a higher steady state concentration. If the parent drug is the active drug then there is an enhanced response; if the metabolite is the active drug then there is a reduced response.

5. DRUG EXCRETION

Drug ionisation Drugs that alter urine hydrogen ion concentration (pH) will alter the degree of ionisation of drugs that are weak acids or bases in the glomerular filtrate and hence the degree to which these drugs can diffuse across the renal tubule back into the plasma. Ammonium chloride acidifies the urine and increases the rate at which basic drugs such as amphetamine, ephedrine and pethidine are cleared by the kidney. Sodium bicarbonate and potassium citrate alkalinise the urine and enhance renal clearance of acidic drugs such as salicylates, phenobarbitone, sulphonamides and nalidixic acid.

This effect has been utilised in the treatment of drug overdosage to expedite the excretion of drugs such as aspirin and phenobarbitone (*see* Chapter 40).

Active transport of drugs by the renal tubule Both basic and acidic drugs may, like uric acid, be actively secreted and reabsorbed by the proximal tubule or undergo either process in the course of excretion (*see* Chapter 2). The specificity of these carrier sites is low and many weak acids such as salicylates, thiazides, sulphonamides, probenecid and penicillin, share the same carrier sites. If two such drugs are prescribed together, the secretion or reabsorption of the one with the lowest affinity for the carrier site will be reduced. Probenecid, a sulphonamide derivative, impairs the excretion of benzylpenicillin, increasing its half-life from 40 to 100 minutes. Phenylbutazone has a similar effect, as have acetylsalicylic acid and indomethacin, the latter two being less effective than probenecid and phenylbutazone. Probenecid also impairs the excretion of salicylate, the uricosuric agent sulphinpyrazone and that of their major metabolites.

Pharmacodynamic Interaction

In this type of interaction there is no alteration in the concentration of either drug in their receptor compartments. Examples of interactions of this nature are again best considered in terms of the sites at which they occur.

1. DRUG INTERACTIONS ON THE SAME TARGET ORGAN

(a) Same receptors Drugs that act at the same receptor sites, if prescribed together, may produce an additive effect or antagonise one another, depending on their relative concentrations at receptor sites, their relative affinities for these sites and the extent to which they are full or partial agonists or antagonists. Examples of such interactions are fully covered in texts on basic aspects of pharmacology.

Clinical examples include the antagonism of the respiratory depression and other central effects of morphine and related narcotic analgesics by the morphine antagonist naloxone (*see* Chapter 40) and the antagonism of the anticoagulant effects of warfarin by viramin K (*see* Chapter 33).

(b) Different receptors Drugs may interact on the same target organ but at different receptor sites.

Adrenaline activates the adenylcyclase system and causes an increase in cyclic 3-5AMP which then acts as the mediator of a number of the beta effects of adrenaline (*see* Chapter 11), e.g. relaxation of bronchial smooth muscle. Theophylline produces the same effect, an increase in cyclic 3-5AMP, by inhibiting phosphodiesterase, the enzyme responsible for cyclic 3-5AMP degradation and also causes bronchial smooth muscle relaxation. Drugs that inhibit different enzymes in a metabolic sequence commonly produce a synergistic effect. Trimethoprim, the dihydrofolic acid reductase antagonist, acts synergistically when prescribed with a sulphonamide (sulphamethoxazole) which inhibits folic acid synthesis (Chapter 35). Cytotoxic drugs used in the treatment of lymphatic leukaemia or malignant lymphomas may have an

additive effect on malignant cells by impairing different aspects of cell metabolism and at different periods in the cell cycle (Chapter 38).

Information on the sites of interaction of CNS depressant drugs is not available, but this is a very common drug interaction. Thus ethanol, both minor and major tranquillisers, anticonvulsants and tricyclic antidepressants may enhance each other's CNS depressant effect and cause drowsiness or coma.

2. DRUG INTERACTIONS AT DIFFERENT TARGET ORGANS The use of drugs that act on different target organs in combination is common practice in therapeutics. For example, in congestive cardiac failure, the positive inotropic agent digoxin is commonly administered with a diuretic which relieves the left ventricular work load by reducing the extracellular and plasma volume and hence venous return.

Hypotensive agents are usually given in combination, each lowering the blood pressure by actions at different sites. Thus, a thiazide diuretic, which dilates resistance vessels by a direct effect, may be prescribed with reserpine, alpha methyldopa or a guanidinium hypotensive agent, all of which reduce sympathetic nervous tone.

Adverse as well as therapeutic effects may be produced by this type of interaction. Diuretics all cause some degree of kaluresis and may cause hypokalaemia which enhances the cardiotoxic effects of digoxin. Patients on monoamine oxidase inhibitors may experience hypertensive crises after eating foods rich in the monoamines tyramine and dopamine or after taking alpha-receptor agonists. Hypertensive crises may also occur in hypertensive patients who take alpha-agonists while on the guanidinium hypotensive agents. Salicylates and phenylbutazone cause gastric erosions and decrease platelet stickiness. When prescribed in conjunction with anticoagulants they greatly increase the risk of haemorrhagic complications.

Consequences of drug interactions

1. An enhancement in response to one or both drugs.
2. A reduction in response to one or both drugs.
3. An alteration in response to one or both drugs.

Interactions that cause an enhanced, a reduced or an altered response are usually of clinical importance for

(a) drugs with a narrow therapeutic index or
(b) for drugs whose effects are closely related to their plasma concentration.

Warfarin fulfils both these criteria and is the drug most frequently considered in relationship to undesirable drug interactions. Drugs that enhance responsiveness to warfarin, such as those that increase its bioavailability, that displace it from plasma protein binding sites, reduce its rate of metabolism or impair haemostatic processes, all predispose to haemorrhagic side effects. Drugs that

reduce responsiveness by reducing its bioavailability or increasing the rate of warfarin metabolism or that increase the rate of synthesis of vitamin K dependent clotting factors, predispose to further thromboembolic phenomena.

An alteration in the quality of the response to a drug has most commonly occurred with MAOIs (*see* Chapter 15).

Predicting drug interactions

Possible drug interactions can be predicted from knowledge of the actions and mechanisms of action of drugs to be prescribed together. There are a large number of charts and tables available now showing possible drug interactions and their consequences. The probability of interactions occurring, however, and their clinical significance, is much more difficult to assess. The reasons for this are that drug interactions are concentration dependent and there are large interindividual differences in the pharmacokinetic parameters of many drugs and in responsiveness to their pharmacodynamic effects.

There are, however, a few predictable drug interactions. For example, when sulphamethoxazole and trimethoprim are prescribed in a fixed dose ratio of 5 to 1 the antibacterial effectiveness of the combination is always much greater than either drug alone (*see* Chapter 35). If isoniazid is administered alone in the treatment of pulmonary TB, resistant organisms emerge, usually within a few weeks of starting therapy. In nearly all instances PAS given concurrently with isoniazid will prevent or delay the emergence of resistant strains.

In circumstances in which the degree of interaction between two drugs is less easily predicted, an empirical approach must be adopted and the effect of adding a second drug to a treatment schedule carefully monitored, e.g. potassium requirement in patients on diuretics differs greatly between individuals with the same disorder and also for the same diuretic used in different disorders. Under such circumstances, the requirement for potassium is best evaluated by monitoring the plasma potassium concentration giving sufficient replacement to maintain a normal value (*see* Chapter 21).

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Chapter 10

Cholinergic and Anticholinergic Drugs

Acetylcholine (ACh) is the chemical transmitter of nerve impulses at autonomic ganglia, at parasympathetic neuroeffector sites, at some sympathetic neuroeffector sites and at the neuromuscular junction. There is strong evidence that ACh is a central transmitter, e.g. in the basal ganglia (*see* Chapter 16). The actions of ACh at peripheral cholinergic synapses are mimicked by the alkaloid muscarine at autonomic neuroeffector sites (muscarinic sites) and by the alkaloid nicotine at autonomic ganglia (nicotinic sites). There are both muscarinic and nicotinic synapses in the CNS but the role of these synapses is not established.

Drugs may affect cholinergic synapses by mimicking or enhancing the effects of ACh (cholinergic agonists and anticholinesterase agents especially) or they may antagonise the actions of ACh at muscarinic sites (antimuscarinic agents) or at autonomic ganglia (ganglion blocking agents) or at the neuromuscular junction (neuromuscular blocking agents). Although a great deal is known about cholinergic and anticholinergic drugs, only those aspects relevant to their use in therapeutics will be considered here.

CHOLINERGIC DRUGS

Cholinergic Agonists

Acetylcholine is rapidly hydrolysed by acetylcholinesterase (AChE) (Fig. 1) after being released from cholinergic nerve terminals, as AChE is present in

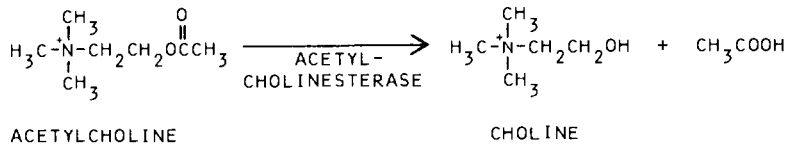


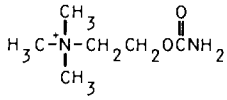
FIG. 1 Hydrolysis of acetylcholine by acetylcholinesterase.

abundant quantities at all cholinergic synapses. Furthermore AChE is present in high concentrations in Rbcs so that ACh is rapidly hydrolysed after i.v. administration. In view of the rapidity with which it is inactivated ACh is of no value therapeutically.

Cholinergic agonists (parasympathetic agents) are of two types, cholinesters

that are either not hydrolysed by AChE (carbachol, bethanechol) or are hydrolysed only slowly (methacholine) and alkaloids, of which pilocarpine is the most commonly used. These agents are most effective at mimicking the muscarinic effects of ACh. The cholinesters do not affect the eye or CNS when administered systemically as their quaternary structure limits access to these sites. They are little used clinically other than in eye-drops to cause miosis in the treatment of glaucoma.

Carbachol

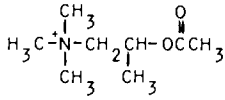


Carbachol causes contraction of the smooth muscle of the gastrointestinal tract, increasing gastrointestinal motility and contraction of the detrusor muscle. It does not affect the heart rate at doses affecting the bowel and bladder and only causes nicotinic effects at high doses. It causes pupillary constriction and contraction of the ciliary muscle only when applied topically to the eye.

Carbachol is not hydrolysed in the gut and is active orally in doses similar to those used subcutaneously. It should never be administered i.v. as after this route of administration it may cause cardiac dysrhythmias, diarrhoea, abdominal cramps, urinary and faecal incontinence, salivation and bronchoconstriction.

Clinical use Carbachol may be used in the treatment of the atonic bladder when there is no obstruction to urine outflow. Occasionally it is used to increase gastrointestinal tone, although bethanechol, which is very similar to carbachol, is usually preferred for this purpose.

Methacholine



Methacholine differs from carbachol in that it is more selective for the cardiovascular system, is hydrolysed by AChE and is relatively inactive orally. It delays atrio-ventricular conduction and may be effective in the treatment of supraventricular tachycardia, although it is seldom used for this purpose clinically. It dilates the blood vessels of the skin and may cause flushing.

Both carbachol (0·25–1·5% solution) and methacholine (10–20% solution) may be applied topically to the eye in the treatment of glaucoma.

Pilocarpine Pilocarpine is an alkaloid with muscarinic activity that is similar in its action to the cholinesters. In therapeutics it is used exclusively as a miotic agent (1–3% solution) applied topically to the eye.

Anticholinesterase Agents

An alternative approach to the administration of agents with effects similar to ACh, is to administer anticholinesterases that enhance the effects of endogenous

ACh by inhibiting AChE, the enzyme responsible for its metabolism. Unlike the cholinergic agonists, anticholinesterase agents enhance the effects of ACh at the neuromuscular junction, as well as the muscarinic effects.

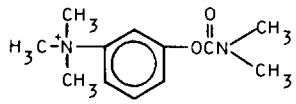
Acetylcholinesterase is widely distributed throughout the body. It is present at parasympathetic neuroeffector sites, in all preganglionic autonomic neurones, post ganglionic cholinergic autonomic neurones, and in motor neurones and the post-synaptic cleft of voluntary muscle and in Rbcs. It is also present in many neurones in the CNS. ACh has a high affinity for active sites on AChE and at the concentrations it achieves at cholinergic synapses under physiological conditions, is very rapidly hydrolysed by AChE and this rapid rate of hydrolysis is the principal factor accounting for its short duration of action. Butyrylcholinesterase (BuChE) which is also widely distributed, being present in high concentration in the plasma, does not hydrolyse ACh as rapidly as AChE and probably contributes little to its hydrolysis in physiological circumstances.

Types of anticholinesterases All agents that act as anticholinesterases compete with ACh for the active sites on AChE. Truly reversible anticholinesterase agents are not hydrolysed by the enzyme and the only example of this type of anticholinesterase used clinically is edrophonium. The two types of anticholinesterases of greatest importance therapeutically, the carbamates and the organophosphate compounds, both acylate AChE and are themselves hydrolysed during interaction with the enzyme.

Carbamates

Carbamates that are used clinically, include the alkaloid and tertiary amine physostigmine that was isolated from the Calabar bean, and the synthetic quaternary ammonium compounds neostigmine, pyridostigmine and various bisquaternary ammonium compounds, e.g. ambenonium. Of these neostigmine is the most widely used.

Neostigmine



The sequence of events in the inhibition of AChE by carbamates is as follows:

$$\text{AChE} + \text{carbamate} \rightarrow \underset{\text{enzyme}}{\text{carbamylated}} \xrightarrow{H_2O} \text{AChE} + \text{carbamic acid}$$

The carbamylated enzyme generally is much less stable than the phosphorylated enzyme, having a half-life of 20–40 minutes after physostigmine and neostigmine and of several hours after the bisquaternary carbamates.

ACTION

Neuromuscular junction In normal subjects transmission at this site is maximal and these agents cause no change except in high doses, but in

patients with myasthenia gravis they increase the muscle power of affected muscles. They also antagonise the actions of competitive neuromuscular blocking drugs such as curare. In high doses they cause muscular fasciculations and eventually paralysis, due to depolarisation of the post-synaptic membrane.

Muscarinic sites—the eye Anticholinesterases lower tension in the anterior chamber of the eye by causing constriction of the pupillary muscles which increases the patency of the canal of Schlemm and hence facilitates drainage of the aqueous humour. They also decrease aqueous humour formation. In the treatment of glaucoma carbamates are applied topically. Administered systematically, quaternary agents only affect the eye after high doses as they diffuse very slowly into the aqueous humour.

Other muscarinic effects are an increase in gastrointestinal motility causing nausea, colic and diarrhoea; increased tone of the detrusor muscle causing urgency of micturition and urinary incontinence; bradycardia, salivation, bronchoconstriction, bronchorrhoea and increased sweating.

Autonomic ganglia Diffusion is probably more significant than AChE at terminating the effects of ACh at autonomic ganglia so that carbamates have little effect on ganglionic transmission, although they antagonise the actions of the bismethonium ganglion blocking agents.

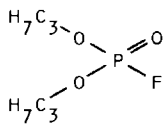
CNS The quaternary carbamates do not cause CNS effects as they do not penetrate the blood brain-barrier in sufficient concentrations at doses that produce pronounced peripheral effects. The tertiary ammonium agent physostigmine, which does cause CNS effects when administered systemically, is only used clinically as a miotic agent applied topically to the eye.

DRUG FATE Neostigmine, pyridostigmine and ambenonium are all poorly absorbed from the bowel, the oral dose being 10–30 times higher than the equipotent parenteral dose. They are distributed in the extracellular space and do not reach the brain or aqueous or vitreous humours.

Neostigmine is excreted as hydroxylated and conjugated metabolites in the urine after oral administration, metabolism taking place principally in the liver, but after parenteral injection most of the drug is excreted unchanged in the urine. Pyridostigmine is mostly excreted unchanged in the urine after oral administration. All the quaternary carbamates have short half-lives, less than 3 hours after i.m. injection. The longer duration of ambenonium is due to the slow rate of hydrolysis of the carbamylated enzyme it forms with AChE and not to a longer half life of the drug itself.

ADVERSE EFFECTS The muscarinic effects outlined above are the principal adverse effects when these agents are being used in the treatment of myasthenia gravis. An overdose of anticholinesterase agents in myasthenia gravis causes an exacerbation of the muscle weakness that does not respond to edrophonium (*see* below). There is no effective reactivator of carbamylated AChE.

Organophosphates



DFP

The organophosphate anticholinesterases in clinical use are dialkylphosphates and the most commonly used of these are diisopropylfluorophosphate (DFP) diethyl-4-nitrophenylphosphate (paraoxon) and tetraethylpyrophosphate (TEPP), all of which are lipid-soluble compounds, and the quaternary compound ecothiopate.

The sequence of events in the inhibition of AChE by these agents is as follows:—

AChE + dialkylphosphate → phosphorylated AChE + H_2O → AChE + phosphoric acid

With the exception of the phosphorylated enzyme formed by diethylphosphates, e.g. paraoxon, which undergoes appreciable spontaneous hydrolysis, there is negligible spontaneous reactivation of the phorphorylated AChE formed by most organophosphates and recovery of normal AChE activity is dependent on synthesis of new AChE, which takes several weeks. The phosphorylated enzyme can be hydrolysed (reactivated) by various agents of which the oximes are the most effective. The reactivating agent has to be administered within a few hours of the organophosphate, as the phosphorylated enzyme becomes unreactivable after this time due to loss of an alkyl or aloxy group. This process is known as ageing.

ACTIONS These are similar to those of the carbamates, but their duration of action is very much longer by virtue of prolonged AChE inhibition. Lipid soluble organophosphates may cause pronounced central effects.

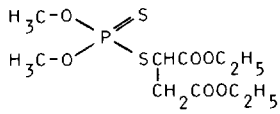
DRUG FATE The lipid soluble organophosphates are rapidly absorbed, widely distributed and rapidly metabolised, mostly by phosphorylphosphatase, to inactive metabolites. The duration of AChE inhibition of these compounds far outlasts the duration of the active drug in the body.

ADVERSE EFFECTS These are similar to those of the carbamates, nausea, vomiting, colic, salivation, diarrhoea, urinary incontinence and bradycardia. Central nervous system symptoms of dizziness and vivid dreaming are also common. In high doses, convulsions, neuromuscular paralysis and central depression of respiration occur, respiratory failure usually being the cause of death in fatal cases.

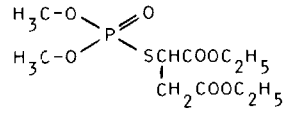
Neurotoxicity Fluorine-containing organophosphates, such as DFP, rarely cause axonal degeneration and demyelination of both central and peripheral neurones, which may present as a peripheral neuropathy or as a spastic

paraplegia. This syndrome, which is independent of AChE inhibition, is similar to that caused by triarylorganophosphates e.g. triorthocresolphosphate.

ORGANOPHOSPHATE POISONING AND TREATMENT Organophosphates are highly effective insecticides, malathione being the most commonly used in the UK. The parent compound is inactive in insects and in man, but is rapidly converted by insects to the potent anticholinesterase agent malaoxon.



Malathione



Malaoxon

In man, conversion to the active metabolite is slow in comparison to the metabolic processes that inactivate malathione so that it is selectively toxic to insects.

In areas of the world where organophosphates are widely used in agriculture, cases of poisoning are not uncommon due to heavy exposure of workers using these compounds who do not take adequate precautions. Signs of poisoning are pronounced fasciculations of all muscles and neuromuscular weakness, salivation, bronchoconstriction and bronchorrhoea, hypotension, sweating and in severe cases, cyanosis and convulsions.

If ventilation is impaired tracheal intubation, sucking out of secretions and positive pressure respiration is the first essential step in therapy. Atropine sulphate (2–4 mg i.v.) will decrease the muscarinic and some of the central effects. Its effect on the pupil may be monitored and it is usually found necessary to repeat the dose every 30–60 minutes to maintain a fully dilated pupil for several hours after poisoning.

The peripheral but not the central effects of organophosphates, are rapidly reversed by the quaternary oxime reactivators, of which pralidoxime (P_2AM) has been most widely used clinically. If these agents are given within a few hours of poisoning (e.g. 0·5–1·0 g of pralidoxime given slowly i.v.), they cause a rapid improvement of both muscarinic and nicotinic effects and should be repeated if signs recur after a period of improvement. The bisquaternary oximes trimedoxime and obidoxime are more potent reactivators than P_2AM but may cause hypotension in high doses through a ganglion blocking effect.

Clinical uses of anticholinesterase agents

Myasthenia gravis

The cardinal symptom in myasthenia gravis is that skeletal muscles tire easily. When this condition is sufficiently severe, signs of motor weakness develop, characteristically affecting extra ocular, bulbar, neck, limb girdles, distal limbs and trunk in that order. Electromyographic (EMG) studies show that the muscle

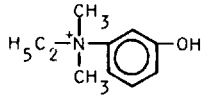
action potential provoked by a single nerve stimulus is of normal amplitude, but the amplitude falls with repeated stimuli.

Studies on the motor end plate of myasthenic patients have shown that there is a fall in the amplitude of consecutive end plate potentials (epps) which is due either to a fall in the size of the quanta of ACh released from the motor nerve terminal in response to a nerve action potential, or a decreased responsiveness of the motor end plate to ACh. The pathogenesis of myasthenia gravis remains uncertain, but there is now a large body of evidence suggesting that the disease has an autoimmune basis and that antibodies are formed to elements of the neuromuscular junction which reduces the number of cholinoceptors on the motor end plate. It is therefore probable that there is both a pre- and post-junctional component to the disordered function of the neuromuscular junction in this condition.

ANTICHOLINESTERASE THERAPY Anticholinesterases are the most effective drugs in the treatment of most cases of myasthenia gravis. Inhibition of AChE on the post synaptic membrane prolongs the duration of action of ACh released from cholinergic nerve terminals and, as a consequence, prevents the fall in amplitude of consecutive end plate potentials that occurs in untreated patients.

In mild and moderate cases of myasthenia, the diagnosis may be confirmed by means of the truly reversible anticholinesterase agent, edrophonium, which competitively inhibits AChE, but is unchanged by the drug-enzyme interaction.

Edrophonium



The edrophonium-AChE complex dissociates very rapidly so that the AChE inhibition does not outlast the presence of the drug in the ECS. When given as a bolus i.v. affected muscles regain normal strength after 1–3 minutes, the drug concentration at enzyme sites rapidly falling to subinhibitory values as the drug is redistributed in the ECS. Its short duration of action makes it unsuitable for maintenance therapy.

Treatment of myasthenia gravis is usually started with neostigmine 15 mg/8 hours and the dose and dose interval are adjusted according to the patient's response. Dose requirements vary enormously and many patients require a dose at 2–4 hour intervals. The dose required by any one patient may also fluctuate considerably. Pyridostigmine, or the longer acting ambenonium, may be added to neostigmine to maintain muscle strength for longer periods and especially through the night. Organophosphates have not proved as effective at controlling the muscle weakness and cause more side-effects, especially central effects (*see* above).

Muscarinic side effects are antagonised by atropine, 0·6 mg orally 6–8 hourly, but this is usually only necessary when higher doses of anticholinesterase agents

are used. Moreover, tolerance eventually develops to these side effects so that atropine therapy is not always necessary in the long term.

Overdosage An overdose of anticholinesterase is described as a 'cholinergic crisis' when inhibition of a high percentage of AChE at the neuromuscular junction causes excessive accumulation of ACh at the post-synaptic membrane and prolonged depolarisation. In a cholinergic crisis the patient's weakness is severe, pupils are usually constricted, fasciculations are seldom obvious and the weakness is not improved with edrophonium. If ventilation is inadequate, tracheal intubation and positive pressure respirations, withdrawal of anticholinesterase therapy and adequate doses of atropine usually result in a restoration of muscle power and of responsiveness to anticholinesterases within 24–48 hours. The clinical manifestation of too low a dose of anticholinesterase, a 'myasthenic crisis', is very similar to a cholinergic crisis, but in mild and moderate cases, can readily be distinguished from it as muscle strength is improved by edrophonium.

In severe cases of myasthenia, especially when onset is in late middle and old age, ACTH or oral glucocorticosteroids may be beneficial. They often cause an initial exacerbation, when patients may require positive pressure ventilation for a period, but in a majority of cases this is followed by a prolonged period of improvement. The initial period of exacerbation may be avoided by starting therapy with a low dose and working up slowly to the high maintenance doses that are usually required. Immunosuppressive drugs, e.g. azathioprine and cyclophosphamide may also cause symptomatic improvement, but their place in therapy has not been fully established.

Thymomas occurs in a proportion of patients with myasthenia gravis and such patients benefit considerably from thymectomy. Failure to respond satisfactorily to medical therapy is usually taken as an indication for thymectomy as many patients benefit from removal of the thymus, even if there is no thymic tumour.

ALTERED DRUG RESPONSIVENESS IN MYASTHENIA GRAVIS Muscle weakness in patients with myasthenia gravis may be made worse by neuromuscular blocking drugs such as curare and pancuronium, that are competitive antagonists of ACh at the neuromuscular junction. Other drugs that have a similar effect include magnesium ions, the antibacterial agents, streptomycin, neomycin, kanamycin, gentamicin and bacitracin, quinine, quinidine and local anaesthetics. Drugs that depress the respiratory centre may, in severe cases, reduce ventilation in myasthenic patients, e.g. narcotic analgesics and hypnotics, minor tranquillisers and ethanol.

Myasthenic patients have decreased sensitivity to the depolarising neuromuscular blocking agent suxamethonium.

Eaton–Lambert syndrome

The Eaton–Lambert or myasthenic syndrome is a disorder of neuromuscular

transmission in which muscle weakness and fatiguability is associated with a delay in the development of the maximum strength of a muscle contraction. The condition is usually associated with an oat cell carcinoma of the bronchus. It can be distinguished from myasthenia gravis on EMG in that a single stimulus causes a muscle action potential of reduced amplitude, but this increases with repetitive stimulation. In the Eaton–Lambert syndrome the release of ACh from cholinergic nerve terminals is impaired. Anticholinesterases are not as effective as in myasthenia gravis, but muscle strength may be improved by guanidine which acts by facilitating ACh release.

Glaucoma

Anticholinesterase agents, applied topically to the eye, are the treatment of choice in the emergency treatment of acute congestive glaucoma and in the long term management of chronic wide angle glaucoma. Physostigmine (1% solution), neostigmine (5% solution) or ecothiophate (0·1%–0·25%) may be used alone or in combination with a cholinergic agonist such as pilocarpine or methacholine. The dose and dose interval is adjusted to obtain an adequate miosis. Local side effects are headache, facial pain, blurring of vision of the affected eye and congestion of the corneal and iris vessels.

Other uses

Neostigmine may occasionally be used in the treatment of atony of the gastrointestinal tract or urinary bladder.

ANTICHOLINERGIC DRUGS

Anticholinergic drugs are drugs whose therapeutic effects are due to antagonism of acetylcholine at cholinergic synapses. Owing to differences between cholinoceptors at different sites, there is no one group of drugs that antagonises the actions of ACh at all cholinergic synapses, but there are agents that are specific for muscarinic sites, for the neuromuscular junction of voluntary muscle and for autonomic ganglia.

Antimuscarinic Drugs

The alkaloid esters atropine and scopolamine occur naturally in various plants such as deadly nightshade (*Atropa belladonna*), Jimson weed (*Datura stramonium*) and in black henbane (*Hyoscyamus niger*) and have been used in therapeutics since the earliest times that therapeutic practices were recorded. Both atropine, which is a racemic mixture of D and L-hyoscyamine, only the L-form being pharmacologically active, and scopolamine which is L-hyoscine, are still used clinically, atropine being the active component of preparations containing belladonna.

There are now a large number of synthetic antimuscarinic agents (Table 2), some differing little from atropine, some are antihistamines, some phenothiazines and others quaternary compounds. As the differences between

Table I
Cholinergic agents

Drug	*Dose*	*Route*	*Dose interval*
Carbachol	0·2–0·8 mg	Oral	6–8 h
	0·25	s.c.	
	0·25–1.5%	T	
Methacholine	50–100 mg	Oral	6–8 h
	2·5–10	s.c.	
	20%	T	
Bethanechol	10–25 mg	Oral	6–8 h
Pilocarpine	0·5–3%	T	

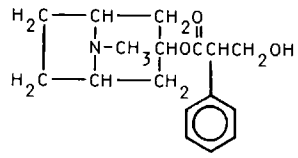
Anticholinesterases

Carbamates	*Dose*	*Route*	*Dose interval*
Physostigmine	1%	T	
Neostigmine	15–45 mg	Oral	3–4
	0·5–2·5	s.c.	
	5%	T	
Pyridostigmine	60–120 mg	Oral	4–6
	1–2	s.c.	
Ambenonium	5–25 mg	Oral	6–8
Organophosphates			
DFP	0·005–0·2%	T	1–7 days
Ecothiophate	0·1–0·25%	T	3–7 days

T = topical to the eye

atropine and alternative antimuscarinic agents are small, the clinical pharmacology of atropine will be considered in detail and that of alternative agents contrasted with it.

Atropine



Atropine is a competitive antagonist of ACh at muscarinic receptors, in that it causes a parallel shift to the right in the log-dose response curve of ACh in intact tissue preparations with muscarinic receptors. After exposure to atropine *in vitro* tissues do not return to a pretreatment sensitivity to ACh for many hours,

indicating that atropine dissociates slowly from muscarinic receptors. Atropine and other non-quaternary antimuscarinic agents have no ganglion or neuromuscular blocking actions, but the quaternary antimuscarinic drugs are weak ganglion blocking agents.

ACTION The clinical effects of atropine are dependent on the degree of parasympathetic tone and are usually most evident when this is high prior to drug administration.

Gastrointestinal tract Antimuscarinic agents decrease both mixing and propulsive movements of the gut and may cause constipation in normal subjects and decrease the frequency of bowel motions in patients with diarrhoea. Even in high doses atropine does not suppress all bowel motility.

Urinary bladder The motility of the detrusor muscle is reduced by atropine and sphincter muscle tone is increased.

The eye Atropine causes dilatation of the pupil (mydriasis), relaxation of the ciliary muscle and paralysis of accommodation (cycloplegia) with impairment of near vision. These effects only occur at high therapeutic doses when the drug is given systemically.

The heart Acetylcholine hyperpolarises the sinus node and causes a bradycardia. Low doses of atropine (0·5 mg or less i.m. or i.v.) also cause a bradycardia through a cholinergic effect. At higher doses it causes a tachycardia at rest when parasympathetic tone is the principle factor determining heart rate.

Bronchial smooth muscle ACh causes bronchoconstriction and an increase in bronchial secretions. Antimuscarinic agents antagonise these effects and cause bronchodilatation and a reduction in bronchial secretion in asthmatic patients.

Exocrine glands Salivation and sweating are reduced by therapeutic doses of atropine and it has been used for this purpose in the treatment of sialorrhoea and hyperhydrosis. Antimuscarinic agents in maximally effective doses, reduce gastric hydrogen ion secretion by 60% and also reduce pepsin secretion, but they do not alter the pH of the gastric contents.

CNS Atropine reduces the bradykinesis, has little effect on the tremor and no effect on the hypokinesia of patients with parkinsonism. These effects are probably due to antagonism of ACh at cholinergic receptors in the globus pallidus (*see* Chapter 16).

Antimuscarinic agents, especially scopolamine, are effective at treating and preventing motion sickness due to an effect on the vestibular pathways in the brain (*see* Chapter 30).

Non-quaternary antimuscarinic agents usually have a slight depressant effect on the CNS at therapeutic doses and may induce drowsiness and a slow wave pattern on the EEG. Scopolamine and diphenhydramine are occasionally used in combination with other CNS depressants as hypnotic agents. This effect is

more pronounced with scopolamine than with atropine, the latter drug sometimes having a weak stimulant effect at low therapeutic doses.

DRUG FATE Atropine and all lipid soluble antimuscarinic agents are rapidly absorbed and reach the CNS and all muscarinic sites. Only 15–25% of an oral dose of a quaternary antimuscarinic drug is absorbed and these drugs do not reach the CNS in effective concentrations when administered at doses that block muscarinic receptors at other sites. Atropine is mostly excreted as metabolites, less than 30% of a parenteral dose being excreted unchanged in the urine. Ninety per cent of a single dose is excreted in 24 hours in the urine. After subcutaneous administration of a therapeutic dose (0·6–1·0 mg), the maximal effect at muscarinic sites, occurs at 15–30 minutes and lasts 5–7 hours. The effects of atropine on the eye develop more slowly and outlast those elsewhere. They may be detectable 24 hours after systemic administration and for 7–10 days after topical administration to the eye, probably due to the slow turnover of the aqueous humour.

ADVERSE EFFECTS The lack of specificity of antimuscarinic agents for particular groups of muscarinic receptors, means that any effect desired for therapeutic reasons is associated inevitably with side effects due to antagonism of ACh at all other muscarinic sites. At low doses dry mouth is the most common side effect and at higher doses tachycardia with palpitations, thirst, dilatation of the pupil with photophobia and eventually blurring of near vision. Constipation is an occasional symptom, urinary retention may be precipitated in patients with bladder neck obstruction and acute congestive glaucoma in patients predisposed to or with pre-existing glaucoma. In hot weather and in subjects undertaking vigorous exercise, the impairment of sweating caused by these drugs may contribute to a rise in body temperature. Symptoms of abnormal CNS function occur in approximately 20% of patients on recurrent doses of non-quaternary antimuscarinic agents and are said to be more common in elderly patients and in those with organic brain disease. They include an acute confusion state, increased excitement with delirium and psychotic episodes. These signs are readily reversed by a lipid soluble anticholinesterase agent such as physostigmine (1–4 mg s.c. or i.m.). Atropine poisoning is rare but is occasionally fatal. A dose of 1 mg of atropine causes a dry mouth, pupillary dilatation, blurred vision and dry flushed skin. After 2–4 mg there is an increase in pulse rate, blood pressure and respiration rate and over 5 mg, restlessness, agitation, clouding of consciousness, disorientation, hallucinations and eventually coma.

CLINICAL USE

As a mydriatic Short-acting antimuscarinic agents such as cyclopentolate (0·1–1·0%) and homatropine (1–2%) are used to dilate the pupil for ophthalmic examination of the lens and fundus occuli. Atropine (1%) is used as maintenance therapy in iridocyclitis to prevent adhesions forming between the iris and lens. Glaucoma and a chronic conjunctivitis are the major complications of chronic therapy and, rarely, systemic effects develop as a

consequence of swallowing excess topical application that drains into the mouth via the tear ducts.

As premedication An antimuscarinic agent, usually scopolamine, is administered to patients within 1–2 hours of a general anaesthetic to decrease bronchial secretions, maintain airway patency and to antagonise any increase in vagal tone that may result from intraperitoneal manipulations.

Peptic ulceration Antimuscarinic agents are occasionally useful in the symptomatic relief of duodenal and gastric ulcers (*see* Chapter 30).

Diarrhoea Antimuscarinic agents decrease abdominal colic and the frequency of bowel motions in diarrhoea. Atropine is usually given with codeine or a related compound for this purpose.

In cardiac dysrhythmias Atropine (0·4–1·0 mg i.v.) increases heart rate in sinus bradycardia and as a consequence cardiac output and blood pressure if the latter is reduced. It may also abolish ventricular extrasystoles and ventricular tachycardia if these are secondary to re-entrant phenomena (Chapter 20). It has been most commonly used for this purpose in patients who develop a bradycardia after a myocardial infarct, but is of little value unless the bradycardia is associated with hypotension or a ventricular dysrhythmia, as it may occasionally cause ventricular tachycardia or ventricular fibrillation. It is seldom of value in chronic maintenance therapy of heart block.

In parkinsonism Antimuscarinic agents are used as adjuncts to L-dopa (*see* Chapter 16), those most commonly used being benzhexol (trihexyphenidyl), orphenidrine and procyclidine. They are also used in the treatment and prophylaxis of drug-indiced parkinsonism.

Motion sickness Scopolamine is highly effective in the prophylaxis of motion sickness, but antimuscarinic agents with antihistamine activity, dimenhydrinate, cyclizine and meclizine, are most commonly used for this purpose.

Asthma Antimuscarinic agents e.g. atropine methyl nitrate and ipratropium, administered as a metered aerosol, cause bronchodilation and a reduction in bronchial secretions in asthmatic patients. The onset of action (30–60 minutes) is slower than that of $beta_2$ adrenoceptor agonist but the duration of action (3 hours) is longer. Dry mouth is the only adverse effect commonly experienced, other systemic adverse effects of antimuscarinic agents very seldom being evident when they are administered by inhalation. Most aerosols, but not ipratropium, contain either adrenaline or isoprenaline. Their place in the management of asthma has not been established, but they are likely to be an alternative to $beta_2$ adrenoceptor agonists.

CHOICE OF ANTIMUSCARINIC AGENT There is no clinical evidence that synthetic antimuscarinic agents are more selective for one group of muscarinic agents than another or that a desired therapeutic effect is achieved at doses that cause fewer side effects than atropine. Quaternary compounds do not cause CNS symptoms and have less of an effect on the eye when administered systemically and may be

preferred in the treatment of gastroinestinal disorders, but are ineffective in parkinsonism and in motion sickness. Otherwise, antimuscarinic agents are chosen on account of their difference in side effects, e.g. hyoscine or promethazine are administered in preference to other drugs in premedication when drowsiness is desirable but are not used in conditions such as motion sickness when drowsiness is undesirable. Agents that do not cause drowsiness, e.g. the antihistamines meclazine and cyclizine are usually preferred in motion sickness.

Table 2
Examples of antimuscarinic agents

		Oral dose
Belladonna alkaloids		
atropine		0·4–1·0 mg
scopolamine		0·4–1·0 mg
Synthetic agents		
Non-quaternary	homatropine	ophthalmic
	cyclopentolate	use only
	trihexyphenidyl	2–5 mg
	benztropine	0·5–2
	procyclidine	2–5
Quaternary	propantheline	7·5–15
	poldine	4
Phenothiazines		
promethazine		12·5–50
ethopropazine		10–100
Antihistamines		
see ethanolamine, piperazine	antihistamines chapter 35.	

Ganglion Blocking Agents

The ganglion blocking agents compete with ACh for cholinergic receptors on the ganglionic post synaptic membrane and prevent depolarisation of the membrane by ACh and the initiation of a post ganglionic nerve action potential. As a consequence, they block both sympathetic and parasympathetic postsynaptic neurones.

Ganglion blocking agents available for clinical use include the bisquaternary ammonium compounds hexamethonium and pentolinium, the sulphonium compound trimethaphan and the tertiary amines mecamylamine and pempidine.

Ganglion blocking drugs were introduced to clinical medicine in the late 1940s and were the first effective agents in the treatment of moderate and severe hypertension. They are now little used, other than in hypertensive crises and in

anaesthesia, as there are equally effective hypotensive agents that produce fewer side effects (*see* Chapter 23).

ACTION

Sympathetic blockade This results in vasodilation of resistance and capacitance vessels, with a consequent fall in both venous return and hence cardiac output, and in peripheral resistance. The net result is a fall in BP. The hypotensive effect is maximal when sympathetic tone is high, i.e. when the patient is standing. There is also an increase in blood flow to the skin, but a reduction to the renal, coronary and cerebral vascular beds.

Parasympathetic blockade This results in dry mouth, reduced tone and motility of the gastrointestinal tract with constipation, reduced detrusor tone with hesitancy of micturition and urinary retention, mydriasis and cycloplegia with blurred vision and impotence. There is a reduction in sweating and in gastric and pancreatic secretions.

DRUG FATE The bisquaternary ammonium compounds are poorly and erratically absorbed from the bowel, only 5–30% of an oral dose being absorbed and parenteral doses being approximately one tenth equipotent oral doses. They are confined to the ECS and do not reach the brain and are excreted unchanged in the urine by glomerular filtration. The sulphonium agent, trimethaphan, is only administered by i.v. infusion as it has a very short duration of action and is excreted unchanged in the urine.

Mecamylamine and pempidine are readily absorbed from the bowel and have a larger volume of distribution than the quaternary compounds reaching the brain and CSF. They are excreted unchanged in the urine at a rate that varies inversely with urinary pH. The mean half-life for pempidine in the plasma is 2 hours and this increases in patients with impaired renal function.

ADVERSE EFFECTS Postural hypotension and symptoms of parasympathetic blockade are inevitable side effects, the most serious being fainting, renal failure due to reduced renal perfusion, paralytic ileus and urinary retention. Some degree of tolerance develops to both the hypotensive and other effects.

CLINICAL USE

Hypertensive crises Trimethaphan is occasionally used as a hypotensive agent in severe hypertension, usually when other drugs have failed to reduce the BP (*see* Chapter 23). The drug is given by continuous i.v. infusion with the head of the bed elevated. Trimethaphan is preferred to other ganglion blocking drugs as it also has a direct vasodilator effect. Ganglion blocking drugs have no place in the routine management of hypertension.

In anaesthesia Ganglion blocking drugs are occasionally used in anaesthesia to lower BP.

Neuromuscular Blocking Agents

The normal sequence of events leading to a muscle contraction is that a nerve

Table 3
Ganglion blocking agents

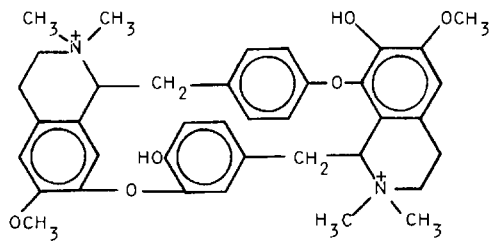
Drug	*Adult daily dose*	*Route*	*Dose interval*
Hexamethonium	125–500 mg	Oral	6–8
Pentolinium	60–200	Oral	6–8
	2·5 mg initial	s.c. i.v.	as required
Mecamylamine	2·5–10 mg	Oral	6–8
Pempidine	5–10	Oral	6–8
Trimetaphan	1–15 mg/min	i.v.	

action potential travels down a motor neurone and releases a fixed quanta of ACh from the nerve terminal. ACh interacts with cholinoceptors on the motor end plate depolarising the end plate, each quanta of ACh causing a miniature end plate potential (mepp). The end plate potential (epp) is the net effect of a large number of mepps and when the amplitude of the epp passes a critical value, a muscle action potential is initiated and the muscle contracts. Neuromuscular blocking agents are drugs that interrupt this sequence by antagonising ACh at cholinoceptors on the motor end plate and are classified in terms of the changes in the polarity of the motor end plate that accompanies neuromuscular blockade.

Non-depolarising Neuromuscular Blocking Agents

Non-depolarising agents compete with ACh released from motor nerve terminals for cholinergic receptors on the motor end plate. There is no reduction in the size or number of quanta of ACh released in response to the nerve action potential, but the amplitude of epp is reduced and when enough blocking agent is present, the epp is not sufficient to initiate a muscle action potential. The motor end plate therefore remains fully polarised during neuromuscular paralysis. The paralysis can be overcome by an anticholinesterase agent such as neostigmine.

D-Tubocurarine



Although curare alkaloids were brought to Europe from South America in the 16th century, and their pharmacology investigated in the 19th century, it was

not until the 1940s that they were used clinically as muscle relaxants. There are a number of alkaloids of curare, derived from several species of plants that are found in South America, of which only D-tubocurarine and alcuronium, a dialyl derivative of toxiferine, are used clinically.

ACTION A bolus (3–15 mg) of D-tubocurarine causes flaccid paralysis of the muscles of the eye, the hands and feet, the head, neck, trunk and limbs, the intercostal muscles and diaphragm, in approximately that order, so that the muscles of respiration, especially the diaphragm, are affected last. There are interindividual differences in responsiveness to D-tubocurarine, and responsiveness is enhanced by prior admission of a depolarising neuromuscular blocking agent.

DRUG FATE D-tubocurarine is a quaternary compound that is only administered i.v. for clinical purposes. It is distributed principally in the ECS, although it achieves concentrations in skeletal muscle similar to that in plasma and is excreted unchanged in the urine.

The renal clearance rate is similar to that of urea and a small proportion of a dose is excreted in the bile. Metabolism is negligible. The fall in the plasma drug concentration with time is triphasic, the slowest phase having a half-life of 2 hours. In renal failure, there is only a slight decrease in the rate of clearance from the plasma, presumably due to an increase in biliary excretion.

The time course of neuromuscular blockade follows closely that of d-tubocurarine in the plasma. Onset is within 1–2 minutes after a therapeutic dose given as a bolus, paralysis lasting 20–40 minutes

ADVERSE EFFECTS

Respiratory failure Although the muscles of respiration are the last to be affected, they are usually paralysed after doses of D-tubocurarine necessary for most surgery, and if artificial respiration is not instituted, death from hypoxia ensues. The quaternary nature of curare prevents its access to the CNS and it has no central effects, respiratory failure being due solely to paralysis of the respiratory muscles.

Histamine release D-tubocurarine can release histamine from intracellular sites and cause hypotension, bronchospasm and urticaria.

Drug interactions Enhanced effect: anaesthetic agents that stabilise the motor end plate, e.g. ether, halothane and cyclopropane, enhance the neuro blocking action of d-tubocurarine and decrease the dose requirement. Drugs that exacerbate muscle weakness in myasthenia gravis (*see* page 122) also enhance the effects of D-tubocurarine.

Antagonism Anticholinesterase agents antagonise the actions of D-tubocurarine. Neostigmine (1–3 mg i.v.) reverses the effects of a therapeutic dose of D-tubocurarine after anaesthesia.

CLINICAL USE

In anaesthesia D-tubocurarine or an alternative neuromuscular blocking

agent is used to maintain muscle relaxation during surgery, allowing lower doses of general anaesthetics to be used. The drug is given i.v., although it can be given i.m., but should only be given to patients already intubated or when facilities for tracheal intubation and positive pressure ventilation are readily available. As there are large differences between patients responsiveness, a small dose (3–5 mg) is used initially and the dose increased until the desired degree of muscle relaxation is achieved.

Other uses D-tubocurarine may be used in the treatment of tetanus and in status epilepticus in conjunction with thiopentone, when the same precautions should be taken as for its use in anaesthetics.

Alcuronium does not differ from D-tubocurarine in its clinical pharmacology. Dimethylcurarine is more potent and has a slightly shorter duration of action, but is otherwise very similar.

Gallamine Gallamine is identical to D-tubocurarine in its effects on neuromuscular transmission. It is a triquaternary compound and is excreted unchanged in the urine by glomerular filtration and has a plasma half-life in patients with normal renal function of 70–80 minutes.

Gallamine differs from D-tubocurarine in that it does not release histamine from histamine stores. It causes an increase in heart rate, in BP and in peripheral resistance and left ventricular work when used with general anaesthetics, due to a decrease in vagal tone, secondary to ganglion blockade.

Pancuronium Pancuronium is a bisquaternary steroidal compound that causes non-depolarising neuromuscular blockade, similar to D-tubocurarine, but is 5–10 times more potent. It has a similar duration of action in equipotent doses, but has advantages over D-tubocurarine and gallamine in that it does not release histamine or cause bronchospasms of hypotension and has no ganglion blocking action.

Depolarising Neuromuscular Blocking Agents

Depolarising neuromuscular blocking agents of which suxamethonium is most frequently used, block neuromuscular transmission at doses that depolarise the motor end plate. This type of blockade is enhanced rather than antagonised by anticholinesterase agents.

Suxamethonium Suxamethonium is a bisquaternary ester (succinyl dicholine) that causes neuromuscular paralysis within 1 minute of i.v. injection (10–30 mg) the sequence of muscles affected being similar to that of D-tubocurarine and the blockade wears off within five minutes.

DRUG FATE Like other neuromuscular blocking agents, suxamethonium is only used i.v. It is distributed in the ECS and is very rapidly hydrolysed to succinyl monocholine and choline by plasma and tissue BuChE (*see* Chapter 5—Pharmacogenetics). Succinyl monocholine has less than one twentieth the neuromuscular blocking effect of the parent ester. Very little suxamethonium is

excreted unchanged in the urine. In patients with genetically determined abnormality or absence of BuChE in plasma and tissues, the response to conventional doses of suxamethonium is prolonged for several hours (*see* Chapter 5).

ADVERSE EFFECTS

Muscle pains Approximately half the patients who receive suxamethonium experience an aching pain in one or more groups of muscles on recovery from the anaesthetic. These may be prevented by prior administration of a non-depolarising neuromuscular blocking agent.

Bradycardia Suxamethonium has a ganglion stimulating effect and causes an increase in vagal tone.

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Chapter 11

Adrenergic Receptor Agonists and Antagonists

The cathecholamines noradrenaline, adrenaline and dopamine are endogenous substances implicated in a large number of physiological and pathological processes. Drugs that modify responses to them are widely used in clinical medicine, especially in the treatment of disorders of the cardiovascular, respiratory and nervous systems.

Physiology of Catecholamines

Disposition Noradrenaline (NA) is the neurotransmitter at sympathetic post-ganglionic synapses except in sweat glands. It is also present in a proportion of neurones in the hypothalamus and brain stem where is may be of importance in the regulation of mood, temperature and ovulation. Neurones in which NA is the transmitter are known as adrenergic neurones. Adrenaline is present in the adrenal medulla and in the brain stem. It has no known local neurotransmitter role, but when released into the blood stream has effects at many sites.

Dopamine (DA) is located in small amounts at all sites of NA synthesis. It is present in highest concentration in neurones which have their cell bodies in the substantia nigra and terminate in the corpus striatum. Dopamine probably acts as a neurotransmitter at these terminals (*see* Chapter 16).

Synthesis and storage Noradrenaline is synthesised from tyrosine in adrenergic nerves by the steps shown in Fig. 1 and is stored there in vesicles. In dopaminergic neurones there is no dopamine beta-hydroxylase and in the adrenal medulla the enzyme phenylethanolamine methyl transferase converts NA to adrenaline.

Release, inactivation and turnover Depolarisation of adrenergic nerve terminals, i.e. the nerve impulse, causes release of NA from vesicles into the synaptic cleft where it interacts with adrenoceptors on the post-synaptic membrane. Noradrenaline is removed from the synaptic cleft by uptake into adrenergic nerve terminals (uptake-1) or into other tissues, e.g. smooth muscle (uptake-2) or it is metabolised by catechol-O-methyl transferase (COMT). Of these processes, uptake-1 is quantitatively the most important. In the cytoplasm of adrenergic neurones, NA is deaminated by the mitochondrial enzyme monoamine oxidase (MAO).

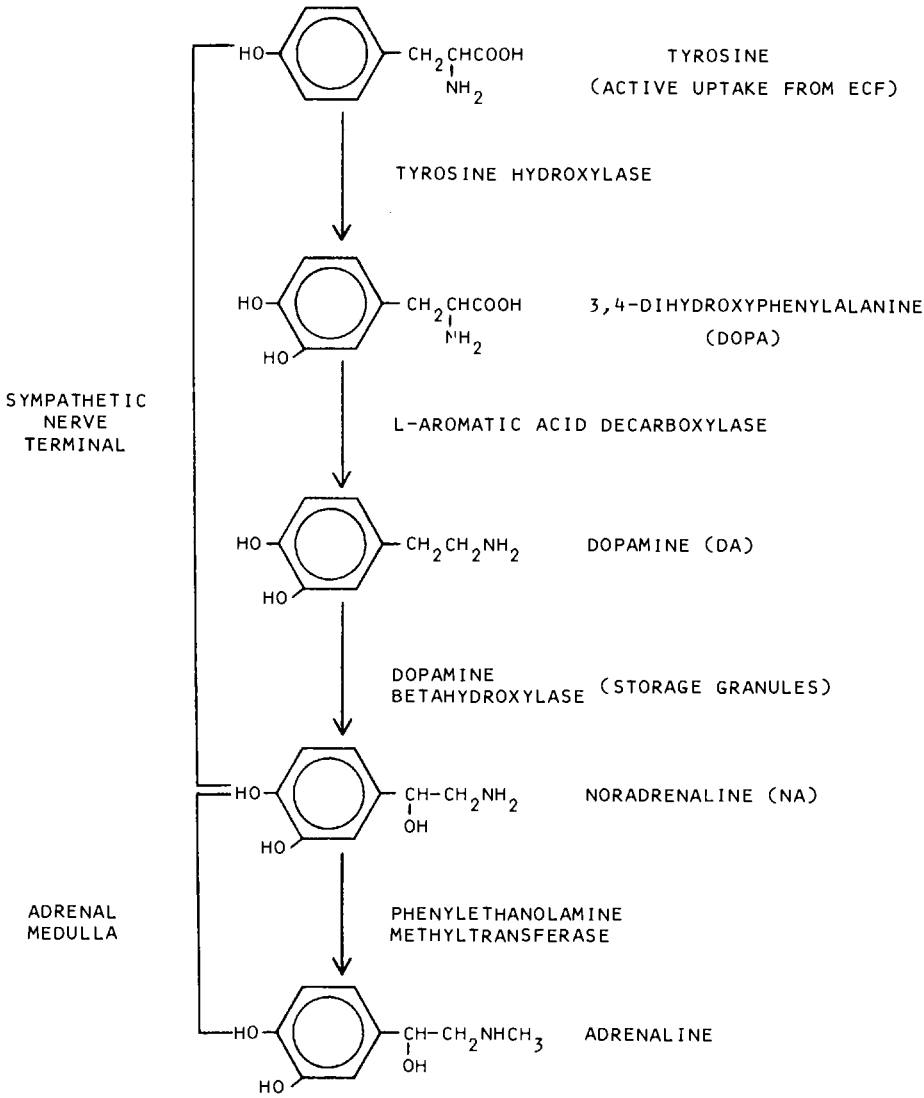


FIG. 1 Biosynthesis of dopamine, noradrenaline and adrenaline from tyrosine.

The turnover rate of catecholamines is not constant, but subject to feedback mechanisms which are not fully established. Noradrenaline in nerve terminals inhibits tyrosine hydroxylase while an increase in NA release is associated with an increase in the activity of both this enzyme and dopamine beta-hydroxylase.

Adrenergic effects Stimulation of the sympathetic nervous system or infusion of adrenaline produces a large number of effects which are classified as alpha or beta effects (Table 1). This classification is based on differences in the characteristics of receptors mediating alpha effects from those mediating beta effects and there are agonists and antagonists that are specific for both types of receptor. The beta effects can be further subdivided into effects mediated by $beta_1$ receptors and those mediated by $beta_2$ receptors.

ADRENERGIC RECEPTOR AGONISTS

Adrenaline

ACTION Adrenaline is a potent agonist of alpha, $beta_1$ and $beta_2$ receptors and when given parenterally produces many of the effects described in Table 1. The predominant effects, and those of greatest therapeutic importance, are those on the cardiovascular system and bronchial smooth muscle.

Cardiovascular system Adrenaline has a positive inotropic and chronotropic effect on the heart. It causes vasoconstriction of arterioles of skin, mucosa, abdominal viscera and kidneys, but dilatation of those in skeletal muscle. The net effect on blood pressure is dose dependent. At low doses it causes an increase in systolic but a decrease in diastolic blood pressure, as it has greater affinity for $beta_2$ than for alpha receptors. At higher doses both the systolic and diastolic values are raised due to effects on alpha and beta receptors. There is a fall in blood flow to the kidney, a rise in that to the myocardium and little change in that to the central nervous system.

Bronchial smooth muscle Adrenaline relaxes smooth muscle and dilates bronchioles of patients with bronchial constriction, increasing the FEV_1/FVC ratio and the FVC itself.

The effects of adrenaline on other tissues are not of therapeutic importance. Adrenaline, like other catecholamines, has no central effects when administered by conventional routes as its high degree of water solubility prevents it diffusing through the blood–brain barrier.

Cellular effects Activation of adrenoceptors in the liver stimulates the membrane bound enzyme adenylcyclase which converts ATP inside cells to the cyclic diester 3'5' AMP (cyclic AMP). Cyclic AMP in turn interacts with a receptor protein to form a proteinkinase. This enzyme phosphorylates the inactive phosphorylase to an active form which initiates glycolysis. Adenylcyclase is situated on membranes of many structures and the adenylcyclase system is probably essential to all adrenergic beta effects, although the link between adenylcyclase activation and changes in smooth muscle tone is unclear. The activation of adenylcyclase is not essential for the mediation of alpha effects and there is no clear understanding of how these effects are brought about.

DRUG FATE Adrenaline is rapidly metabolised by COMT in the plasma and

Table 1
Distribution of adrenoceptors

Tissues containing only alpha receptors		*Effect of alpha receptor agonist*
Arteriolar smooth muscle (sm)	skin	constrict
	mucosa	
	cerebrum	
Vein sm	systemic	constrict
Sphincter sm	stomach	constrict
	intestines	
	bladder	
Pilomotor sm		contract
Iris sm	radial	contract
Glands	salivary	viscid secretions
	sweat	sweating in hands and feet
	pancreas (alpha cells)	decreased exocrine secretion
	male genitalia	ejaculation

Tissues containing only beta receptors		*Effects of beta receptor agonist*
	$beta_1$ receptors	
sino-atrial node		positive chronotropic effect
atrio-ventricular node and conducting pathways		
Myocardium		positive inotropic effect
	$beta_2$ receptors	
Bronchial sm		dilatation
Stomach (body) sm		decreased motility and tone
Detrusor sm		relaxation

Tissues containing alpha and $beta_2$ receptors		*Effect of alpha and $beta^2$ agonist*
Vascular sm	skeletal muscle abdominal viscera kidneys lungs coronaries	At all sites alpha agonists constrict and beta agonists dilate. Net effect of adrenaline, or sympathetic stimulation, is to dilate vascular beds of skeletal muscle, myocardium and lungs and to constrict those of the abdominal viscera and kidneys.
Pancreas Fat Liver	lipolysis glycogenolysis gluconeogenesis hyperglycaemia	Alpha agonist decrease insulin release; beta agonist increase insulin release. These effects are caused by adrenaline and noradrenaline, adrenaline being the more potent. They are antagonised by beta blockers.

monoamine oxidase in the liver, like NA, the main product of metabolism being vanillyl mandelic acid.

ADVERSE EFFECTS

Cardiac dysrhythmias—adrenaline may cause ventricular extrasystoles and all types of tachydysrhythmia.

Myocardial ischaemia—as a consequence of the positive intropic and chronotropic effects of adrenaline, there is an increase in oxygen demand by the myocardium which may precipitate myocardial ischaemia in patients with coronary artery disease.

Hypertension the increase in systolic blood pressure increases the probability of a cerebrovascular accident, especially in hypertensive patients.

CLINICAL USE

Administration Adrenaline is usually administered subcutaneously in a dose of 0·1–1 mg or topically in a concentration of 1/10 000–1/1000. It is included in some local anaesthetic preparations to prolong their anaesthetic effect. As adverse effects on the myocardium are common and sometimes fatal after i.v. administration, this route should be avoided where possible.

Indications

1. Asthma. In children incapable of using an inhaler, subcutaneous adrenaline is still commonly used in the treatment of an acute attack. The availability of parenteral forms of specific $beta_2$ receptor agonists (*see* below) however has rendered adrenaline obsolete in the treatment of asthma.
2. Anaphylaxis. Adrenaline is rapidly effective in the treatment of hypotension, bronchospasm and urticaria that may occur in this condition as it antagonises many of the effects of histamine.
3. Vasoconstriction. Adrenaline is used for its vasoconstrictor effect in the administration of local anaesthetics to prolong their duration of action. It is also used to staunch bleeding in superficial injuries.

Noradrenaline

ACTION Although NA is the neurotransmitter at sympathetic postganglionic synapses and mediator of both alpha and beta effects when released from postganglionic sympathetic nerve terminals, it has a higher affinity for alpha and $beta_1$ receptors than for $beta_2$ receptors and when administered parenterally the $beta_2$ effects are not evident.

Cardiovascular system Noradrenaline causes a rise in both systolic and diastolic blood pressure by increasing the smooth muscle tone of resistance vessels. This leads to a reflex bradycardia. There is also an increase in the tone of capacitance vessels, but no change in cardiac output. Blood flow to the kidneys and cerebrum falls and there is a fall in circulating blood volume.

The effect of NA on other tissues is of no therapeutic importance. NA

administered systemically does not cause bronchial dilatation and has no central effects.

DRUG FATE Noradrenaline is inactive orally. When given i.v. it has a very short duration of action as it is rapidly metabolised by COMT in the plasma and by MAO in liver, kidney and gut wall. The catabolic products are shown in Fig. 2.

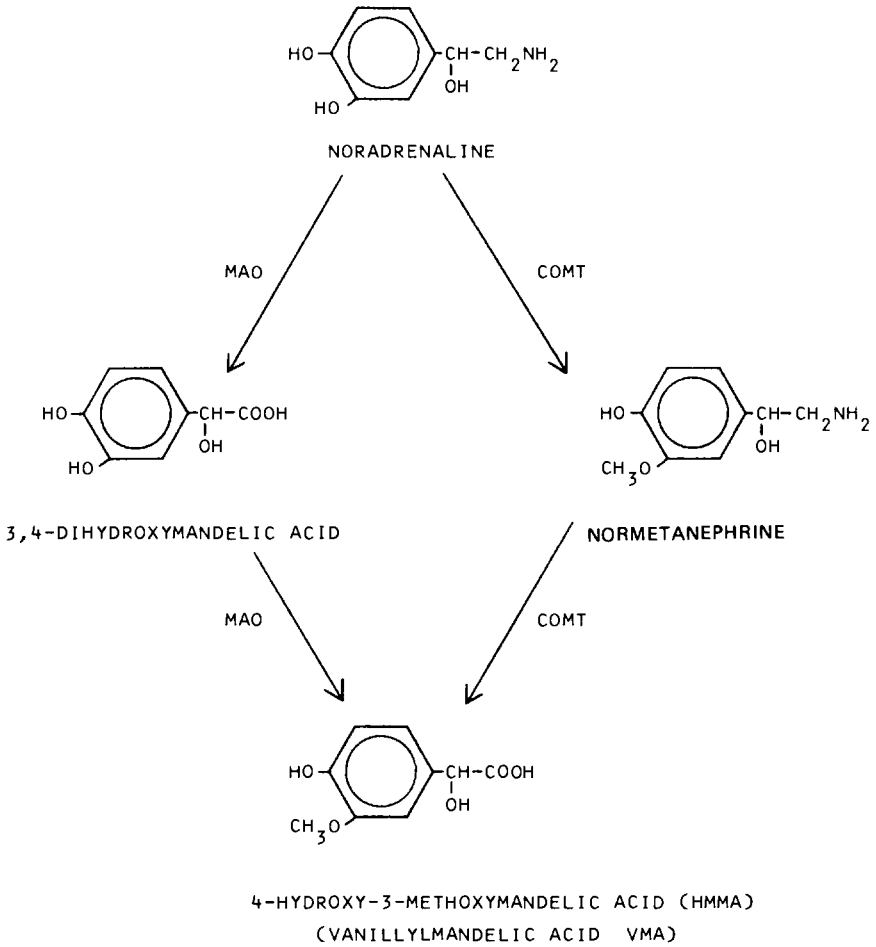


FIG. 2 Main catabolic products of noradrenaline

Uptake 1 and uptake 2 also contribute to the removal of infused NA. Very little NA is excreted in the urine unchanged, the major metabolite being vanillyl mandelic acid (VMA).

ADVERSE EFFECTS

Hypertension noradrenaline infusion may cause intracranial haemorrhage or left ventricular failure as a consequence of its hypertensive effect.

CLINICAL USE

Shock In hypotensive states a NA infusion will cause a rise in vasomotor tone and a rise in blood pressure. The value of this pressor effect is doubtful in most instances, as it is usually associated with a fall in renal blood flow which may expedite, rather than prevent, acute renal tubular necrosis due to renal hypoperfusion.

Nasal decongestant Noradrenaline applied topically to the nasal mucosa causes vasoconstriction and increases nasal airway patency and for this reason NA is sometimes used in the treatment of colds and vasomotor rhinitis.

Methoxamine and phenylephrine These agents are selective alpha receptor agonists with no beta agonist activity. Phenylephrine is orally active and both compounds have a longer duration of action than noradrenaline. Their clinical uses are similar to those of NA.

BETA RECEPTOR AGONISTS

Isoprenaline

ACTION Isoprenaline is an agonist for both $beta_1$ and $beta_2$ receptors, but has no alpha-agonist activity (*see* Fig. 3).

Cardiovascular system It causes an increase in cardiac output and heart rate and a rise in systolic but a fall in diastolic blood pressure.

Bronchial smooth muscle It causes dilatation of bronchial smooth muscle in asthmatic patients and relieves breathlessness. It also causes dilatation of the pulmonary vascular bed (a $beta_2$ effect) and this usually exacerbates the ventilation-perfusion abnormality in an asthmatic attack, causing a slight fall in pO_2.

The other effects of isoprenaline are not of clinical importance.

DRUG FATE Isoprenaline is readily absorbed from the gut. After oral administration the great majority of a dose is metabolised during its first passage through the gut and liver, an oral dose being approximately 1000 times that of an equipotent i.v. dose. After i.v. administration most of the drug is excreted unchanged in the urine, the rest undergoing sulphate conjugation and O-methylation and being cleared from the plasma with a half-life of 2–3 hours. Tolerance rapidly develops to the cardiovascular effects of isoprenaline and the effect of a single bolus injection is very short lived. After inhalation, the symptomatic relief and effect on FEV_1/FVC in asthmatics usually lasts 20 minutes–2 hours, depending on the dose administered and the severity of the asthma.

ADVERSE EFFECTS

Cardiac dysrhythmias Isoprenaline causes palpitations at therapeutic doses and may cause ectopic beats and all types of tachydysrhythmia. After the introduction of pressurised inhalers for isoprenaline administration there was a sharp rise in the incidence of sudden death in children with asthma. This

was partly attributed, in retrospect, to fatal dysrhythmias induced by large doses of this drug.

CLINICAL USE

Administration Small droplets of isoprenaline may be inhaled as an aerosol, this route of administration only being effective in patients with a peak expiratory flow rate of 100 l/min or greater. Onset of action is rapid (1–2 min) and the effective dose small (4–800 μg). The drug is also active sublingually (5–20 mg) but cardiovascular effects are more pronounced than after inhalation. Slow release oral preparations are used in the treatment of heart block but are of doubtful value.

Indications

1. Asthma. Isoprenaline, usually by inhalation, is most effective in the symptomatic treatment of asthma, but its place in the therapy of this condition has largely been taken by selective $beta_2$ agonists (*see* below and Chapter 35).
2. Heart Block (*see* Chapter 22).
3. Shock. Isoprenaline, given by continuous infusion, may increase tissue perfusion including renal perfusion, in hypotensive states. It acts by increasing cardiac output and causing a fall in central venous pressure and a rise in urine output, but responsiveness cannot be predicted on clinical grounds.

Salbutamol, Orciprenaline and Terbutaline

These drugs are structurally similar to isoprenaline and are selective $beta_2$ agonists with only slight $beta_1$ agonist activity (Fig. 3). Their maximal bronchodilator effect is similar to that of isoprenaline and at doses that achieve this effect, they produce only a small increase in heart rate and fall in blood pressure.

They are orally active with a duration of action of 4–6 hours and are metabolised more slowly than isoprenaline. They may be administered orally, by inhalation or by injection. Adverse effects are few, but they all cause a fine tremor, palpitations and a fall in diastolic blood pressure.

There are a number of other beta agonists, e.g. isoetharine and rimiterol, which have no advantages over salbutamol, orciprenaline or terbutaline.

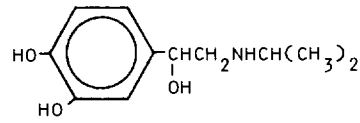
CLINICAL USE

Asthma These are drugs of first choice in the treatment of asthma. An inhaler is used to relieve symptoms during an attack and in more severe cases a tablet may be taken 8 hourly to prevent or reduce the severity of attacks.

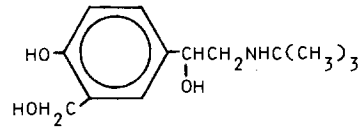
Salbutamol i.v. is occasionally administered in hypotensive states in which cardiac stimulant drugs are contra-indicated, as it causes vasodilatation of renal arterioles and increases renal blood flow.

These drugs decrease uterine tone in the last trimester of pregnancy and may be administered to prevent uterine contractions.

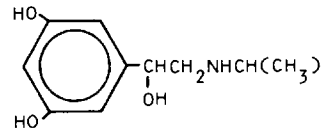
ISOPRENALINE



SALBUTAMOL



ORCIPRENALINE



TERBUTALENE

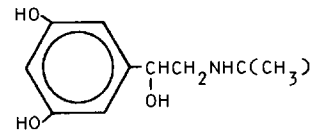
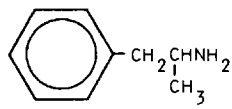


FIG. 3 Structural formulae of some beta receptor agonists

INDIRECT-ACTING ADRENERGIC AGENTS

There are a large number of agents with adrenergic activity whose effects are mediated partly by the release of NA from adrenergic nerve terminals and partly by a direct action on adrenoceptors. These agents therefore produce both alpha and beta adrenergic effects. Of these, some (ephedrine and amphetamines) have prounouced central effects, the rest having only peripheral effects.

Amphetamine



ACTION Amphetamine causes similar systemic effects to adrenaline, but has pronounced central effects. It is a racemic compound, the D and L isomers

having similar peripheral effects, but the D-isomer is 3–4 times as potent with respect to the central effects.

The actions of amphetamine are mostly mediated by its effects on catecholamine disposition. It depletes both central and peripheral neurones of NA, DA and 5HT, impairs their reuptake by nerve terminals and has some MAO inhibitary activity. The peripheral effects are mediated by NA release and the central effects are probably mediated by DA or NA release.

Analeptic effect Amphetamine increases psychomotor activity and alertness. It overcomes spontaneous drowsiness, the drowsiness that occurs in narcolepsy and that induced by central nervous system depressants. This effect is probably due to the stimulation of the ascending reticular pathways in the brain stem. The drug does not remove the need for sleep, but only delays its gratification.

Anorectic effect It decreases appetite and may induce weight loss in both normal and obese patients (*see* Chapter 41).

Anticonvulsant effect It may prevent petit mal convulsions, possibly by increasing the degree of alertness of the child, but it is not a drug of first choice in this condition. It is often also of benefit in the management of hyperkinetic children.

DRUG FATE Amphetamine is orally active and has a duration of action of 4–6 hours. Since it is not metabolised by COMT, most of an oral dose is metabolised by the liver, deamination being the principle metabolic pathway. Approximately 20–30% of an oral dose is excreted unchanged in the urine and as it is a base, the proportion varies with the urine pH, being increased by acidification.

ADVERSE EFFECTS

Drug dependence Amphetamine has a high liability to abuse and this effect has severely limited its clinical use.

Withdrawal symptoms are few, drowsiness being the most evident.

Acute psychoses These may occur in patients on amphetamines, the clinical features being indistinguishable from an acute attack of schizophrenia. This occurs usually after taking large doses, but in some patients may occur after quite small doses.

Tolerance In addicts, the dose requirement of amphetamine increases with time and this occurs in some patients being treated for narcolepsy or obesity.

Drug interactions Amphetamine antagonises the hypotensive effects of alpha methyldopa and the guanidinium hypotensive agents.

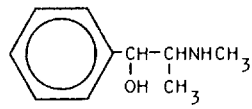
CLINICAL USE

Narcolepsy Amphetamine is useful in decreasing drowsiness in this disorder. Many patients become tolerant of its effects and end up taking large daily doses.

Obesity *See* Chapter 41.

Other amphetamines Dexamphetamine and methamphetamine are similar to amphetamine but have more pronounced central effects.

Ephedrine



Ephedrine is similar to amphetamine in having both alpha and beta effects brought about partly by direct action and partly by releasing endogenous NA. It has both central and peripheral effects and is orally active, with a duration of action of 4–6 h. It has much less of a central analeptic effect than amphetamine and has a lower liability to abuse.

ADVERSE EFFECTS

Cardiac dysrhythmias As for adrenaline. Urinary retention may occur in elderly men with prostatic hypertrophy.

Drug interactions Amphetamine antagonises the hypotensive effects of methyldopa and the guanidinium hypotensive agents.

CLINICAL USE

Asthma Like adrenaline, it is still widely used in the treatment of asthma in children, although it is no longer a drug of first choice in this condition.

Nasal decongestant Pseudoephedrine, the L-isomer of ephedrine, is a common constituent of remedies available without a doctors prescription for colds and hayfever as it causes vasconstriction of the nasal mucous membrane. It is

Preparations

Preparations	*Adult dose*	*Route*	*Dose interval*
Adrenaline	0·1–1·0 mg	i.m. or s.c.	
Noradrenaline	5–25 μg/min	i.v.	
Isoprenaline	10 mg	sublingual	2–4 h
	30–60 mg oral	slow release	4–6 h
	160–800 μg	inhalation	4–6 h
	2–8 μg/min	i.v.	
Salbutamol	4 mg	oral	4–6 h
	100–200 μg	inhalation	4–6 h
	2–20 μg/min	i.v.	
Orciprenaline	20 mg	oral	6 h
	500 μg	inhalation	4–6 h
	500 μg	s.c.	
Terbutaline	5 mg	oral	4–6 h
	500 μg	s.c.	
Amphetamine Dexamphetamine	5–10 mg	oral	4–6 h
Ephedrine	15–60	oral	4–6 h
Metaraminol	5 mg	i.m.	
	0·5 mg	i.v.	

more suitable than racemic ephedrine for this purpose as it has less effect on the central nervous system.

Pressor agents There are a number of adrenergic agents with peripheral but no central effects, that are used principally as pressor agents, e.g. metaraminol, mephentermine and hydroxyamphetamine. These agents act both directly and by release of endogenous NA. The cardiovascular effects of these agents are very similar to those of adrenaline, but they have a longer duration of action as they are not so rapidly metabolised.

CLINICAL USE

Shock The effectiveness of these agents in hypotensive states is little different from that of noradrenaline (*see* above). If they are used, it is necessary to monitor their effect on urine flow and central venous pressure, as well as on blood pressure, to obtain some information on their effect on renal perfusion.

ADRENOCEPTOR ANTAGONISTS (BLOCKERS)

Alpha-Blockers

Alpha-receptor blockers have only a very limited use in clinical medicine at the present time. Ergot alkaloids, which were the first agents found to have alpha-blocking activity, will not be discussed here as alpha blockade contributes little to the actions on which the therapeutic use of these agents depends.

Phenoxybenzamine and dibenamine These agents are haloalkylamines which, like the nitrogen mustards, form a highly reactive carbonium ion *in vivo* which alkylates alpha-adrenoceptors. This is an irreversible reaction. They block both pre-synaptic and post-synaptic alpha receptors, but like other alkylating agents, they are not selective for alpha-adrenoceptors only. They are potent inhibitors of both uptake-1 and uptake-2 (*see* page 132) and also antagonise some of the effects of histamine and 5-hydroxytryptamine and to a lesser extent, acetylcholine.

Cardiovascular effects The response of the cardiovascular system depends on the sympathetic tone of the patient and as this is difficult to evaluate clinically, the response is often unpredictable. In normotensive and in most hypertensive patients there is orthostatic hypotension and tachycardia. The tachycardia is partly a reflex response to a fall in peripheral resistance, but as these drugs also block pre-synaptic alpha receptors, it is enhanced in this instance by the increase in NA from adrenergic nerve terminals consequent upon this action. In patients with phaeochromocytoma and a high plasma NA concentration, the hypotensive response may be dramatic. In hypotensive states associated with an increase in sympathetic tone, these drugs increase renal and splanchnic blood flow, but not that to the heart and central nervous system. They have some antidysrhythmic properties, but these are of no clinical value.

These agents are poorly absorbed from the bowel. They are given i.v. as they are tissue irritants. They have a duration of action of 1–3 days and their metabolic fate is unknown.

The principle adverse effects, palpitations and myocardial ischaemic episodes, are the consequence of the reflex response to hypotension. Drowsiness is evident with phenoxybenzamine and this drug may also cause convulsions.

Phentolamine and tolazoline The cardiovascular effects of these agents, of which phentolamine is the more potent, are similar to those of phenyoxybenzamine, but their duration of action is much shorter. The hypotension caused by phentolamine (5 mg i.v.) in patients with a phaeochromocytoma lasts for only 3–5 minutes. Both agents have positive inotropic and chronotropic effects mediated by release of endogenous NA which may be evident at therapeutic doses. They both stimulate gastrointestinal motility and may cause diarrhoea and this can be prevented by atropine. They also have histamine-like effects causing an increase in gastric acid secretion and peripheral vasodilatation.

CLINICAL USE OF ALPHA-BLOCKERS

Phaeochromocytoma Phentolamine is used to control blood pressure during removal of the tumour and in the control of acute hypertensive episodes in other circumstances caused by high plasma concentrations of catecholamines, e.g. the 'cheese reaction' (*see* Chapter 15) in patients on MAOIs. A pronounced hypotensive response to phentolamine has been used to diagnose a phaeochromocytoma as such a response does not occur in normal or hypertensive subjects. However, it is not without risk and is not very specific. It has now been superseded as a diagnostic method by chemical methods in which catecholamine or metabolites are measured in the plasma and/or urine.

Peripheral vascular disease Alpha-blockers may improve blood supply to the skin of the hands and feet in some patients with Raynaud's disease, but they do not affect blood supply to muscles. Their value in other types of peripheral vascular disease has not been demonstrated.

Shock Phenoxybenzamine may improve renal blood flow in some hypotensive patients, but this response is not invariable and cannot be predicted on clinical grounds.

Hypertension Alpha-blockers have no established place in the management of hypertension. Their principal limitations are that the response is unpredictable and the enhanced beta adrenergic effects, consequent upon a reduction in peripheral resistance and blockade of pre-junctional alpha receptors, may cause palpitations and precipitate myocardial ischaemia.

Preparations

	Adult dose/24 h	*Route*	*Dose interval*
Phenoxybenzamine	10–20 mg	oral	12–24 h
Tolazoline	100–200 mg	oral	6 h

Beta-Blockers

Beta-blockers are widely used in the treatment of cardiovascular disease. There are a number of these agents in current medical use (Table 2) but as the differences between them are not great, the clinical pharmacology of propranolol, the most widely used agent, will be described in detail and the remaining agents contrasted with it.

Propranolol

ACTION Propranolol is a competitive antagonist of both $beta_1$ and $beta_2$ receptors. It is a racemic compound, the L-isomer being at least 100 times more potent than the D-isomer. It blocks beta adrenoceptors peripherally and in the central nervous system and most of its therapeutic effects are the consequence of actions on the cardiovascular system.

Antianginal Propranolol has a negative inotropic and chronotropic effect. It reduces the myocardial oxygen demand more than its oxygen supply and so increases oxygen availability to the muscle. Taken prophylactically, it reduces the incidence of angina in patients with myocardial ischaemia (Chapter 24).

Hypotension There is a fall in systolic and diastolic blood pressure with propranolol affecting both the lying and standing blood pressure. The cardiac output is reduced, the peripheral resistance either unchanged or increased and there is no consistant effect on the plasma volume. (For mechanisms *see* Chapter 23.)

Antidysrhythmic The beta blocking effect of propranolol on the sinus and a-v nodes causes a sinus bradycardia. Propranolol also reduces the heart rate in supraventricular tachycardias. In doses higher than those producing maximum beta-blockade, propranolol has a local anaesthetic (quinidine-like) effect on the heart. As it is effective as an antidysrhythmic agent at lower doses than those necessary to produce this effect, it probably contributes little to its antidysrhythmic action.

DRUG FATE Propranolol is absorbed from the gut reaching a peak plasma concentration 1–2 hours after an oral dose. It is very rapidly metabolised in the liver, mostly by hydroxylation and conjugation, most of the drug in the hepatic portal vein being metabolised in one pass through the liver. It is more active after oral than intravenous administration and this is probably due to the fact that a major metabolite, 4-hydroxypropranolol, is a more effective beta-blocking agent than the parent compound. Propranolol is 90% protein bound in the plasma and is concentrated in the tissues, having a volume of distribution of 150 l. After oral administration the $t_{\frac{1}{2}}$ is 3–4 hours, increasing to 5–6 hours in doses over 160 mg/24 hours. There are considerable interindividual differences in peak plasma concentrations achieved after oral dosing due to differences in rates of metabolism during the first pass through the liver. Neither propranolol or the active metabolite 4-hydroxypropranolol accumulate in renal failure.

ADVERSE EFFECTS

Left ventricular failure In therapeutic doses, propranolol causes an increase in left ventricular end diastolic pressure and in patients with impaired left ventricular function this may be sufficient to precipitate left ventricular failure.

Asthma Propranolol increases airways resistance and in asthmatic patients may precipitate an attack of bronchospasm.

Heart block Propranolol may cause complete heart block in patients with impaired atrio-ventricular conduction.

Miscellaneous Propranolol reduces exercise tolerance by up to 40% in normal subjects and in many patients causes weakness and tiredness. Sudden withdrawal in patients with myocardial ischaemia may precipitate severe myocardial ischaemia and infarction and in such patients drug withdrawal should be in stages. Hypoglycaemia occurs in some patients as propranolol blocks the stimulant effect of endogenous catecholamines on glycogenolysis and gluconeogenesis. Drowsiness and vivid dreams and after high doses ataxia and visual hallucinations may occur. There is an increase in the incidence of Raynaud's syndrome in subjects on propranolol.

CLINICAL USE

Administration Propranolol is administered orally usually starting with a small dose (20–40 mg) and increasing as required. The effects of the drug outlast the presence of the drug and metabolites in the plasma after chronic administration so that despite the short half-life, a dose interval of 8–12 hours is usually adequate. As there are quite large interindividual differences in the doses required to produce a given effect, the dose must be established empirically in each patient, monitoring the therapeutic effect and pulse rate.

i.v. administration Rapid i.v. administration of quite small doses of propranolol (5–10 mg) may cause ventricular ectopics. It may also precipitate pulmonary oedema in patients with impaired left ventricular function. It should therefore only be administered slowly (over 5 minutes) via this route.

Indications The uses of propranolol in angina, hypertension and tachydysrhythmias are outlined in Chapters 24, 23 and 22 respectively.

Thyrotoxicosis Many of the symptoms of thyrotoxicosis, such as sweating, tremor and palpitations, are mediated at least in part by catecholamines and are relieved by propranolol. This drug is effective at slowing the tachycardia in this condition when digoxin is usually ineffective.

Hypertrophic obstructive cardiomyopathy Propranolol may relieve the symptoms of angina and syncope in this rare condition by reducing the pressure gradient across the obstruction to the outflow from the left ventricle, through its depressant effect on cardiac output.

Miscellaneous In anxiety states propranolol ameliorates many of the somatic symptoms, e.g. palpitations, sweating and tremor, without affecting psychic anxiety and it suppresses many symptoms in patients withdrawing from narcotic analgesics. It is also often effective at reducing tremor through a

mechanism not related to beta-blockade, in essential tremor. It may be effective at preventing migraine and in large doses it has given symptomatic relief to some schizophrenic patients, although in neither of these conditions is there general agreement about it efficacy.

Practolol Practolol is a relatively selective antagonist for $beta_1$-receptors and at equipotent therapeutic doses produces much less of an increase in airways resistance than propranolol and it rarely precipitates an attack of asthma. After intravenous administration, practolol produces less depression of cardiac output than equipotent doses of propranolol and oxprenolol. Unlike propranolol, practolol is a partial agonist, i.e. in the absence of adrenaline and noradrenaline, it has some $beta_1$-agonist activity (intrinsic sympathomimetic activity). The relevance of this effect clinically is not clear.

Practolol is orally active and is excreted mostly unchanged in the urine. Like propranolol and other weak bases, it is concentrated in the tissues, having a volume of distribution of 110 l, but it does not readily penetrate the blood-brain barrier. It is cleared from the plasma at a similar rate to creatinine and the plasma concentration declines with a $t_{\frac{1}{2}}$ of 10–14 hours and this increases in renal failure.

ADVERSE EFFECTS Attacks of bronchospasm are much less frequent than with propranolol, but it may precipitate left ventricular failure in subjects with impaired left ventricular function.

Occulocutaneous syndrome A small number of patients on chronic practolol therapy develop a systemic lupus erythematosus-like syndrome, or kerato conjunctivitis sicca with conjunctival scarring and visual disturbances. Rashes also occur and vary in morphological appearance, the most characteristic being an erythematous psoriasiform eruption. Other reactions include mucosal ulceration, retroperitoneal and peritoneal fibrosis and pleurisy. As a consequence of these adverse effects, chronic practolol therapy should not be used, but the drug is still useful in the short term management of cardiac dysrhythmias.

Other Beta-Blockers

There are a large number of beta-blockers now available and their actions differ little from those of propranolol. They have been classified according to their selectivity for beta receptors, their partial agonist activity (intrinsic sympathomimetic activity) and whether they have a quinidine-like action on the heart.

$Beta_1$ selective antagonists These agents antagonise the effects of catecholamines mediated via $beta_1$-receptors to a greater degree than they do those mediated via $beta_2$-receptors. Thus at equipotent doses they are less liable to cause an increase in airways resistance and hence to precipitate attacks of asthma. As obstructive airways disease is common this is an important advantage over non selective beta-blockers. However, as none of these agents is wholly selective for $beta_1$-receptors, they are best avoided in patients with asthma, and if they are used in

such patients, airways resistance should be monitored before and during therapy.

Practolol was the first selective beta$_1$ antagonist. It was used widely for several years before it became apparent that chronic oral therapy may be associated with severe skin and eye disorders (*see* above). As a consequence of those adverse effects, practolol is no longer recommended for chronic usage but is useful, given i.v. in the short term treatment of cardiac dysrhythmias as it causes less myocardial depression, at equipotent antidysrhythmic doses than does propranolol.

Atenolol and metoprolol appear effective alternatives to practolol but their chronic adverse effects have not been fully evaluated.

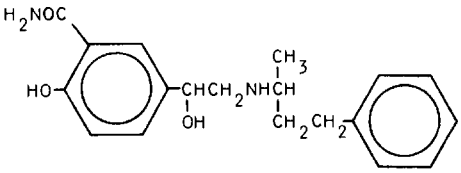
Partial agonist activity Beta-blockers with this characteristic are more likely to cause cardiac dysrhythmias when given as i.v. bolus doses than are pure antagonists but cause less myocardial depression. The importance of this characteristic has not been established clinically.

Quinidine-like action Some beta-blockers, like propranolol, have a membrane stabilising or local anaesthetic effect on the myocardium and conducting pathways quite independent of their beta-blocking action. There is no evidence that such an action is of clinical importance.

DRUG FATE Most of the newer beta-blockers are similar to propranolol in that they are cleared from the plasma mostly by metabolism and have short half-lifes (*see* table). The exceptions are practolol and sotolol which are excreted mostly as unchanged drug in the urine and have longer half-lives.

Combined Alpha- and Beta-Blockade

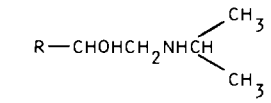
Labetalol



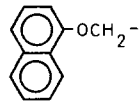
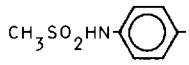
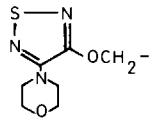
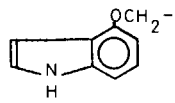
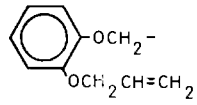
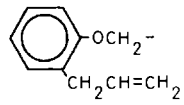
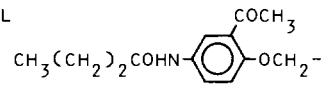
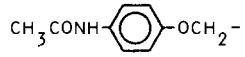
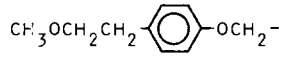
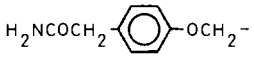
Labetalol is a competitive antagonist of both alpha- and beta-receptors and has been introduced as a hypotensive agent. It is a more effective beta-blocker than alpha-blocker and is 4–6 times less potent than propranolol as a beta-blocker. It is an effective hypotensive agent in all grades of hypertension, lowering lying, standing and post-exercise BP. In contrast to propranolol it only affects the standing and post-exercise pulse rate and hypotension is associated with a fall in peripheral resistance.

Labetalol is orally active but undergoes rapid hepatic metabolism to inactive glucuronides and less than 5% of an oral dose is excreted unchanged in the urine. Labetalol may precipitate asthma or pulmonary oedema in predisposed patients but at equipotent beta-blocking doses is less liable to do so than propranolol. Other adverse effects include postural hypotension, failure of ejaculation, dizziness and vivid dreams but these are generally less frequent than with adrenergic neurone blocking agents. It binds to melanin in the tissues but

Table 2
Some beta blocking drugs

BASIC FORMULA: 

NON-SELECTIVE

NAME	R	PARTIAL AGONIST	$T_{\frac{1}{2}}$	DOSE (MG/24H)
PROPRANOLOL		–	1.5-4	40 - 360
SOTALOL		–	4-5	200 - 600
TIMOLOL⁂		–	4-5	15 - 45
PINDOLOL		+	3-4	15 - 45
OXPRENOLOL		+	2-4	80 - 480
ALPRENOLOL		+	2-3	100 - 800
ACEBUTOLOL		+	5-6	200 - 900
	SELECTIVE			
PRACTOLOL		+	10-14	100 - 400
METOPROLOL		–	3-4	100 - 400
ATENOLOL		–	5-9	100 - 200

⁂TERMINAL CARBON CARRIES THREE METHYL GROUPS

adverse effects on the retina have yet to be reported. Preliminary studies have shown that labetalol is effective alone or in combination with a diuretic in all grades of hypertension. Given i.v. in a dose up to 2 mg/kg over 5 mins it causes a rapid fall in BP that may be sustained up to 6 h. It is a useful agent in the management of hypertensive emergencies and in the control of blood pressure during anaesthesia and in the management of a phaeochromocytoma.

Dopamine

Dopamine is the precursor of NA. Its role in physiology and in the pathophysiology of a number of diseases of the neuro-endocrine system is currently being investigated intensively. It is much less prevalent in the body than adrenaline and NA and is present in substantial amounts only in neurones originating in the substantia nigra. Small amounts are found at other sites in the central nervous system including the limbic system and hypothalamus.

ACTION Dopamine does not readily penetrate the blood-brain barrier so that the effects it produces when administered systemically are mediated by peripheral receptors.

Cardiovascular Dopamine has a positive inotropic and chronotropic effect on the myocardium mediated by interaction with $beta_1$-receptors and its actions are antagonised by beta-blocking drugs. It causes vasodilatation of the renal and mesenteric vascular beds especially and also those of the coronary and intracerebral beds. This effect is not antagonised by alpha- or beta-blocking drugs, but is by the dopamine antagonists haloperidol and the phenothiazines (*see* below). Intravenous infusion in doses below 10 μg/kg/min causes an increase in cardiac output, but no change in heart rate or blood pressure, an increase in renal blood flow with a consequent increase in glomerular filtration rate and urine output and a fall in blood flow to skeletal muscle.

ADVERSE EFFECTS Tachycardia and ventricular tachydysrhythmias are the most common adverse effects. It acts on both $beta_2$- and alpha-receptors peripherally and at low doses the $beta_2$ effects prevails and may result in hypotension. At doses above 10 μg/kg/min, however, the alpha effect supervenes and hypertension is common. These effects are less evident with a synthetic derivative of isoprenaline dobutamine, which has similar actions to dopamine but produces little change in peripheral arterial tone at doses causing a similar increase in myocardial contractility. Angina, nausea and vomiting are occasional adverse effects of both drugs.

CLINICAL USE

Hypotension Dopamine is probably more effective than alpha- and beta-adrenergic agonists in normovolaemic hypotensive states. It is given i.v. by continuous infusion starting at 1μg/kg/min and increasing as is indicated. The blood pressure, electrocardiogram, urine flow and central venous pressure should be monitored during therapy.

Dopamine agonists

There are a number of dopamine agonists that are being currently investigated and whose sites of action are principally in the central nervous system. Of these the ergot derivative bromocriptine (2-bromo-α-ergocryphine) gives most promise of therapeutic usefulness.

Bromocriptine has similar effects to L-dopa on parkinsonian patients and its place in the therapy of this condition is being evaluated (*see* Chapter 16). It also lowers prolactin plasma levels in women in whom infertility is secondary to hyperprolactinaemia. It is thought to act on dopamine receptors in the hypothalamus inhibiting the release of prolactin. By a similar mechanism it inhibits puerperal lactation. It also lowers growth hormone secretion in acromegalic patients and may be of therapeutic value in such patients.

The adverse effects of bromcriptine, nausea and vomiting, postural hypotension and involuntary movements, are similar to those of L-dopa.

There are a number of alternative dopamine agonists, apomorphine and norpropyl-apomorphine and another ergot analogue lergotrile. They have similar potentially therapeutic and adverse effects to bromcriptine.

Dopamine antagonists

The butyrophenones (e.g. haloperidol) and the phenothiazines antagonise the actions of dopamine. It is not established how far this action contributes to the therapeutic and adverse effects of these drugs as they have many other actions (*see* Chapter 14).

Both cause an increase in dopamine turnover in basal ganglia and in the limbic system, probably as a consequence of an increased release of dopamine secondary to blockade of dopamine receptors. It is widely accepted that this is the basis of the ability of both groups of drugs to cause extrapyramidal disorders at high therapeutic doses and it may contribute to their tranquillising effects. They both cause an increase in prolactin release, which probably accounts for the occasional side effect of galactorrhoea.

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Chapter 12

Anaesthetic Agents

Anaesthetic agents are drugs that reversibly impair neuronal function. General anaesthetics impair neuronal function of the CNS and at therapeutic concentrations, their most prominent effect is the induction of unconsciousness. Local anaesthetics are administered in close proximity to a peripheral nerve and their most prominent clinical effect is analgesia in the distribution of the nerve anaesthetised.

Membrane action of anaesthetics Both general and local anaesthetics act on neuronal membranes. They interact with hydrophobic components of the membranes causing them to swell and most general anaesthetics, e.g. halothane, chloroform and ether, cause an increase in the fluidity of membrane phospholipids.

The neuronal membranes most susceptible to the physical changes caused by general anaesthetics are those of central synapses. General anaesthetics reduce synaptic transmission either by impairing synthesis and release of transmitter substances at central excitatory synapses or by an action on the post-synaptic membrane, reducing responsiveness to the transmitter. The conduction of impulses in nerve fibres is little affected at the concentrations they achieve in the body after therapeutic doses.

Local anaesthetics, by contrast, stabilise neuronal membranes and impair impulse conduction in nerve fibres. The rising phase (phase 1) of nerve and muscle action potentials is caused by the rapid influx of sodium ions (Chapter 22). Local anaesthetics stabilse excitatory membranes by reducing the sodium conductance of membranes and hence prevent this rapid phase of sodium conductance and membrane depolarisation.

There are a large number of drugs with anaesthetic properties at concentrations higher than those they achieved in nervous tissue at therapeutic concentrations, tranquillisers, narcotic analgesics, anticonvulsants, etc. However, only those agents used clinically as general or local anaesthetics will be considered in this chapter.

GENERAL ANAESTHETIC AGENTS

General anaesthetics are used clinically to reduce the pain and suffering that are the consequence of surgical procedures. Ether and chloroform were the first to be used, but there are now a number of other agents with advantages over the older drugs. General anaesthetics may be classified in terms of their chemical structure, their physical properties (i.e. their boiling point which determines

whether they are a volatile liquid or a gas) and on their route of administration (Table 1).

Table 1
Inhalation anaesthetics

Type of chemical	*Anaesthetic*	*Boiling point*	*Physical state*
Ethers	diethylether	35	volatile liquid
	divinylether	28	volatile liquid
	ethylvinylether	36	volatile liquid
	fluroxene	43	volatile liquid
	methoxyflurane	105	volatile liquid
Halogenated saturated hydrocarbons	chloroform	61	volatile liquid
	halothane	50	volatile liquid
	ethylchloride	12	volatile liquid
Unsaturated hydrocarbons	ethylene	−103	gas
	trichlorethylene	87	volatile liquid
Inorganic oxide	nitrous oxide	−89	gas
Alicyclic hydrocarbon	cyclopropane	−34	gas
Intravenous anaesthetics			
Barbiturates	thiopentone methohexitone		
Phenoxyacetic amines	propanidid		
Steroids	alphaxalone alphadolone acetate	althesin	
Arylcycloalkylamines	ketamine		

Therapeutic actions General anaesthetics affect all excitable membranes and their effects are therefore diverse. However, the actions that determine their usefulness during surgery are those on the nervous system, and may be considered under three headings, hypnotic action, analgesic action and neuromuscular blocking action. The relationship of these three actions to an increasing dose of anaesthetic was described by Guedel who identified four stages of anaesthesia during ether anaesthesia (*see* below). However, anaesthetic agents differ in the degree to which any one of these effects is evident at any given dose or blood concentration (e.g. diethylether, nitrous oxide and cyclopropane produce analgesia at subhypnotic doses, but halothane, the barbiturates and methoxyflurane do not) so that the stages of anaesthesia established for ether are not always an adequate guide for the depth of anaesthesia produced by other agents. Nowadays, moreover, seldom if ever is a single anaesthetic agent used to produce hypnosis, analgesia and muscle relaxation, general anaesthetics themselves being used most often to maintain unconsciousness.

INHALATION ANAESTHETICS

Inhalation anaesthetics include all volatile liquids and gases. These drugs differ from other drugs in two ways—they are administered by inhalation and they are mostly excreted as unchanged drugs via the lungs. They are drugs of type 1 (Chapter 5) in that their anaesthetic effect is closely related to their plasma concentration, so that the time course of anaesthesia is determined by the pharmacokinetics of the individual agents.

Pharmacokinetics Inhalation anaesthetics are administered by the principle route of their elimination. Consequently, the same factors that determine the accumulation of anaesthetic agents in the blood will also determine their excretion. Hepatic metabolism contributes little to the rate that these drugs are eliminated from the body so that during their administration very little anaesthetic is excreted. Therefore, unlike other drugs, the extent to which these drugs accumulate in the blood and tissues is not determined by the rate at which they are excreted.

Inhalation anaesthetics accumulate in the blood in three phases. During the initial rapid phase, the anaesthetic concentration builds up in the alveoli. During the second phase, drug in the alveoli equilibrates with that in the blood and the well-perfused tissues (heart, brain, liver, kidneys etc). In the third and slowest phase, drug in the blood equilibrates with that in poorly perfused tissues (muscle, bone, fat etc). The rate of accumulation is determined by the rate and depth of ventilation (minute volume), the blood flow to the lungs (i.e. the cardiac output) and by the solubility of the anaesthetic in blood and tissues. Of these three factors, the solubility in the blood and tissues is the most important.

The solubility of an anaesthetic agent is the volume of gas per unit of solvent measured at equilibrium (Ostwald coefficient). Values for some commonly used anaesthetics in blood at 37°C are given in Table 2.

Table 2

The blood solubility of inhalation anaesthetics and its relationship to anaesthetic pulmonary clearance rate

Anaesthetic	*Solubility in blood* (a) *at 37°C*	*Pulmonary clearance* (b) *rate %*
Diethylether	15	5
Methoxyflurane	13	6
Chloroform	10·3	7
Halothane	2·3	26
Nitrous oxide	0·47	66
Cyclopropane	0·41	66

(a) Volume of gas per unit volume of blood at equilibrium at 37°C.

(b) Pulmonary clearance is expressed as the % fall in blood anaesthetic concentration during one passage through the lungs.

As shown in the table, anaesthetics vary considerably in their solubility in blood and as this is the major determinant of the rate at which they accumulate in and are eliminated from the blood, the pharmacokinetics of anaesthetics of low solubility and of those with a high solubility will be considered separately.

Low solubility anaesthetics e.g. nitrous oxide and cyclopropane. During induction of anaesthesia the concentration of low solubility anaesthetic agents very rapidly reaches equilibrium in the blood (Fig. 1). Conversely, on cessation

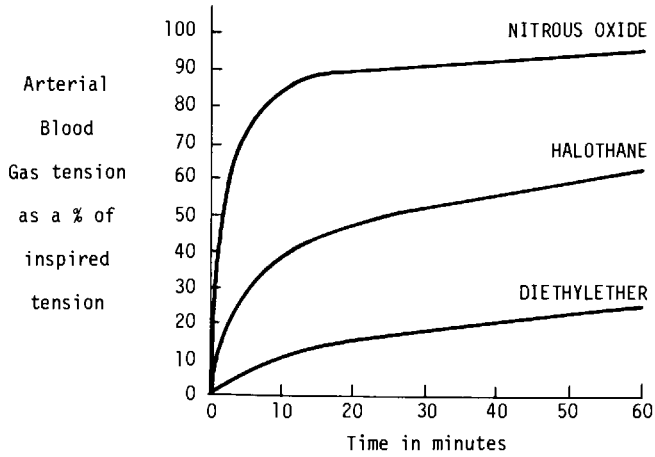


FIG. 1 The relationship between the concentration of anaesthetic in inspired air to that in arterial blood for an anaesthetic of low (N_20), intermediate (halothane) and high (diethylether) solubility in the blood.

of the anaesthetic it is excreted via the lungs very rapidly as these agents have a high pulmonary clearance rate. The rate of accumulation of such agents varies little with minute volume, but does vary directly with the cardiac output, i.e. with the rate of delivery of blood to the lungs.

High solubility anaesthetics e.g. diethylether, chloroform and halothane. The concentration of high solubility anaesthetics in the blood equilibrates very slowly with that in the alveolus. During continuous administration with such agents, induction is slow and they go on accumulating in the blood for many hours. Halothane is less soluble than ether and chloroform and hence accumulates to a lesser extent. On cessation of anaesthesia, elimination is slow as the pulmonary clearance rates for these agents is low. The rate of accumulation and excretion is little affected by variations in cardiac output, but varies directly with changes in minute volume. For practical purposes the rate of induction using such agents can be increased by administering a loading dose that is several times the maintenance dose and both induction and recovery can be expedited by coadministration of CO_2 to stimulate ventilation.

Relative potency There are large differences in potency between anaesthetic agents. One of the most useful estimates of the potency of an anaesthetic is the minimal alveolar concentration (MAC) of the agent which just prevents a gross muscular response to a surgical incision in 50% of patients. The variation in potency between agents is in part explained by differences in lipid solubility as MAC varies inversely with the oil/gas partition coefficient (Fig. 2) being highest

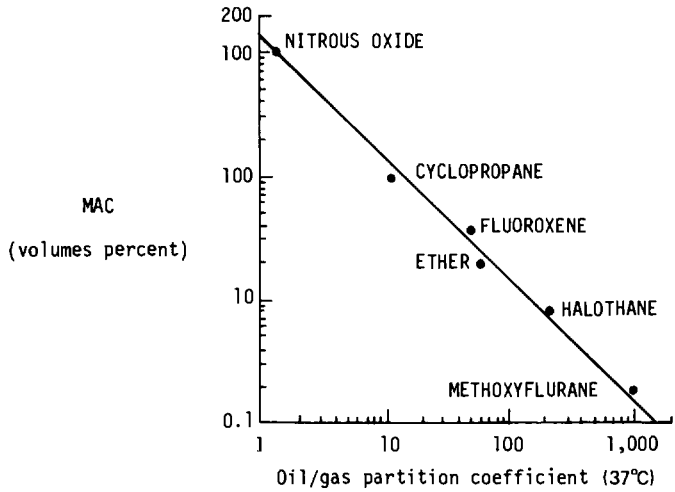


FIG. 2 Relation between MAC and oil/gas partition coefficient. (From Saidman *et al.*, 1967.)

for methoxyflurane and lowest for nitrous oxide. The solubility of anaesthetics in blood and tissues varies with their oil/gas partition coefficients and the differences in anaesthetic concentration in the brain, at a given level of anaesthesia for a number of different anaesthetic agents, are generally less than the differences in concentrations in inhaled air (Table 3).

Table 3

Anaesthetic concentration in inspired air, in blood and in brain during surgical anaesthesia

Anaesthetic	*Volumes % in inspired gas*	*Concentrations in blood mM*	*Concentrations in brain*
Diethylether	3–10	7–21	8–23
Methoxyflurane	1–3	3–20	75–500
Chloroform	1–3	2–6	2–6
Halothane	1–3	2–10	5–25
Nitrous oxide	50–80	30–70	33–80
Cyclopropane	5–25	4–5	5–7

Most anaesthetics achieve a concentration in the brain similar to that in the blood and have a volume of distribution of approximately 1 l/kg. The highly lipid soluble methoxyflurane and to a lesser extent halothane, achieve a concentration in the brain higher than that in the blood and also accumulate in fat tissue. The practical significance of anaesthetic potency is only evident for nitrous oxide as this agent causes anaesthesia in concentrations of 50–85% of inhaled gas and inevitably caused hypoxaemia, unless the inspired air is enriched with oxygen.

THE ETHERS

Diethylether was the first general anaesthetic to be used clinically, being first administered during surgery in the 1840s and it was still used widely up to the introduction of halothane. It is now very little used in the UK, but some aspects of its clinical pharmacology will be discussed as they provide a basis for contrast with agents that are currently popular.

Diethylether $CH_3CH_2O-CH_2CH_3$

Diethylether (ether) is a volatile liquid with a pungent smell. The vapour is heavier than air and is inflammable and explosive.

ANAESTHETIC EFFECTS Ether is a potent hypnotic, analgesic and muscle relaxant and used alone can provide adequate anaesthesia for abdominal surgery. The period of induction is slow and the stages of anaesthesia described by Guedel as a guide to the depth of anaesthesia are as follows:

Stage I	Analgesia	Without hypnosis and sufficient for minor surgical procedures.
Stage II	Delirium	Consciousness is lost, but the patient may become excited and struggle. Muscle tone may be increased, he may move his limbs and be incontinent. Changes in BP and respirations are common.
Stage III	Surgical anaesthesia	Breathing becomes regular. Eyelids no longer move in response to touch; corneal, cough and swallow reflexes are lost.
		Four planes of surgical anaesthesia have been described.
	Plane 1	Both intercostal and diaphragmatic breathing occurs. Eyes move about spontaneously.
	Plane 2	The depth of ventilations decreases and eye movements cease.
	Plane 3	Paralysis of intercostal muscles occurs, but diaphragmatic breathing continues.

	Plane 4	Paralysis of the diaphragm occurs.
Stage IV		Respirations have ceased, pupils dilate and the light reflex is lost. Eventually the BP falls.

DRUG FATE It is highly soluble in blood and therefore accumulates slowly during continuous administration at a constant dose (Table 2) reaching 90% of its equilibrium value in about 20 hours. Onset of action (induction) and recovery are slow. Ether is excreted unchanged via the lungs, very little of the drug undergoing metabolism.

ADVERSE EFFECTS

Irritant Ether is a tissue irritant and during induction causes coughing, swallowing, salivation, an increase in bronchial secretions and nausea and vomiting if sufficient is swallowed. If ether is the sole anaesthetic agent post-operative nausea and vomiting are common.

Respirations are not depressed until stage III due in part to the respiratory stimulant effect of ether on the bronchial mucosa. Hypotension is an indication of overdosage and cardiac dysrhythmias and hepatotoxicity do not occur.

Drug interactions The actions of other anaesthetics are additive with ether and it is quite commonly used in combination with N_2O, when a lesser dose is required to maintain surgical anaesthesia.

Ether enhances the muscle relaxant properties of the competitive neuromuscular blocking agents such as curare and pancuronium.

CLINICAL USE Before the advent of halothane and the intravenous barbiturates, ether was commonly used to induce anaesthesia (10–20% concentrations for 10–20 minutes) and for the maintenance of anaesthesia (3–10% concentrations). It is cheap and does not cause cardiac dysrhythmias or hepatotoxicity. However, it is now very seldom used as an anaesthetic, its principal disadvantages being that it is explosive and a tissue irritant.

OTHER ETHERS The newer ethers improve little on diethylether. Generally the addition of a halide moeity decreases flammability and dose requirement and increases the liability to cardiotoxicity. Methoxyflurane is the only ether used in the UK but fluroxene is also used in the USA.

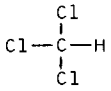
Methoxyflurane This agent is a halogenated ethyl methylether with a high boiling point (Table 1) so that the maximum concentration that is possible in inspired air is 4 volumes %. Its main advantage over diethylether is that it is not inflammable. It is highly soluble in blood and more so in lipids and achieves a concentration in brain and adipose tissue many times that in blood (Table 3). Methoxyflurane is excreted very slowly, approximately 50% of a dose being metabolised and the metabolic products excreted in the urine. Induction and recovery therefore are slow. It increases myocardial sensitivity to catecholamines and may cause cardiac dysrhythmias. Hepatotoxicity is negli-

gible. Its main adverse effect is on the kidney as it may cause a high urine output and a rise in plasma creatinine. Nephrotoxicity is dose-related and has been attributed to the fluoride ion released from the parent compound by metabolism. On account of this adverse effect, methoxyflurane is only used in circumstances when the anaesthetic is brief as in obstetrics.

Fluroxene Fluroxene (trifluorethylvinylether) is less inflammable than diethylether, only being flammable at volumes of 4% or greater, the range of concentrations used clinically being 3–8 volumes %. It is less soluble in blood than diethylether and has a quicker onset and offset of action. Cardiac dysrhythmias, however are more common as it sensitises the myocardium to the actions of cathecholamines.

SATURATED HALOGENATED HYDROCARBONS

Chloroform



Chloroform was first used clinically in the 1840s, only a few years after diethylether and was widely used up to the 1950s. It is now obsolete, having been replaced by the less toxic halothane. Chloroform is a volatile liquid with a sweet odour that is not inflammable.

ANAESTHETIC EFFECT This differs little from ether. Chloroform is a potent analgesic, hypnotic and muscle relaxant. It does not have the irritant properties of ether and does not therefore stimulate respirations and the ventilatory minute volume falls as the depth of anaesthesia increases. Hypotension occurs at anaesthetic doses, but is severe only at doses greater than those necessary for surgery.

DRUG FATE This is very similar to ether, induction and recovery being slow. The drug accumulates in blood and tissues throughout anaesthesia and overdosage results from failure to realise this feature of the anaesthetic's pharmacokinetics. Chloroform is mostly excreted unchanged via the lungs, less than 10% undergoing hepatic metabolism.

ADVERSE EFFECTS

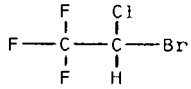
Cardiac dysrhythmias Chloroform increases the myocardial sensitivity to catecholamines. Nodal and ventricular tachydysrhythmias are common, especially during induction, and may be fatal. They may be treated and prevented by beta-adrenergic blocking agents such as propranolol.

Hepatotoxicity Chloroform causes hepatocellular damage in a small number of patients, the incidence being greater than that for halothane, but the prognosis is similar (*see* below).

CLINICAL USE There is a higher incidence of severe adverse effects with

chloroform anaesthesia than with ether, halothane or nitrous oxide which has resulted in chloroform becoming obsolete.

Halothane



Halothane is a volatile liquid with a sweet odour and a boiling point of 50°C. It is not inflammable. It decomposes on exposure to light, tarnishes metals with which it comes in contact and is highly soluble in rubber.

ANAESTHETIC EFFECT Halothane is a potent hypnotic, but a weak analgesic agent and does not cause analgesia at subhypnotic doses. Muscle relaxation is poor and insufficient for abdominal surgery if the drug is used alone. It is not an irritant. It causes very little respiratory depression at concentrations used clinically, but as respiratory depression increases with depth of anaesthesia, a fall in minute volume is usually a sign of overdosage.

Halothane reduces salivation, inhibits the vomiting, laryngeal and pharyngeal reflexes and causes bronchodilation by a direct smooth muscle relaxant action. It depresses uterine contractions and reduces uterine tone.

DRUG FATE Halothane is very rapidly absorbed, but accumulates in blood and tissues slowly due to its high blood solubility. Induction and recovery are more rapid than for ether, but are still quite slow. A variable fraction (5–20%) is metabolised by hepatic microsomal enzymes and excreted as metabolites in the urine, the remainder being excreted unchanged by the lungs. As with other drugs, the rate at which it is metabolised is determined chiefly by genetic factors. No activity has yet been attributed to metabolites.

ADVERSE EFFECTS Halothane is well tolerated generally. It is not a tissue irritant and rarely causes post-operative nausea and vomiting when used as the sole anaesthetic.

Cardiovascular effects Halothane increases vagal tone, decreases sympathetic tone and has a direct vasodilator effect. It is also a direct myocardial depressant. The clinical consequences of these effects are bradycardia, the pulse rate sometimes falling to 20–40/min, and hypotension. The bradycardia is prevented by antimuscarinic agents administered as premedication. The hypotension, which may be useful in decreasing operative blood loss, is seldom severe, but if necessary can be counteracted by volume replacement. Pressor agents with beta agonist activity are best avoided as halothane increases the myocardial sensitivity to catecholamines. Its vasodilator effect may result in heat loss during the anaesthetic. A proportion of patients develop a pronounced shake on recovery from halothane that passes off within minutes.

Hepatotoxicity Halothane may cause hepatocellular damage resulting in the development of jaundice post-operatively. The reported incidence is very low, varying between 1/6000–1/20 000 exposures and over 80% of cases occur after

multiple exposures. Hepatocellular failure may be severe, 40–50% of cases ending fatally, early onset of jaundice (1–6 days post anaesthetic) and a prolonged prothrombin time being poor prognostic signs.

Malignant hyperpyrexia Halothane is one of a number of agents used in anaesthesia that may precipitate a malignant hyperpyrexia in susceptible individuals (*see* Chapter 5, Pharmacogenetics).

Drug interactions The hypotensive effect of halothane may be enhanced by other hypotensive agents. Phenothiazines used as premedication, though producing little hypotensive effect alone, may enhance the hypotensive effect of halothane.

CLINICAL USE Halothane and nitrous oxide are the most commonly used general anaesthetics. The success of halothane results from its non-inflammability, the absence of irritant effects, its high potency and low toxicity. Anaesthesia may be induced with halothane, starting with 0·5% and increasing gradually to 3–4%, although induction is usually achieved with an intravenous barbiturate. Anaesthesia is maintained by a concentration of 1–2%, either alone, or with nitrous oxide. Supplementary analgesia may not be necessary, but if it is, this is usually achieved with nitrous oxide. A competitive neuromuscular blocking drug such as pancuronium, is used if muscle relaxation is required. The bronchodilator effect of halothane makes it effective in patients with obstructive airways disease. Its relaxant effect on the uterus makes it useful for manipulations of the gravid uterus before term, but may predispose to haemorrhage if used in concentrations greater than 0·5% during a Caesarean section or for removal of retained products.

Ethylchloride Ethylchloride is a highly volatile liquid with a boiling point of 12°C. It used to be used for induction of anaesthesia but is now obsolete. It causes freezing of the skin and local anaesthesia, if applied topically and it is occasionally used for this purpose. It is unsuitable topically as a local anaesthetic for surgery.

UNSATURATED HYDROCARBONS

Anaesthetics of this chemical class are seldom used as general anaesthetics and will be discussed only briefly.

Trichlorethylene Trichlorethylene is a volatile liquid with a sweet odour. It is not inflammable.

The anaesthetic effects of trichlorethylene differ little from those of chloroform. It provides analgesia at subhypnotic doses, has a similar time course of anaesthesia to chloroform and may cause cardiac tachydysrhythmias and hepatocellular damage. Rapid shallow respirations often occur during induction. It may cause toxic and explosive compounds with soda lime and should never be used in a closed circuit system of anaesthetic administration. Its principal clinical use has been in maintenance anaesthesia with nitrous oxide

when halothane is contraindicated. It is potentially a useful anaesthetic during pregnancy as it does not relax the uterus.

Ethylene This gas has similar anaesthetic properties to nitrous oxide and cyclopropane. It is lighter than air, inflammable and explosive and for these reasons is now obsolete.

INORGANIC OXIDE

Nitrous Oxide N_2O

Nitrous oxide was the first agent ever to be described as having anaesthetic properties and although these were demonstrated at a similar time as those of ether, it was not widely used in clinical medicine until the 1940s. Nitrous oxide is a sweet smelling gas that is not inflammable or explosive.

ANAESTHETIC EFFECT Nitrous oxide is a potent analgesic at subhypnotic doses (10–40 volumes % inspired air). It is not a potent hypnotic and given alone at one atmosphere pressure only induces hypnosis at a dose (80 volumes %) that causes hypoxaemia. It does not cause muscle relaxation.

DRUG FATE It is rapidly absorbed, the rate of uptake being to 1 l/min during the initial stages of anaesthetic. Its low solubility results in a rapid onset of action, a maximal blood concentration being achieved in 20–30 minutes. It is excreted unchanged via the lungs and recovery from anaesthesia is rapid.

ADVERSE EFFECTS Nitrous oxide is very well tolerated, adverse effects being few. It is not an irritant, it does not depress respirations, rather causing a slight increase in pO_2 when administered with adequate oxygen, and causes only a slight fall in BP. Post-operative nausea and vomiting is infrequent and when used for surgical anaesthesia, tissue toxicity is negligible. Unlike other gaseous anaesthetics it does not form explosive mixtures with oxygen or air.

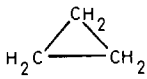
Hypoxia The main drawback to nitrous oxide is its low potency. It produces its desired analgesic and anaesthetic effect only at concentrations (50–80%) sufficient to reduce the concentration of inspired oxygen and to cause hypoxaemia unless the inspired air is enriched with oxygen. It is essential therefore to administer nitrous oxide with oxygen and the maximum concentration tolerated clinically of N_2O is 80%.

On cessation of anaesthesia, the large volume of N_2O taken up by the tissues is rapidly cleared from the blood to the lungs resulting in a fall in alveolar and arterial oxygen concentration. This phenomenon, diffusion hypoxia, may be prevented by persisting in the administration of oxygen during the recovery period.

Bone marrow depression This may occur if nitrous oxide anaesthesia is maintained for over 24 hours, as has occurred in the past in the treatment of tetanus. It has not been reported after its use for shorter periods.

CLINICAL USE Nitrous oxide/oxygen mixture is very widely used for maintenance anaesthesia, usually in combination with a more potent hypnotic such as halothane or repeated doses of intravenous barbiturates. Neuromuscular blocking agents are used in addition if relaxation is required. Its popularity as a general anaesthetic is based upon its analgesic effectiveness, the rapidity of onset and offset of action, its non-explosiveness, cheapness and freedom from adverse effects.

ALICYCLIC HYDROCARBON

Cyclopropane 

Cyclopropane is a gas that is heavier than air and has an unpleasant odour. It is inflammable and explosive.

ANAESTHETIC EFFECT Cyclopropane is more potent than N_2O and in the highest concentrations used clinically (25–35%) oxygen enrichment of the inspired air is not essential. It can be used alone as an effective analgesic at subhypnotic doses and is an effective hypnotic and muscle relaxant, although in abdominal surgery a neuromuscular blocking agent is usually used in addition. It differs from ether in that respirations are depressed at all stages of anaesthesia and CO_2 accumulates if ventilations are not assisted; pupils dilate and eye movements cease at a lighter level of anaesthesia. The difference between the therapeutic and lethal dose of cyclopropane is said to be larger than for the volatile liquid anaesthetics, although this may reflect the greater rapidity with which cyclopropane achieves its maximal effect at any dose.

DRUG FATE Cyclopropane has a low degree of solubility in blood and, as a consequence, its pharmacokinetics are very similar to those of N_2O. It is excreted exclusively via the lungs, but as the volume absorbed during anaesthesia is small, diffusion hypoxia does not occur.

ADVERSE EFFECTS Cyclopropane has little irritant effect, although occasionally it causes laryngospasm. It increases parasympathetic tone and if an antimuscarinic agent is not used as a premedication it may stimulate bronchial secretions and cause bradycardia. Sympathetic tone is also increased resulting in a slight increase in cardiac output, heart work and BP. On recovery from the anaesthetic, hypotension is common, but seldom severe; nausea and vomiting and headaches are also common. Hepatotoxicity does not occur.

Cardiac dysrhythmias As with the halogenated volatile anaesthetics, cyclopropane sensitises the myocardium to the effects of catecholamines. Tachydysrhythmias occur of which nodal rhythm and ventricular extra systoles are the most common and are exacerbated by hypercapnia, hypoxaemia and high doses of cyclopropane.

CLINICAL USE Cyclopropane is usually, but not always, administered by a

closed circuit system. Although induction is quite rapid, it is seldom used for this purpose. It can be used alone or in combination with other anaesthetics, to maintain anaesthesia.

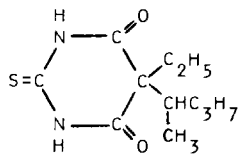
The main advantages of cyclopropane are its potency as an analgesic and hypnotic agent and its rapid rate of onset of action and recovery. The main disadvantages are its explosive properties, its expense and the requirement usually for a closed circuit method of administration, the relatively high incidence of post-operative symptoms and its ability to cause cardiac dysrhythmias.

INTRAVENOUS GENERAL ANAESTHETICS

Barbiturates

The barbiturates used for general anaesthesia are the thiobarbiturates, e.g. thiopentone, thiamylal and thialbarbitone and the methylated oxybarbiturates hexobarbitone and methohexitone. Thiopentone is the oldest of these and the most widely used and the clinical pharmacology of this agent only will be discussed in detail.

Thiopentone



Thiopentone is available as the sodium salt and is a yellow hygroscopic powder, the solution being unstable if left for more than 48 hours. It is insoluble in water and is made up in alkaline solution pH 10·5–11·0. It reacts with acids and acid salts such as suxamethonium, D-tubocurarine, etc., and with oxidising agents but not with atropine. Unlike the longer acting barbiturates it is highly lipid soluble, a characteristic shared by all short acting barbiturates.

ANAESTHETIC EFFECT After i.v. administration, sleep is induced within seconds so that the stage of delirium is very brief. It has no analgesic effect at subhypnotic doses and may actually enhance painful stimuli at these doses. Muscle relaxation occurs at doses sufficient to depress ventilation, but this is seldom adequate for abdominal surgery. Respiratory depression increases with the depth of anaesthesia and hypotension is usually slight due to a myocardial depressant effect and a fall in cardiac output.

DRUG FATE Thiopentone is administered i.v. as it does not achieve anaesthetic concentrations in the CNS via the oral route. In the plasma 70–75% is protein bound. It has an apparent volume of distribution similar to that of total body water and its high lipid solubility enables the drug in the plasma to equilibrate rapidly with tissue water of organs with a high blood flow (e.g. heart, CNS, kidneys, lungs).

The drug is rapidly metabolised by hepatic microsomal enzymes, approximately 15% of a dose being metabolised per hour. After oral administration 10–50% is metabolised during the first passage through the liver. One of the metabolites, pentobarbitone, is the oxygen analogue of thiopentone and has hypnotic properties.

The onset and offset of anaesthesia is determined by the drugs pharmacokinetics. The drug concentration in the brain follows closely that in the blood so that onset of anaesthesia is rapid after i.v. bolus administration. Thereafter, the drug in the plasma is rapidly redistributed to organs of lesser blood flow than the brain, e.g. skeletal muscle, skin, etc., and the plasma and brain concentrations therefore fall rapidly. Recovery from anaesthesia corresponds with the fall in the brain concentration and usually takes 10–30 minutes, but increases with the size of the dose. The drug accumulates slowly in fat depots and after 50–100 minutes the concentration in adipose tissue is much higher than in the plasma and other tissues.

ADVERSE EFFECTS Serious adverse reactions to thiopentone are very few. There is increased sensitivity to respiratory reflexes due to an increase in vagal tone. Cough, hiccough and rarely laryngospasm may occur, the incidence increasing with the dose of anaesthetic, but may be prevented by premedication with an antimuscarinic agent and narcotic analgesic. Post-operative nausea and vomiting and 'hang-over' are quite common when the drug is used alone.

Tolerance This develops rapidly to the CNS depressant effect, the higher the induction and maintenance doses, the higher the plasma concentration on waking. In practice, the lowest dose necessary to produce the desired level of anaesthesia is used.

Tissue irritant All short acting barbiturates are tissue irritants. At a concentration of 5%, thiopentone causes thrombophlebitis in approximately 5% of cases, the incidence decreasing with the concentration used. Extravascular extravasation causes tissue necrosis. Given intra-arterially it may cause gangrene distal to the injection site.

Overdose Thiopentone depresses respirations and the cardiovascular system causing respiratory failure and hypotension.

The drug does not increase myocardial sensitivity to catecholamines and does not cause cardiac dysrhythmias. It is not hepatoxic. Sensitivity reactions are rare, but anaphylacic responses have occurred and thiopentone may precipitate an acute attack of porphyria.

CLINICAL USE

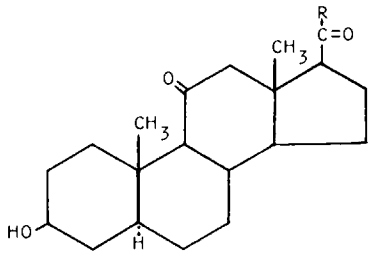
Induction of anaesthesia Thiopentone (3–5 mg/kg) is the agent most widely used in the induction of anaesthesia. Hypnosis occurs within seconds of starting an infusion and the dose is then titrated against the level of anaesthesia produced. It may be used to maintain unconsciousness by means of repeated i.v. doses, the total anaesthetic used being 2–4 times the induction dose per hour in

most cases but decreases with time. It is usually used in combination with other agents (*see* below) but may be used alone for short surgical procedures such as dental surgery, orthopaedic manipulations and for electroconvulsive therapy. In view of the respiratory depressant effect it should only be used when there are adequate facilities for intubation.

Status epilepticus Prolonged thiopentone anaesthesia may be used in status epilepticus that has not responded to other drugs. Respiratory depression at anticonvulsant doses may necessitate positive pressure ventilation.

ALTERNATIVE BARBITURATES The alternative thiobarbiturates and the methylated oxybarbiturates do not differ qualitatively from thiopentone, having similar physicochemical properties, anaesthetic and adverse effects and pharmacokinetic properties. Methohexitone is 2–3 times as potent as thiopentone and is the most widely used of the newer agents. It is metabolised a little more rapidly than thiopentone but recovery rates are similar.

Alphaxalone—Alphadolone Acetate (Althesin)



R

$-CH_3$ ALPHAXALONE

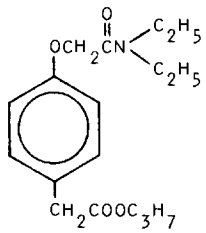
$-CH_2OCCH_3$ (O) ALPHADOLONE ACETATE

This fixed dose combination (0·9% alphaxalone w/v, 0·3% alphadolone acetate w/v) of lipid soluble steroids is now widely used as an alternative intravenous anaesthetic to the barbiturates. Alphaxolone has only half the anaesthetic potency of alphadolone but the mixture is more soluble than alphadolone alone. This combination induces anaesthesia, analgesia and muscle relaxation. It has a higher therapeutic index in experimental animals than thiopentone and at equipotent anaesthetic doses in man causes less respiratory depression. It has a rapid onset and offset of action and is principally removed from the plasma by biliary excretion and hepatic metabolism, most of a dose being excreted in the faeces. Adverse effects, other than those due to overdosage, are few although allergic reactions, mostly skin rashes, occur more frequently than with thiopentone. It does not cause histamine release or local irritation. There are no metabolic effects at anaesthetic concentrations.

PHENOXYACETIC AMINES

Compounds of this group, of which propanidid is the best tried clinically, are related to oil of cloves and are known as eugenol derivatives.

Propanidid



Propanidid is an oil and is insoluble in water. It is available as a viscid solution formed by adding a surface active agent, polyethoxylated castor oil.

Induction of anaesthesia with analgesia is very rapid after i.v. propanidid, but muscle relaxation is poor. Respirations are initially stimulated and then depressed and there is a slight fall in BP. Recovery is usually complete in 10–15 minutes. Propanidid is an ester and is hydrolysed by plasma and tissue esterases, the drug being undetectable in the blood 15–25 minutes after stopping the administration.

Involuntary muscle movements, nausea and vomiting are the most common adverse effects. Thrombophlebitis is more common than after thiopentone, but it causes less tissue damage if extravascular extravasation occurs. Post-anaesthetic psychotic episodes are a novel adverse effect and the drug may also cause haemolysis. It causes histamine release occasionally, with consequent hypotension and bronchospasm.

Propanidid is little used as it has no clear-cut advantages over the barbiturates and because of the dangers associated with its histamine-releasing properties.

ARYLCYCLOALKYLAMINES

Ketamine Ketamine hydrochloride is a derivative of phencyclidine which was the first arylcycloalkylamine anaesthetic to be investigated. It was eventually withdrawn because of the frequency with which it caused hallucinations post-operatively.

Ketamine is administered intravenously (2–4 mg/kg). It induces a sense of detachment from the environment during induction, hypnosis and analgesia, but little muscle relaxation during anaesthesia and amnesia on recovery. Respirations are not depressed and heart rate and BP are elevated, but it does not cause dysrhythmias. Recovery takes several hours. Adverse effects are few, but a small number of patients experience unpleasant dreams and occasionally hallucinations on recovery. The rise in BP may be harmful with hypertensive patients and in those with cardiovascular and cerebrovascular disease. Salivation may be excessive if premedication is not adequate and there is a rise in CSF pressure.

This agent is of established value in children for diagnostic radiological procedures and in hypotensive states when the hypertensive effects may be advantageous.

DRUG USAGE IN GENERAL ANAESTHESIA

The principle drug effects desired during general anaesthesia are analgesia, hypnosis (and amnesia) and muscle relaxation and to a lesser degree, hypotension to diminish blood loss. If a single agent is used to achieve all these effects, e.g. halothane, there is a fixed relationship between the extent to which any of these effects are evident at any one dose. Under such circumstances an increase in any one effect is only achieved by increasing all the other effects as well. This problem can be overcome by using a number of narrow spectrum agents in combination, each being used to achieve a given effect, e.g. analgesia, hypnosis, etc. The use of a number of narrow spectrum drugs during anaesthesia is the preferred method in modern anaesthetic practice.

In Table 4 is set out the drug groups used to achieve the various anaesthetic objectives.

Table 4

The indications for use of some drugs commonly used in general anaesthesia

Premedication	*Induction of anaesthesia*	*Hypnosis*	*Analgesia*
Narcotic analgesics	short acting barbiturates	halothane	N_2O
Minor tranquillisers	alphaxalone–alphadolone	short acting barbiturates	narcotic analgesics
Major tranquillisers	propanidid	ethers	ether
Antimuscarinic agents		cyclopropane	cyclopropane
Muscle relaxation			
Induction	suxamethonium		
Maintenance	pancuronium D-tubocurarine gallamine		

PREMEDICATION The objectives of premedication are to alleviate preoperative apprehension and hence endogenous catecholamine secretion; to suppress secretions, especially bronchial secretions; to provide a prophylactic plasma concentration of analgesic and antimuscarinic agent and so to counteract the increase in vagal tone caused by suxamethonium, thiopentone, halothane and operative procedures.

There are a large number of drugs that may be used for this purpose. Tranquillisers both minor, such as the benzodiazepines, and major, such as the phenothiazines or butyropheonones, may be used to alleviate anxiety. Narcotic

analgesics, e.g. morphine or pethidine, help in sedation and provide prophylactic analgesia. Antimuscarinic agents, e.g. atropine or scopolamine reduce bronchial secretions and prevent the parasympathomimetic effects of anaesthesia or surgery.

INDUCTION Intravenous short acting barbiturates or alphaxalone—alphadolone acetate combination are used almost invariably to induce anaesthesia. Suxamethonium is used to facilitate tracheal intubation.

ANALGESIA Nitrous oxide is used during anaesthesia to obtain an adequate degree of analgesia and may be enhanced, when necessary, by a narcotic analgesic or by lowering the level of consciousness.

MAINTENANCE ANAESTHESIA Halothane is now the most widely used agent for controlling the level of consciousness and its hypotensive effect may also be of value in reducing blood loss. Repeated doses of thiopentone or an alternative inhalation anaesthetic are occasionally used.

MUSCLE RELAXATION A competitive neuromuscular blocking agent such as pancuronium, D-tubocurarine or gallamine are commonly used to achieve muscle relaxation sufficient for major abdominal surgery and to enhance the relaxant effects of halothane and thiopentone (Chapter 10).

RECOVERY The competitive muscle relaxants are rapidly antagonised by neostigmine. The maintenance anaesthetic is stopped 20–30 minutes before the end of the operation if its hypnotic and respiratory effect wears off slowly, e.g. halothane. Nitrous oxide is only stopped when recovery of consciousness is desired and oxygen administration is continued until this has occurred to avoid diffusion hypoxia. Post-operatively there is usually a hangover of the analgesic effect of the various agents used during the anaesthesia for a number of hours. Thereafter, narcotic analgesics are used for 24–48 hours in doses insufficient to cause a serious degree of respiratory depression and not for long enough to induce dependence.

LOCAL ANAESTHETICS

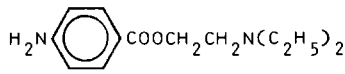
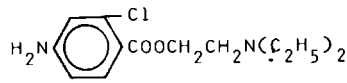
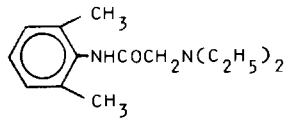
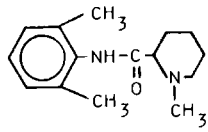
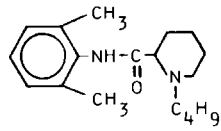
Local anaesthetics are drugs that cause a reversible block in nerve function at therapeutic concentrations. There are a large number of agents with local anaesthetic effects, e.g. alcohols, phenols, phenothiazines, some beta-blockers, quinidine, anticonvulsants, etc., but many of these cause tissue damage at anaesthetic concentrations or systemic adverse effects. The only agents used clinically as local anaesthetics are either tertiary or secondary amines. Coccaine was the first drug to be used for its local anaesthetic effect in the latter part of the 19th century. A large number of synthetic amine local anaesthetics have subsequently become available with structural similarities to cocaine and have rendered cocaine obsolete.

Therapeutic effect The amine local anaesthetics have pKs between 8·0–9·0

and hence are mostly ionised at physiological pHs. They consist of a hydrophilic amine group, an intermediate chain and a lipophilic aromatic group (Table 5) and are all either esters or amides.

Table 5

Some commonly used local anaesthetics

Agent	*structural formula*	*relative potency*	*maximal tolerated dose (mg)*	*concs. used clinically*
	Esters			
procaine		1	1000	2–4%
chlorprocaine		1	1000	2–4%
amethocaine		10	100	0·25–2%
	Amides			
lignocaine		2	500	0·5–2%
mepivacaine		2	500	0·5–2%
bupivacaine		6	200	0·25–0·5%

The local anaesthetic amines compete with calcium for binding sites on neuronal membranes. They reduce sodium conductance and prevent depolarisation of the neuronal membrane and the passage of a nerve action potential. They

have similar effects on all excitable membranes and as anaesthesia only occurs at relatively high concentrations in nerve membranes, they have to be administered close to their site of action.

Local anaesthetics are used clinically for the purpose of achieving local analgesia. They impair the function of motor and autonomic neurones and obtund all modalities of sensation, small nerves being more susceptible than large ones. The local anaesthetics are similar in their therapeutic and adverse effects, but differ in their relative potency, their mode of metabolism and in their duration of action. Lignocaine is the most widely used in clinical practice.

DRUG FATE With the exception of procaine, local anaesthetics in their unionised form are well absorbed after topical administration. After depot administration (s.c., i.m., or epidural) a peak plasma concentration is achieved at 10–30 minutes. Procaine is more rapidly absorbed from depot sites than the other agents as it causes local vasodilatation and an increase in blood flow to the site of the drug.

In the blood local anaesthetics are protein bound, over 90% of bupivocaine being bound after doses in the therapeutic range. Lignocaine is 85% protein bound at plasma concentrations around 2μg/ml and this falls to 20–30% at concentrations of 12μg/ml or more. These agents readily diffuse across cell membranes and the blood-brain and placental barriers, the concentration achieved in the umbilical vein being 50–60% that in maternal arterial blood. As they are weak bases, they are concentrated in the more acid intracellular water and have apparent volumes of distribution 1–3 L/kg.

All local anaesthetics are removed from the plasma by metabolism, very little unchanged drug being excreted in the urine and their duration of action is determined by the rate at which they are metabolised. Esters, such as procaine (*see* Table 5) are hydrolysed by BuChE in the plasma and tissues and have a much shorter duration of action than the amides that are metabolised in the liver. The plasma half-life of lignocaine is approximately 90 minutes (*see* Chapter 22) and that for bupivocaine 120–150 minutes and after equipotent analgesic doses, bupivocaine has a duration of action 1·5–2·0 times that of lignocaine. Their duration of anaesthetic action can be prolonged by the co-administration of the vasoconstrictor adrenaline which reduces the blood supply to the depot site. Lignocaine and bupivocaine administered with 1/200 000 adrenaline have durations of action 2 and 4 hours respectively. Adrenaline should not be used when local anaesthetics are applied to appendages, e.g. fingers, toes, penis, as severe ischaemia may lead to tissue damage distal to the site of injection.

ADVERSE EFFECTS

Local All local anaesthetics have local irritant properties if applied in sufficient concentrations, e.g. the minimal irritant concentration of procaine is 150 times the minimal anaesthetic concentration, the equivalent value for lignocaine being 25. The concentrations used clinically are well below those that cause local irritation.

Allergic reactions are uncommon, but occur more frequently with ester than with amides. Dermatitis is the most common manifestation, especially after topical application, but bronchospasm and anaphylaxis may also occur.

Systemic In general, the more potent the anaesthetic and the longer its duration of action, the higher the incidence of systemic adverse effects. Furthermore, as systemic effects only occur at quite high plasma concentrations (e.g. 10μg/ml or greater for lignocaine) these are most commonly seen when the latter drug is administered i.v. for its antidysrhythmic effect or when these agents are used during prolonged procedures, e.g. epidural blockade for childbirth. The approximate upper limit of the dose for local anaesthetics is shown in Table 5.

On CNS Like cocaine, local anaesthetics initially stimulate the CNS, causing excitement, euphoria, yawning, nausea and vomiting. The patient may complain of perioral paraesthesiae and numbness of hands and feet. Muscle tremors occur at higher concentrations as do convulsions, usually grand mal, followed by CNS depression.

On CVS Hypotension, bradycardia and cardiac dysrhythmias are uncommon in adults when the drugs are administered for their local anaesthetic effect, but have been recorded in neonates delivered after epidural anaesthesia.

ROUTES OF ADMINISTRATION For most clinical purposes, local anaesthetics are administered topically to the skin or eye or by injection, either infiltrating the area to be anaesthetised or by applying the agent close to the nerve, inervating the area (nerve block). The third method, spinal anaesthesia, is used when a wide area of anaesthesia is desired, e.g. for abdominal surgery or childbirth, but as there are serious hazards using this route of administration it should be carried out by an anaesthetist.

Spinal anaesthesia Local anaesthetic is introduced into the subarachnoid space and the level of anaesthesia in the spinal cord is determined by the specific gravity of the local anaesthetic preparation and the position of the patient, e.g. if anaesthesia is to be confined to the lumbar region, a hypertonic solution is used and the patient is kept in the sitting position. Adverse side effects include hypotension due to elimination of sympathetic tone which may result in syncope and impaired organ perfusion. The paralysis of the nerves of respiration occurs if the level of anaesthesia is higher than T2 and if the anaesthetic reaches the brain, respiratory paralysis occurs as a result of depression of the respiratory centre. In epidural anaesthesia, as local anaesthetic does not enter the subarachnoid space directly, the extent to which the agent diffuses is limited and respiratory depression is not a problem, although hypotension is inevitable. Using epidural anaesthesia it is possible to anaesthetise the nerves supplying the vagina and perineum, but not those of the abdominal musculature and this technique is now widely used in labour as it enables a painless vaginal delivery.

CHOICE OF AGENT Lignocaine is the most widely used local anaesthetic and the

more recently introduced prilocaine and mepivacaine have no distinct advantages over it. Bupivacaine has a longer duration of action with no increase in systemic toxicity and is favoured for prolonged procedures such as epidural anaesthesia.

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Chapter 13

Hypnotics and Minor Tranquillisers

There are a large number of drugs that depress the central nervous system which, if given in sufficient dosage, induce sleep. Prescribed at night such drugs, e.g. barbiturates and benzodiazepines, are called hypnotics and during the day, for the amelioration of symptoms of anxiety, minor tranquillisers or sedatives. Thus there is no pharmacological basis to differentiate a hypnotic from a minor tranquilliser, the difference in their effects being determined by the circumstances in which they are used.

The term sedative is also used to describe the major tranquillisers, but as there are important differences between the major and minor tranquillisers (*see* below) it will not be used in this text.

The principal differences between the major and minor tranquillisers are:

1. The major tranquillisers are much more effective at ameliorating the symptoms of psychotic states and they do so at subhypnotic doses.
2. The abuse-liability (i.e. liability to cause drug addiction) is high for most minor tranquillisers but is low for major tranquillisers.
3. The hypnotic effect of the major tranquillisers is much less evident than with the minor tranquillisers. They only cause unconsciousness at doses many times the upper limit of the therapeutic dose range.

Although the benzodiazepines are considered with the minor tranquillisers, they differ quantitatively from the other agents in that they have a lower abuse liability and in high doses do not cause the same degree of CNS depression.

Hypnotics and minor tranquillisers are amongst the most commonly prescribed drugs, between 10–20% of the adult population in Europe and the USA using such drugs at some time during a year. Most have a high abuse liability exceeded by few other drugs and a very large number of patients are dependent on them. They are also the drugs most commonly used in attempted and successful suicides. Their widespread use and the implications that this may have with regard to the health of both individual patients and of the community as a whole, and the possible interactions that these drugs may have with other therapeutic agents, makes knowledge of their pharmacology essential for all practising doctors.

Insomnia and anxiety are symptoms experienced quite commonly by all members of the community, usually being normal responses to stress of some

kind. They may also be symptoms of psychiatric illnesses such as depressive illness, anxiety states or schizophrenia. The use of drugs in the treatment of these symptoms is only justified when other measures have failed and when any associated psychiatric disease has been treated.

Chloral hydrate and the barbiturates were both introduced into clinical medicine in the 19th century and only in the last 20 years have agents with distinct advantages over them been developed. As the barbiturates have been most widely used and thoroughly studied these agents will be considered first and the other hypnotics compared with them.

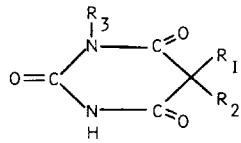
BARBITURATES

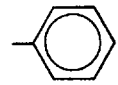
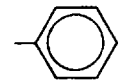
ACTION Barbiturates are weak acids and are all derivatives of barbituric acid (Table 1). They are CNS depressants, depressing neruronal activity at all sites in the CNS. Their hypnotic effect is probably due to depression of neuronal

Table 1

Structure of some barbiturates

Barbiturate nucleus



DRUG	R_1	R_2	R_3
PHENOBARBITONE	$-CH_2CH_3$		-H
BARBITONE	$-CH_2CH_3$	$-CH_2CH_3$	-H
METHOBARBITONE	$-CH_2CH_3$		$-CH_3$
AMYLOBARBITONE	$-CH_2CH_3$	$-CH_2CH_2CH(CH_3)_2$	-H
BUTOBARBITONE	$-CH_2CH_3$	$-CH_2(CH_2)_2CH_3$	-H
SECOBARBITONE	$-CH_2CH{=}CH_2$	$-CH(CH_3)CH_2CH_3$	-H
PENTOBARBITONE	$-CH_2CH_3$	$-CH(CH_3)CH_2CH_3$	-H

activity in the ascending reticular formation (the reticular activating system) as neurones at this site are responsible for the maintenance of wakefulness and are highly sensitive to the depressant effects of barbiturates and related compounds. The effect of these drugs on synaptic events in the CNS is not established. Although they depress many aspects of cell function *in vitro* the relationship between their hypnotic effect and these changes is unclear.

The clinical uses of barbiturates depend on the following effects:

Anaesthesia Any CNS depressant in high doses induces general anaesthesia. Only the highly lipid soluble barbiturates, the thiobarbiturates, e.g. thiopentone and the methylated oxybarbiturates, e.g. hexobarbitones, are used for this purpose and they are considered in Chapter 12.

Hypnosis Barbiturates shorten the time taken in falling to sleep, increase the duration of sleep and decrease motor restlessness during sleep. As with other CNS depressants, such as general anaesthetics and ethanol, they may cause an initial period of disinhibition when the patient is euphoric and more talkative and active than normal. Low doses of barbiturates may thus produce similar behavioural changes as CNS stimulants such as amphetamine. Barbiturate-induced sleep is not similar to physiological sleep as that phase of sleep that is associated with rapid eye movements (REM sleep) is temporarily suppressed, the proportion of total sleep spent in this phase being reduced from 25 to 15% approximately. This effect wears off over 2 weeks if barbiturates are administered each night. Deeper phases of sleep are associated with slow waves on the EEG (phases 3 and 4) and are little affected by barbiturates.

Minor tranquilliser These drugs diminish the severity of both psychic and somatic manifestations of anxiety at doses that usually induce some drowsiness. This effect is more evident when anxiety is a symptom of a neurotic rather than psychotic illness.

Anticonvulsant All barbiturates in therapeutic use have anticonvulsant activity. The long acting agents phenobarbitone and methobarbitone are the most effective anticonvulsants and are the only barbiturates used for this purpose clinically, the others only having this effect at hypnotic doses (Chapter 17).

DRUG FATE All barbiturates are rapidly absorbed from the bowel, diffuse readily across cell membranes and are distributed in total body water. They are partially bound to plasma albumin, the degree of binding being most for the lipid soluble thiopentone (70–75%) and least for the most water soluble agents barbitone (20% or less) and phenobarbitone (35–55%). They compete with other acidic drugs for albumin binding sites, e.g. sulphonamides, probenecid and sulphonylureas.

Barbiturates are mostly cleared from the plasma by metabolism, the principle pathways being side chain oxidation and conjugation reactions. Barbiturates are potent inducers of hepatic microsomal enzymes, phenobarbitone being the

most effective in this respect and they may increase the rate of plasma clearance of other drugs administered concomitantly (*see* Chapter 9). For the intermediate and short acting barbiturates, very little unchanged drug is excreted in the urine. But 70–90% of a dose of barbitone (pK 7·8) and 30–50% of phenobarbitone (pK 7·6) is excreted unchanged in the urine and as these agents have pKs between 7–8, the rate of renal excretion is appreciably increased if the urinary pH is maintained in the alkaline range.

After intravenous administration, the plasma concentration-time curve for these drugs falls exponently. The barbiturates may be classified on the basis of their plasma half-lives into long acting agents, barbitone, phenobarbitone and methobarbitone, with plasma half-lives in adults of 70–150 hours; intermediate acting agents, amylobarbitone, butobarbitone, etc. with half-lives of 10–40 hours and short acting barbiturate anaesthetics, thiopentone, hexobarbitone, etc. with half-life values of 5 hours or less. Only the intermediate and long acting agents are used as hypnotics and minor tranquillisers. All of these agents affect behaviour for up to 24 hours after a single dose and accumulate in the plasma for the first few days or weeks of repeated administration depending on their half-lives.

ADVERSE EFFECTS

Drowsiness Is an inevitable side effect if these drugs are used during the day but it usually wears off within a few weeks on regular dosage. There may be an initial period of elation, similar to ethanol intoxication, before the hypnotic effect becomes evident. If they are used as hypnotics a hangover, notably drowsiness and headache, are not uncommon symptoms. Barbiturates depress the respiratory centre at therapeutic doses and in patients with obstructive airways disease and CO_2 retention, they may exacerbate hypoxaemia and occasionally cause respiratory arrest.

As a suicidal agent High doses of barbiturates produce coma, impair ventilation causing hypoxaemia and hypercapnia and depress the vasomotor centre, myocardium and vascular smooth muscle, causing hypotension. In most subjects, the lethal dose is 10–20 times the conventional therapeutic dose. As a consequence, barbiturates are effective suicide agents and until the widespread use of benzodiazepines, were the agents most commonly used in attempted suicide. They are still the drugs most commonly used in drug induced suicide.

Drug dependence Barbiturates have a high abuse liability, there being a very large number of patients dependent on them in the community. The dose requirement of dependent patients varies from 100 mg each night to 2 g or more per day. Withdrawal from the chronic use of high doses (800 mg/day or more) is associated with an acute organic psychosis identical to delirium tremens (*see* Chapter 18). Convulsions are almost invariable and respond readily to phenobarbitone. After only two weeks of normal doses, withdrawal is associated with an increase in REM sleep, insomnia, dreaming and

nightmares, which may last for weeks. Similar signs and symptoms have been noted after a single large overdose.

Drug tolerance Tolerance to the hypnotic effect of barbiturates may develop within two weeks so that a given dose no longer has a hypnotic effect. In some patients who use barbiturates for their sedative effect, the dose requirement increases until the maintenance dose is in the lethal range for non-dependent subjects. Tolerance to the CNS depressant effect of barbiturates is not based on an alteration in the rate of drug metabolism, but rather an altered response of the vital centres in the CNS to the drug. This may develop very quickly as after a barbiturate overdose, when patients may wake up after a variable period of unconsciousness with plasma concentrations of barbiturate higher than those when they became unconscious.

Drug interactions Barbiturates have an additive effect with other CNS depressants such as ethanol, antihistamines and other hypnotics and minor tranquillisers and advice about this interaction should be offered to patients, especially in relationship to driving.

Enzyme induction Barbiturates may reduce the plasma half-life and hence the effectiveness of drugs with which they are prescribed, e.g. warfarin, phenytoin, tolbutamide, glucocorticoids and digitoxin (Chapter 9). They also may precipitate acute attacks of porphyria by a similar mechanism.

Miscellaneous Rashes of all types occur occasionally, but are relatively rare. In subjects with liver disease and hepatic encephalopathy there is an increased sensitivity to the CNS depressant effects of these drugs which may precipitate hepatic coma.

CLINICAL USE

Administration Barbiturates are administered half an hour before the desired time of sleeping. When taken as a minor tranquilliser the long acting preparations may be taken only once in 24 hours (e.g. before going to bed), but the intermediate acting preparations are taken at least twice a day to maintain a fairly steady plasma concentration. The hypnotic dose is similar to the day time sedative dose and both are established empirically, the range for all agents being 50–200 mg.

Indications Phenobarbitone is an effective drug in the treatment of cortical epilepsy. Thiopentone and related short acting barbiturates are commonly used in the induction of anaesthesia. As hypnotics and minor tranquillisers, the barbiturates have been largely replaced by the benzodiazepines as the latter are ineffective as suicide agents, have a lower abuse liability and do not induce liver enzymes at therapeutic doses.

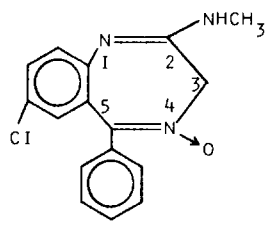
BENZODIAZEPINES

The benzodiazepines are currently the most widely prescribed drugs in the western world. They are weak bases and are mostly highly lipid-soluble. There are a number of agents available that have the same spectrum of pharmacologi-

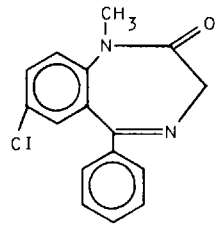
cal actions, differing principally in their pharmacokinetic characteristics. Diazepam is the most widely used agent.

Table 2

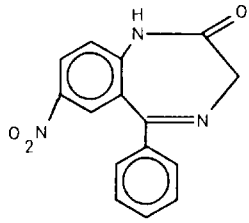
Structure of some benzodiazepines



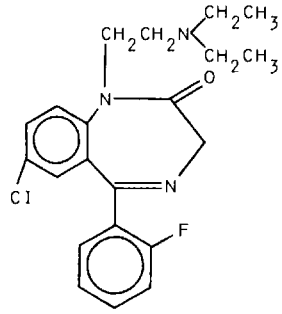
CHLORDIAZEPOXIDE



DIAZEPAM



NITRAZEPAM



FLURAZEPAM

ACTION

Hypnotic and minor tranquilliser These drugs are as effective as barbiturates at inducing sleep and at relieving psychic and somatic symptoms of anxiety. Administered during the day, they are active at doses that cause less drowsiness than equipotent doses of barbiturates. In animals, they depress neuronal activity in the limbic system (amygdala and hippocampus) as doses lower than those affecting the reticular activating system and other parts of the brain and their hypnotic and sedative actions may be due to an effect at this site. Benzodiazepines depress REM sleep and also slow wave sleep (stages 3 and 4). Enuresis, somnambulism and night terrors are associated with slow wave sleep and these drugs may be of value in these conditions.

Anticonvulsant Benzodiazepines, which have conformational similarities to phenytoin, are effective in animals against convulsions induced by electric shocks and convulsant drugs. In man, diazepam is effective in status epilepticus i.v., but in conscious subjects has anticonvulsant properties only at hypnotic doses. Most other benzodiazepines, like diazepam, are ineffective at sub-hypnotic doses, but clonazepam, which is the most potent anticonvulsant benzodiazepine, is effective against both cortical and subcortical epilepsy (Chapter 17).

Muscle relaxant Skeletal muscle tone is depressed by benzodiazepines and they are more effective than a placebo in spastic states due to neuromuscular disease. The site and mode of action responsible for this effect are not established.

DRUG FATE All benzodiazepines are rapidly absorbed from the bowel but absorption from i.m. sites is incomplete as a proportion of the dose precipitates out and is absorbed very slowly. In the plasma, they are extensively bound to plasma albumin (e.g. diazepam is 95% bound) and their apparent volumes of distribution are similar to that of total body water.

These drugs are cleared from the plasma by hepatic metabolism, negligible amounts of unchanged drug being excreted in the urine. Most agents form active metabolites. Diazepam undergoes N–1 demethylation to oxazepam which has CNS depressant actions similar to diazepam and is now marketed as a minor tranquilliser (oxazepam). Flurazepam also undergoes N–1 dealkylation to an active metabolite, most of the flurazepam being dealkylated during one pass through the liver. Chlordiazepoxide also forms active metabolites. Oxazepam is conjugated to an inactive form.

The plasma half-life of flurazepam is very short but for the N–1 dealkylated metabolite is 50–100 hours. The half-life of nitrazepam is approximately 25–35 hours, diazepam 10–40 hours, clonazepam 30–40 hours and oxazepam 25–50 hours. Thus for all these agents the parent drug or active metabolite will accumulate in the plasma for days or weeks during repeated administration. Temazepam (3-hydroxydiazepam) is a recently introduced benzodiazepine with a short $t_{\frac{1}{2}}$ (5–8 h) and which forms no active metabolites. Unlike other benzodiazepines, the active drug does not accumulate in the plasma if administered every night.

Benzodiazepines do not induce hepatic microsomal enzymes at therapeutic doses and are safer drugs than barbiturates to administer to subjects with hepatic damage.

ADVERSE EFFECTS The adverse effects of benzodiazepines are less severe and fewer than those of barbiturates.

Drowsiness, ataxia, impaired memory and hangover occur, but are less frequent than with equipotent doses of barbiturates being reported most commonly in the elderly and in non-smokers. Respiratory depression is slight in the therapeutic dose range, but in subjects in respiratory failure with CO_2

retention it may be clinically important. Intravenous diazepam is safe in the great majority of patients but occasionally causes hypotension and respiratory depression.

Abuse liability Benzodiazepines have some abuse liability but this is much less than that of barbiturates. Dependent patients may tolerate very large doses and the withdrawal syndrome is similar to that of barbiturates.

Overdose Benzodiazepines alone or in combination with other drugs are the most commonly used drugs in cases of self-poisoning. Very seldom have they caused death when taken alone, patients being able to survive after very large doses. The very high degree of safety of benzodiazepines when taken as an overdose is the main advantage of these drugs over barbiturates.

CLINICAL USE

Hypnotic Nitrazepam and flurazepam are the most commonly used agents for this purpose, although they probably have few advantages over cogeners. Withdrawal insomnia and dreaming are less of a problem than with barbiturates.

Minor tranquilliser Diazepam is most widely used for this purpose. It is more effective than a placebo in anxiety states, whether or not depression is also present, but is ineffective in schizophrenia and related psychotic states.

Anticonvulsant Intravenous diazepam is the drug of choice in status epilepticus (Chapter 17). Clonazepam has a broader spectrum of anticonvulsant effects both in children and adults and is safer in large doses than the more commonly used anticonvulsants. It is the drug of choice in myoclonic seizures and is an effective alternative to diazepam and chlormethiazole in status epilepticus.

Muscle relaxant In doses sufficient to cause drowsiness, diazepam reduces muscle tone in anxiety and spastic states and may reduce the frequency and severity of muscle spasms. Diazepam is as effective as other centrally acting muscle relaxants and causes less serious adverse effects. The main adverse effect of alternative centrally acting muscle relaxants are, for mephenesin and related compounds, nausea and vomiting and leucopenia, for baclophen, nausea and vomiting, giddiness and other central symptoms and for dantrolene, changes in liver function tests and hepatocellular damage.

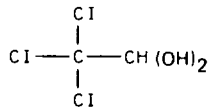
Anaesthetic Intravenous diazepam is very widely used for clinical investigative procedures such as endoscopy and cardioversion and occasionally to

Preparations

	Adult dose range mg	*Route*	*Dose interval*
Chlordiazepoxide	10–100	Oral, i.v., i.m.	12–24
Diazepam	6– 40	Oral, i.v., i.m.	8–24
Oxazepam	10– 60	Oral	12–24
Nitrazepam	5– 15	Oral	24
Flurazepam	15– 30	Oral	24

induce anaesthesia. It causes antegrade amnesia more than does an equipotent dose of a thiopentone. Respiratory and cardiovascular complications are rare but the recovery period is more prolonged than after thiopentone.

Chloral Hydrate



Chloral hydrate was the first hypnotic in clinical use and was widely used in the late 19th century before the advent of the barbiturates. It is still quite commonly used, especially in children, although it suffers from the same drawbacks as the barbiturates.

ACTION Chloral hydrate is an effective hypnotic, but is not used as a minor tranquilliser during the day. Its effects on sleep are similar to those of the barbiturates and tolerance develops within two weeks of its continuous administration.

DRUG FATE Chloralhydrate is rapidly reduced by reductases in RBCs and liver to trichlorethanol, an active metabolite, which probably accounts for much of its hypnotic effect. Trichlorethanol has a $t_{\frac{1}{2}}$ of 8 hours and is partly glucuronated and excreted in the urine and partly oxidised to trichloracetic acid. Negligible amounts of unchanged drug are excreted in the urine. Ethanol inhibits the oxidation of trichlorethanol, increases its plasma concentration and enhances its CNS depressant effect.

ADVERSE EFFECTS Nausea and vomiting due to gastric irritation are common. In most preparations, e.g. Welldorm (dichloralphenazone), chloral hydrate is prepared in a form which is slowly hydrolysed in the bowel so avoiding high concentrations in the stomach.

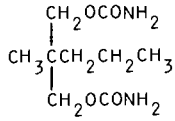
Overdose Chloral hydrate has a narrow therapeutic index, 5–10 times a normal dose occasionally proving fatal, patients dying of respiratory depression and hypotension. Pinpoint pupils are a common sign after an overdose and liver and kidney damage may also occur.

Drug abuse Chloral hydrate has a relatively high abuse liability. Dependent patients are able to tolerate huge daily doses. The withdrawal syndrome is similar to that caused by barbiturates.

CLINICAL USE Chloral hydrate is still widely used as a hypnotic, especially for use in children and the elderly by whom it is said to be better tolerated than other hypnotics, although there is no convincing evidence that this is the case. Its short duration of action relative to other agents appears to be its major advantage and its safety may well be explained in part by the fact that it is commonly prescribed in sub-hypnotic doses.

MISCELLANEOUS AGENTS

Meprobamate

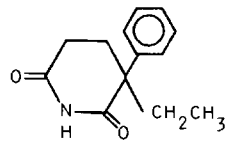


This drug, which was originally introduced as a muscle relaxant, was the first drug to really challenge the pre-eminent position of the barbiturates as hypnotics and minor tranquillisers. However, extensive clinical use has failed to demonstrate major advantages over barbiturates.

Meprobamate is as effective as barbiturates as a hypnotic and minor tranquilliser and its effect on the EEG and in human performance tests are very similar. It also has some anticonvulsant action against petit mal, but it is not as effective as trimethadione. Although it has been used successfully as a suicide agent, it is probably safer than the barbiturates. The drug itself is quite rapidly metabolised, having a half-life of 10–12 hours and approximately 10% is excreted unchanged in the urine.

In clinical practice meprobamate has largely been replaced by the benzodiazepines as a hypnotic, minor tranquilliser and muscle relaxant.

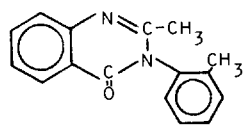
Glutethimide



This agent is closely related to the barbiturates chemically and pharmacologically. It has mostly been used as a hypnotic, but has no advantages over the barbiturates affecting sleep in the same way. It is a highly effective suicide agent, the lethal dose being quite close to the therapeutic dose and a fluctuating level of consciousness, hypotension and muscle spasms are common clinical signs of overdosage. Glutethimide forms an active metabolite 4-hydroxyglutethimide which contributes to its effects both at normal and toxic doses. It has a half-life of approximately 10 hours and is metabolised chiefly in the liver, very little unchanged drug being excreted in the urine.

Methyprylon is similar both chemically and pharmacologically to glutethimide.

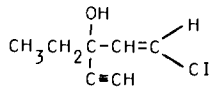
Methaqualone



This drug is usually prescribed in combination with the antihistamine diphenhydramine. Both are effective hypnotics and have an additive effect on sleep. Methaqualone is hydroxylated by hepatic microsomal enzymes and has a $t_{\frac{1}{2}}$ of 10 hours. Alone, or in combination with diphenydramine, it has a high abuse

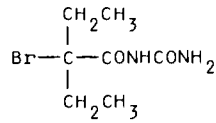
liability and is an effective suicide agent. Signs of severe overdose, apart from unconsciousness, are hyper-reflexia, neuromuscular spasms and convulsions, flattening of T waves on the ECG and pulmonary oedema.

Ethchlorvynol



This drug has hypnotic, minor tranquilliser and anticonvulsant activity. It differs from the barbiturates in having a shorter duration of action ($t_{\frac{1}{2}}$ 4–6 hours) being cleared from the plasma mostly by metabolism, but it has a high abuse liability and a narrow therapeutic index.

Carbromal



Bromide was used extensively as a sedative in the latter half of the 19th century. Carbromal is one of a number of hypnotics containing bromide, which releases the bromide ion on hydrolysis in the body. It has no advantages over other hypnotics. Chronic administration can cause accumulation of bromide ions which have the same distribution as chloride ions, but are not actively transported out of cells and are excreted in the urine with a half-life of 10–12 days. Bromism may result from chronic carbromal ingestion and with a plasma bromine concentration of 10–15 mM, the signs are acne, cerebral retardation, cerebellar dysfunction, hyper-reflexia, extensor plantar responses and gastro-intestinal symptoms. The risk of bromism developing makes carbromal a more dangerous drug than most other hypnotics.

Preparations

	Adult hypnotic dose (mg)	*Paediatric dose*
Chloral hydrate	500–1000	60 mg/year of age
Dichloralphenazone	650–1300	
Meprobamate	400– 800	
Glutethimide	250– 800	
Methaqualone	250– 500	
Diphenhydramine	25– 50	
Ethchlorvynol	250–1000	
Carbromal	250– 500	

Antihistamines and Antimuscarinic Agents Drowsiness is a common side effect of many lipid soluble antimuscarinic agents and antihistamines (*see* Chapters 10 and 39) and several have been promoted specifically as hypnotic agents and are often available without prescription, e.g. methapyrilene, scopolamine and diphenhydramine. Both groups of drugs have a wide range of

side effects and there is little evidence demonstrating the efficacy of these drugs as hypnotics.

Chlormethiazole *See* Chapter 17, p. 223.

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Chapter 14

Major Tranquillisers

Major tranquillisers are drugs that are effective in the treatment of psychotic states which include schizophrenia, hypomania and mania, psychotic depression and organic brain syndromes. In most psychotic states there is no clear understanding of the neurochemical disorders causing the disease and drug treatment is, as a consequence, entirely empirical.

The first tranquilliser drugs to be used in the management of psychotic patients were the barbiturates and bromine, but, as these drugs are only effective against psychotic symptoms at hypnotic doses, the patients on them were usually maintained in a state of semiconsciousness. With the advent of the phenothiazines in the early 1950s it became possible, for the first time, to manage severely disturbed patients without using physical methods and without reducing their level of consciousness with hypnotic drugs. The major tranquillisers have been an important factor in humanising the management of psychiatric patients who, in previous eras had been regarded as suffering from incurable degenerative diseases and been locked away in huge psychiatric institutions organised along custodian lines. Since the introduction of these drugs, it has become possible to manage many such patients at home and the duration of the average admission to hospital has fallen substantially.

THE PHENOTHIAZINES

Phenothiazines were first synthesised in the 19th century, but investigation of their pharmacological activity did not take place until the 1930s and 40s when their antihistamine and other activities were evaluated. Drowsiness was noted to be a side effect of the antihistaminic phenothiazines and this led to their use in anaesthesia as agents that potentiated the actions of barbiturates. Shortly after this, in 1952, the success of chlorpromazine in the treatment of psychotic states was first reported.

There are a large number of phenothiazines, but the differences between the various agents are quantitative only (Table 1). The clinical pharmacology of the group will be discussed and the major differences between groups will be detailed at the end.

ACTION

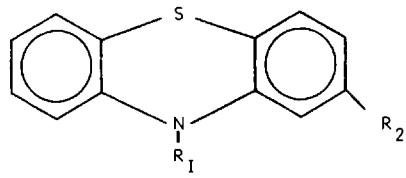
Major tranquilliser Phenothiazines reduce psychomotor activity and at non-hypnotic doses induce a sense of indifference to the environment. They relieve many of the symptoms of schizophrenia and other psychotic states on both subjective and objective criteria. They are most effective at relieving

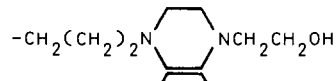
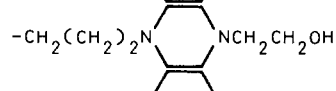
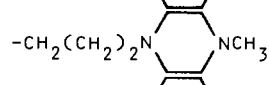
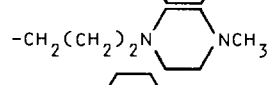
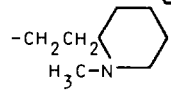
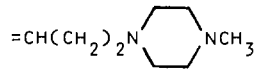
anxiety and delusions, including paranoid delusions. They also relieve anxiety symptoms in depressed patients and are effective in hypomania and mania. They facilitate the management in hospital of patients with psychotic states and organic brain syndromes, and other severely disturbed patients, and enable many to be managed at home.

Table 1

Structural formulae of some commonly used phenothiazines and thioxanthenes

Basic structure



DRUG	R_1	R_2
CHLORPROMAZINE	$-CH_2(CH_2)_2N(CH_3)_2$	-Cl
PROMAZINE	$-CH_2(CH_2)_2N(CH_3)_2$	-H
PERPHENAZINE		-Cl
FLUPHENAZINE		$-CF_3$
TRIFLUOPERAZINE		$-CF_3$
PROCHLOROPERAZINE		-Cl
THIORIDAZINE		$-SCH_3$
CHLORPROTHIXENE	$=CH(CH_2)_2N(CH_3)_2$	-Cl
THIOTHIXENE		$-SO_2N(CH_3)_2$

Anaesthesia Initial doses of phenothiazines cause mild sedation, increase sleeping time without affecting REM sleep and enhance the hypnotic effects of CNS depressants. When given in conjunction with narcotic analgesics they induce a sense of indifference, analgesia and amnesia. This combination of drugs is known as neuroleptanalgesia and is widely used in anaesthesia in Europe.

Analgesic With the exception of methotrimeprazine, these drugs are not used as analgesics alone, but they enhance the effectiveness of narcotic analgesics in severely ill patients by altering patients' responsiveness to pain.
Antiemetic They are potent antiemetics against nausea mediated by impulses arising from the chemoreceptor trigger zone, e.g. drug induced nausea (*see* Chapter 30).
Chorea They decrease involuntary movements in Huntingdon's chorea and in hemiballismus.

SITE AND MODE OF ACTION Phenothiazines and other major tranquillisers can be differentiated from the minor tranquillisers in experimental animals in that they abolish conditioned reflexes at doses that do not affect the animals' response to noxious or threatening stimuli, whereas the minor tranquillisers affect both conditioned and non-conditioned reflexes. They do not depress the reticular activating system directly but block access to it of some sensory stimuli thus acting as selective filters of sensory input.

On peripheral structures, phenothiazines block adrenergic alpha receptors, dopamine receptors, muscarinic cholinergic receptors and have some antihistaminic and antitryptaminergic activity. They are also effective local anaesthetics. The contribution of these various actions at the tissue level to their major tranquilliser and other therapeutic actions remains unclear. However, it appears that their ability to induce Parkinsonian involuntary movements is due to blockade of dopamine receptors in the corpus striatum (*see* Chapter 16). Conversely, their therapeutic benefit in Huntingdon's chorea and in hemiballismus is probably mediated by the same mechanism, as these conditions are thought to result from a relative preponderance of dopaminergic activity within the corpus striatum. There is also evidence that they block dopamine receptors in the limbic system and, as abnormalities in the function of this system have been implicated in schizophrenia, it is possible that actions at this site contribute to their major tranquillising effects.

DRUG FATE Phenothiazines are readily absorbed from the bowel. In the plasma, they are highly protein bound (e.g. chlorpromazine is 91–99% protein bound at therapeutic concentrations). They are also highly bound to tissues, reaching concentrations in the brain over sixty times that in the plasma and even higher concentrations in hair, lung and liver. They are extensively metabolised by the liver, a large number of metabolites having been identified in animals and in patients undergoing treatment. The two most important metabolic pathways are ring hydroxylation and conjugation, and sulphoxide formation. They are excreted rapidly into the bile and undergo very active enterohepatic circulation. Very little unchanged drug is excreted in the faeces and small amounts may be detected in the urine months after a single dose.

After oral administration, the plasma concentration of chlorpromazine falls with a half-life of 15–30 hours and is unaffected by moderate degrees of impaired liver cell function or by coadministration of enzyme inducing drugs. There is a

poor correlation between drugs responsiveness and drug-plasma concentrations.

ADVERSE EFFECTS Phenothiazines are, in general, safe drugs. Unlike the minor tranquillisers they have a low abuse liability producing mostly unpleasant symptoms in normal subjects. They are very safe drugs, deaths from overdose occurring mostly in children. Low doses do not depress respiration in patients with normal respiratory function but may do so in those with hypercapnia and they have an additive effect with other respiratory depressants.

Drowsiness is usually slight and passes off within two weeks of chronic therapy. Postural hypotension with symptoms of dizziness and fainting are also quite common, partly due to peripheral alpha-adrenergic antagonism and partly to a depressant effect on the vasomotor centre. A sizeable proportion of schizophrenic patients on phenothiazine therapy develop symptoms of depression, but it is not clear whether this represents a drug effect or part of the natural history of the condition. Chronic butyrophenone therapy is said to be associated with a higher incidence of depression and thioxanthine therapy a lower incidence. Dry mouth and tachycardia are the commonest manifestations of antimuscarinic activity, but blurred vision, urinary retention etc. may also occur.

Extrapyramidal syndromes Extrapyramidal disorders may occur within the therapeutic dose range. They are most common in elderly patients and are often dose limiting. Parkinsonism is the most common syndrome produced but others, including motor restlessness (akathesia), associated with aching and weakness of the limbs and joint pains, and tardive dyskinesia, may occur. Tardive dyskinesia is characterised by repetitive involuntary movements, usually of the muscles of face and neck, e.g. chewing, grimacing, occulogyric crises or torticollis. It is probably mediated by a different mechanism than other phenothiazine induced extra pyramidal disorders. It may occur either during or more commonly on stopping therapy and less than 40% of patients recover spontaneously. L-dopa and anti-muscarinic agents make it worse and it is thought to be due to a preponderance of dopaminergic activity in the CNS, the consequence of prolonged blockage of dopamine receptors.

In general, the more lipid soluble agents with potent antipsychotic effects most readily induce such syndromes. Thioridazine does so less frequently than other agents at equipotent antipsychotic doses. The parkinsonism usually responds well to antimuscarinic agents which are commonly given prophylactically if the drugs are used in high doses. The treatment of tardive dyskinesia is much less satisfactory, however. It may improve if the dose of phenothiazine is increased but this may cause an exacerbation of the parkinsonism.

Jaundice This occurs in a small proportion of patients, usually in the first 1–2 months of therapy. It is principally cholestatic but is also associated with serological and histological evidence of hepatocellular dysfunction. The mechanism is assumed to be an immune reaction to the drug or a metabolite as it is quite commonly associated with a rash, eosinophilia and neutropenia and

recurs on repeated exposure. It usually clears within 1–2 months of stopping the drug but some patients, usually elderly, have died in liver cell failure. There is no clear evidence that chlorpromazine causes jaundice more commonly than other phenothiazines or the thioxanthines, although this is a widely held clinical impression.

Skin rashes Urticarial, maculopapular or petechial rashes quite commonly occur and clear on stopping the drug. Photosensitivity reactions may also occur on exposed surfaces so that patients on these drugs should avoid sunlight. Excessive pigmentation is quite common after chronic administration.

Eye signs Thioridazine can cause a pigmentary retinopathy with a decreased sense of light intensity and some visual impairment when used in high doses (800 mg/day or more). This has not been reported with other phenotiazines, although they have been associated with corneal and lens pigmentation.

Miscellaneous effects Phenothiazines alter hypothalamic function and may cause galactorrhoea, amenorrhoea or testicular atrophy, an increase in serum prolactin and marked weight gain. T wave changes and ventricular extrasystoles have quite commonly been reported in patients on phenothiazines and the incidence of sudden death with no post-mortem cardiac abnormalities is higher in these patients than in psychiatric patients not so treated. They have occasionally caused aggranulocytosis and neutropenia and changes in circulation lymphocytes. High doses of phenothiazines may cause an increase in fit frequency in established epileptics or induce seizures in non-epileptic patients. Conversely, in epileptics with severe personality disorders phenothiazines may decrease fit frequency.

Drug interactions Phenothiazines enhance the effects of central nervous system depressants such as ethanol and the minor tranquillisers. The interaction with MAOIs is not predictable, but occasionally the latter drugs enhance the central effects of the phenothiazines. These drugs antagonise the hypotensive effect of guanidinium hypotensive agents.

CLINICAL USE

Major tranquilliser Phenothiazines are most widely used in the management of schizophrenia but are also of value in the management of hypomania and mania, in psychotic depression and in organic brain syndromes.

Administration They are given i.m. for acutely disturbed patients, the effect coming on within 30–60 minutes. Maintenance therapy is by daily oral doses and for patients who cannot be relied upon to take their medicine regularly, fluphenazine decanoate, an i.m. depot preparation, may be administered every two weeks to monthly. The size of dose is established empirically and the duration of therapy is determined by the natural history of the condition. In schizophrenia, relapse is more common in patients not taking a maintenance dose of phenothiazines than in those on therapy.

OTHER USES

Antiemetic Phenothiazines are antiemetics of first choice when emesis is

induced by causes other than motion or a local gastric abnormalities (*see* Chapter 30). The agents with potent central effects are most effective and produce few peripheral effects at therapeutic doses.

Analgesic Phenothiazines are not used alone as analgesics, but may be used in conjunction with narcotic analgesics in the management of pain in severely ill patients.

Anaesthetic Neuroleptanalgesia is little used in the UK and USA but is popular in Europe.

Hypothermia Phenothiazines impair temperature regulation and in ambient temperatures below 37°C may cause hypothermia. In neurosurgery and in the management of severe head injuries, this effect is utilised to reduce neuronal damage by decreasing metabolic demands of neuronal tissue.

Huntingdon's chorea Phenothiazines and butyrophenones are the drugs of choice in this condition and in hemiballismus.

Preparations

Remarks	*Drug*	*Dose range mg/24 h*
Peripheral side effects (dry mouth, tachycardia, hypotension) often marked at sedative doses	Chlorpromazine Promazine	75–1000
Central side effects (extrapyramidal syndromes) often marked at sedative doses.	Perphenazine Fluphenazine	4–24 2–15
Potent antiemetics	Prochlorperazine Trifluoperazine Fluphenazine decanoate (i.m. depot)	5–25 5–25 25–100 (14–28 days)
Extrapyramidal syndromes uncommon at sedative doses. May cause pigmentary retinopathy.	Thioridazine	100–500

OTHER MAJOR TRANQUILLISERS

Thioxanthines e.g. thiothixene and flupenthixol. These are closely related to the phenothiazines chemically and their clinical pharmacology is similar to that of the highly lipid soluble agents with prominent CNS effects.

The butyrophenones e.g. haloperidol and triperidol. Although differing chemically from the phenothiazines, the butyrophenones have pharmacological properties almost indistinguishable from the most potent phenothiazines and

can be used in their stead in most clinical circumstances. Extrapyramidal syndromes are readily induced and are usually dose limiting. The butyrophenones have a long duration of action, 2–4 days, and if the drug is given once daily the maximum effect will not develop for 1–2 weeks. They do not cause jaundice.

Butyrophenones are not superior to the phenothiazines as major tranquillisers but are useful alternatives for patients who develop adverse effects, e.g. rashes or jaundice.

Rauwolfia alkaloids Reserpine is the most important clinically of a number of alkaloids derived from the climbing shrub, *Rauwolfia serpentena*, which is indigenous to India. Extracts from this plant have been used for centuries by Hindu doctors for the treatment of a large number of disorders, amongst them madness, but its pharmacology was not systematically evaluated until the 1950s. Although reserpine has potent antipsychotic effects its principal use is as a hypotensive agents (*see* Chapter 23).

Major tranquillising action Reserpine has similar effects to the phenothiazines calming psychotic patients and inducing in them a sense of indifference to the environment without causing sleep. At maximally tolerated doses it is less effective than phenothiazines and it induces depression with its attendant danger of suicide in a proportion of schizophrenic patients. On these accounts it is now seldom used as a major tranquilliser.

Reserpine is not an effective antiemetic. It has no anticonvulsant effect and in experimental animals lowers the threshold to convulsions, and may increase the incidence of fits in epileptic patients.

Hypotensive action Reserpine is an effective agent in the management of mild and moderate degrees of hypertension (*see* Chapter 23).

DRUG FATE Reserpine is a very potent compound with a complex chemical structure that is usually effective at a dose of 2 mg/24 h or less. Little is known of its fate in man except that it is orally active, is widely distributed to the tissues and has a duration of action that outlasts detectable amounts of the drug in the body.

ADVERSE EFFECTS

Depression This occurs in a small percentage of patients, usually in those with a past history of depressive or neurotic illness.

Extrapyramidal syndromes These occur at higher doses and are similar to those due to the phenothiazines, but are probably mediated by a different mechanism (*see below*).

Miscellaneous effects Dry mouth, drowsiness and nasal stuffiness are common. Reserpine increases vagal tone by a central mechanism and causes bradycardia and an increase in gastric acid secretion which may exacerbate symptoms of a peptic ulcer.

MODE OF ACTION The evaluation of the pharmacological effects of reserpine has provided a hypothesis relating biochemical changes in the brain to changes in mood and in extrapyramidal neuronal function.

Reserpine depletes both central and peripheral neurones of monoamines (noradrenaline, dopamine and 5-hydroxytryptamine) causing irreversible changes in the intraneuronal granuoles in which these amines are stored and hence leakage into the cytoplasm where they are degraded by monoamine oxidase. As the effect is irreversible, the rate of return to normal of the monoamine content of the neurones is determined by the synthesis of new storage granuoles. In experimental animals, a clear relationship has been established between depletion of monoamines and signs of extrapyramidal dysfunction. Much less clear is the relationship between monoamine stores and mood changes in man as there is no adequate animal model for human affective disorders. However, it is now widely accepted that the ability of reserpine to cause depression, extrapyramidal syndromes and hypotension are related to the depletion of central neurones and peripheral sympathetic neurones of monoamines.

OTHER AGENTS Deserpidine is another Rauwolfia alkaloid identical in its effects to reserpine, but reputedly having fewer central effects at equihypotensive doses. *Tetrabenazine* is a synthetic agent with actions similar to reserpine, but having a shorter duration of action. It may induce depression and extrapyramidal disorders and has no advantages over the phenothiazines.

CLINICAL USE Reserpine and related compounds are very seldom used as major tranquillisers as they are less effective and have more side effects than the phenothiazines. Reserpine is still quite commonly used as a hypotensive agent.

Preparations

	Dose range mg/24 h
Haloperidol Triperidol	1–10
Reserpine	0·25–2·0
Deserpidine	0·10–3·0
Tetrabenazine	75–150

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Chapter 15

Drugs in the Treatment of Affective Disorders

Depressive illness is the affective disorder for which treatment is most commonly sought. Hypomania is also common, but as it seldom causes unpleasant symptoms, treatment is usually only required when the disorder is moderately severe. The natural history of affective disorders is variable and often unpredictable. They have been classified as those precipitated by environmental factors and those for which no such factors can be identified. However, there is considerable overlap in the symptoms of depressive states with those of psychotic illnesses and anxiety states so that clinical classifications are seldom universally accepted or reliable guides to therapy. Therapeutic measures are best considered in accordance with their ability to relieve individual symptoms or groups of symptoms.

ANTIDEPRESSANTS

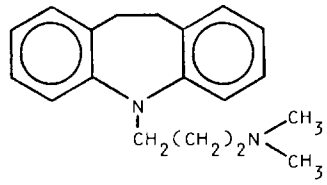
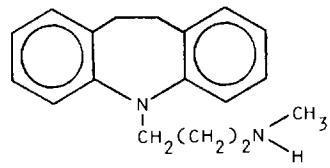
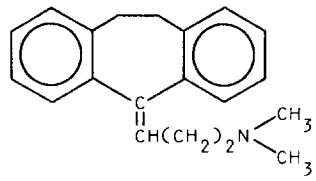
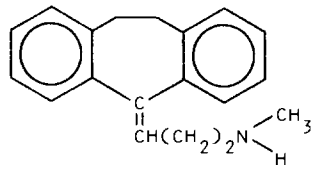
The first successful physical means of treating depressive illness was electroconvulsive therapy (ECT) and it still compares favourably with drug therapy in moderate and severe depressions despite the very extensive use of antidepressant drugs. The clinical evidence suggests that while a relatively small proportion of depressed patients gain considerable benefit from antidepressant drugs, for the majority these drugs are not very effective and their widespread use is not evidence of their effectiveness but only of the absence of other more effective and equally convenient forms of therapy. They are not without danger, however, as both tricyclic antidepressants and monoamine oxidase inhibitors are effective suicide agents. As with the phenothiazines, the antidepressant drugs have facilitated the change in fashion in psychiatry from managing patients in hospital to managing them at home.

Tricyclic Antidepressants (dibenzazepines)

The original drugs in this group are similar in chemical structure to the phenothiazines (Table 1) and it was this structure that determined their generic name. Subsequently, other antidepressant drugs with similar pharmacological properties have been derived but with different chemical structures e.g. compounds that are monocyclic (tofenacin), bicyclic (viloxazine) and tetracyclic (maprotiline, mianserin).

ACTION Tricyclic antidepressants are capable of relieving the symptoms of depression and increasing psychomotor activity or drive in a majority of

Table 1
Some commonly used tricyclic antidepressants

Name		*Adult dose range/24 h*
Imipramine		30–300
Desipramine		30–300
Amitriptyline		30–300
Nortriptyline		30–300

depressed patients. They are most effective when there are no obvious precipitating environmental factors, when the depression is mild or moderate and when it is not associated with psychotic symptoms.

Tricyclic antidepressants have mild hypnotic effects. They increase the total duration of sleep and depress REM sleep, tolerance soon developing to this effect, and there is a rebound of REM sleep on stopping therapy. There is considerable variability in the hypnotic effects between individual agents, those with greatest hypnotic action, e.g. amitriptyline, doxepin and dothiepin being most useful when anxiety is a prominent symptom of a depressive illness. In subjects without depression these drugs are not used as hypnotics or sedatives, being less effective than the minor tranquillisers.

Mode of action Tricyclic antidepressants and pharmacologically related compounds all enhance the functional activity in the brain of the biogenic amines noradrenaline (NA), 5-hydroxytryptamine (5-HT) and to a lesser extent dopamine (DA). They do this mostly by inhibition of the active carrier mechanisms whereby these amines are transported from their sites of action at synaptic clefts into their respective neurones. Thus they prolong the time individual amine molecules remain in the vicinity of the receptors, so increasing amine–receptor interactions. The relative importance of triptaminegic and nor adrenergic neurones in determining mood is not resolved but there is clinical evidence to suggest that the drugs that impair 5-HT re-uptake e.g. the tertiary amines imipramine, amitriptyline and clomipramine, are most effective at elevating the mood of depressed patients where as those that impair NA re-uptake e.g. the secondary amines protriptyline, desipramine and nortriptyline and the tetracyclic maprotiline are most effective at increasing psychomotor activity or drive.

Other effects of tricyclic agents are similar to the phenothiazines. Most are potent antimuscarinic agents and have some antihistamine and antitryptaminergic activity. The contribution these actions have to their antidepressant effects is not known but the antimuscarinic effects are prominent side effects.

DRUG FATE Tricyclic antidepressants are orally active and have a disposition similar to that of the phenothiazines, attaining concentrations in the tissues many times that in the plasma. They are highly bound to plasma proteins (over 90%) and the parent compounds are cleared from the plasma almost exclusively by metabolism. The tertiary amines imipramine and amitriptyline undergo N-dealkylation in the liver to form the active metabolites, desmethylimipramine and nortriptyline respectively, the metabolites themselves having long half-lives. The demethylated compounds are hydroxylated by liver microsomal enzymes and excreted in the urine mostly as conjugates.

In general the plasma half-life of these drugs varies with their degree of protein binding, e.g. the $t_{\frac{1}{2}}$ of desmethylimipramine is 12–26 hours, but that for the more highly bound nortriptyline 18–32 hours and is 4–5 days for protriptyline. The rate of metabolism is genetically determined and varies widely in the population, the plasma concentration at steady state in subjects on a given dose varying 10–40 fold. In moderate or severe liver failure there is little enhanced response to the central effects of these drugs.

ADVERSE EFFECTS Side effects are quite troublesome on these drugs and are often dose limiting.

Central effects Drowsiness is a prominent side effect with amitriptyline, doxepin and dothiepin, to which tolerance usually develops within a few weeks. Rarely patients become manic or confused. These drugs lower the threshold for convulsions and may increase fit frequency in epileptic patients. A fine tremor

develops in some patients and extrapyramidal signs may develop when large doses are used.

Antimuscarinic Dry mouth, blurred vision and constipation are the most common antimuscarinic effects and rarely urinary retention. Others include mydriasis and exacerbation of glaucoma, tachycardia and postural hypotension. Autonomic side effects are most common with protriptyline and least with viloxazin, mianserin and iprindole. In view of the effect of these drugs on heart rate it is probably unwise to use them in patients with established myocardial ischaemia, although doxepin and maprotiline are the safest to use in such patients.

Allergic reactions such as skin rashes, bone marrow depression and liver disease occur occasionally, the latter being less frequent than with phenothiazines.

Drug abuse Like the phenothiazines, these agents have a low abuse liability. However, they are commonly used in attempted suicide, usually being taken with other drugs. The signs of acute overdosage are unconsciousness, depression of respiration, fixed dilated pupils, areflexia or hyper-reflexia, extensor plantar responses, myoclonic seizures, hyperpyrexia, tachycardia and hypotension. ECG abnormalities are common consisting of an increased QT interval ST segment and T wave changes, supraventricular and ventricular tachydysrhythmias. Deaths from overdosage may occur and are more common than after overdosage of phenothiazines or benzodiazepines.

Drug interactions CNS depressants enhance the drowsiness that occurs with these agents. MAOIs have been used in combination with tricyclic antidepressants and have been generally well tolerated. However, occasionally MAOIs increase the sensitivity of patients to tricyclic agents and precipitate overdose effects at doses within the therapeutic range. Tricyclic antidepressants antagonise the hypotensive effects of the guanidinium hypotensive agents (e.g. guanethidine) as they prevent these agents being taken up into sympathetic nerve terminals and they should not be used in patients undergoing treatment with these drugs (*see* Chapter 9).

CLINICAL USE

Administration Tricyclic antidepressants are given by mouth starting with a small dose and increasing at 1–2 week intervals as it may take this time or longer for the full effect of a given dose to become evident. The drugs are usually prescribed 2–3 times per day, but a single dose at night may be adequate, the hypnotic effects then being used to advantage. In most instances treatment is continued for six months or more to prevent a clinical relapse.

There is a relationship between the amelioration of depression and the plasma concentration of antidepressant drugs and both low and high plasma concentrations may be associated with a failure to respond. As there are major

Table 2

Some factors determining choice of agent

Psychomotor stimulants	desipramine nortripyline protriptyline
Sedatives	amitriptyline doxepin dothiepin
Neutral	imipramine dibenzepine
Low anti-muscarinic activity	iprindole mianserin viloxazine
Low cardiotoxicity	doxepin maprotiline
Dopaminergic effects	nomifensin viloxazine

inter-individual differences in the rate that these drugs are metabolised their therapeutic effectiveness may be enhanced by drug plasma concentration monitoring.

Choice of agent As the differences between agents are small and quantitative only, choice can best be determined by the nature of the symptoms relieved by the individual drugs and their various side effects (*see* Table 2).

Monoamine oxidase inhibitors (MAOIs) (Table 3)

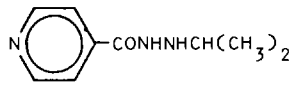
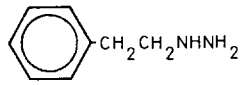
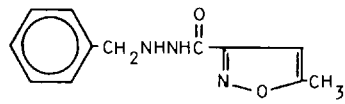
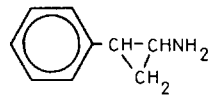
The mood-elevating properties of MAOIs were first noticed in patients with tuberculosis who were being treated with iproniazid, a cogener of isoniazid. Subsequently, iproniazid, but not isoniazid, was found to be a potent MAOI.

ACTION Monoamine oxidase inhibitors are effective antidepressants in relieving mild and moderate depression and are most effective when there is an obvious precipitating event. The degree of improvement is often only moderate and develops over 1–4 weeks.

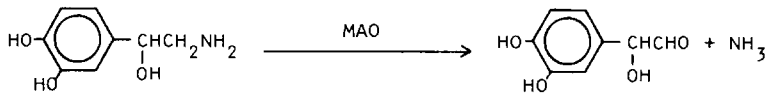
Mode of action MAOIs inhibit the enzyme monoamine oxidase in low concentrations. Inhibition is irreversible, i.e. the effect of these drugs is only overcome by regeneration of new enzyme. Monoamine oxidase is a mitochondrial enzyme

Table 3

Some MAOIs

Name		*Adult dose /24 h*
	Hydrazine containing agents	
Iproniazid		100–150
Phenelzine		15–45
Isocarboxyzide		20–90
	Amphetamine-like agents	
Tranylcypromine		20–40

that facilitates the oxidation of monoamines to aldehydes:



NORADRENALINE

The aldehyde of noradrenaline is either reduced by aldehyde reductase, the major route of metabolism in the CNS, or oxidised by aldehyde dehydrogenase, the major route of metabolism outside the CNS.

Monoamine oxidases are located in sympathetic nerve terminals, in monoamine containing neurones in the CNS, in mucosal cells of the gastrointestinal tract and in the liver. Inhibition of these enzymes causes an accumulation of NA, 5-HT and dopamine (DA) in the cycloplasm of neurones containing them, which leak out into the synaptic clefts.

Inhibition of MAOs in mucosal cells of the bowel wall and especially in the liver facilitates the absorption of amines such as tyramine and dopa, that are normally rapidly metabolised by MAO in the bowel wall and liver. When MAO is inhibited, these amines reach the systemic circulation in appreciable amounts and may cause an acute rise in blood pressure (*see* drug interactions).

The relationship between MAO inhibition and antidepressant effect in man

has not been firmly established because of difficulties in studying amine disposition in the human brain and of correlating such changes with therapeutic effects, but post mortem studies carried out on depressed patients treated with MAOIs have demonstrated an increase in NA and 5-HT in the brain. Some MAOIs (e.g. tranylcypromine) also have effects similar to amphetamine in that they release amines from presynaptic nerve terminals. The relevance of this effect to their antidepressant action is not certain.

DRUG FATE MAOIs are orally active, but there is little information concerning their metabolism and excretion in man. In experimental animals, the active drug is removed from the plasma by metabolism. From information on the metabolism of other drugs with a hydrazine side chain e.g. isoniazid, hydrallazine, the MAOIs containing this group (*see* below) are likely to be acetylated and to display genetic polymorphism (*see* isoniazid, Chapter 35).

In moderate and severe liver disease the central effects of MAOIs are enhanced.

ADVERSE EFFECTS

Hypotension MAOIs may cause postural hypotension, the frequency of this effect varying between agents. Pargyline is a MAOI that is marketed solely for its hypotensive porperties (*see* Chapter 23). Other autonomic disturbances including dry mouth, blurred vision, constipation and hesitancy of micturition are also common.

Central effects Drowsiness is common with the hydrazine containing MAOIs which cause a profound depression of REM sleep throughout therapy with a rebound on stopping. The amphetamine-like agents often cause increased alertness, insomnia and agitation. Occasionally hypomania and manic reactions occur with both types of agent.

Hepatocellular damage Very infrequently patients on MAOIs develop jaundice, the abnormalities on liver function tests and histology being identical to those in viral hepatititis. Indeed, the incidence of this reaction is similar to that of viral hepatitis so that the culpability of MAOIs in this situation is still in doubt. The mortality of patients on MAOIs who develop jaundice is between 20–50% and is appreciably higher than that of infective hepatitis. Jaundice is more commonly associated with the hydrazine containing MAOIs.

Drug abuse MAOIs have a low abuse liability, although tranylcypromine is sometimes taken in conjunction with amphetamines. These drugs are quite commonly taken in attempted suicide, most commonly in conjunction with other drugs. Fatalities occur after an acute overdose and the signs are similar to those of tricyclic antidepressants, hyperpyrexia and hypertension being prominent.

DRUG AND FOOD INTERACTIONS MAOIs may interact with a wide range of chemicals and the potentially lethal effects of some of these interactions has been the principle factor limiting their use.

Interactions due to monoamine oxidase inhibition Tyramine and dopamine are quite common constituents of a number of foods and in patients on MAOIs, reach the systemic circulation in appreciable amounts. They release NA and 5-HT from nerve terminals in the CNS and the peripheral sympathetic nervous system, and when MAOs are inhibited, the response is enhanced as these amines are present in the nerve terminals in greater concentrations than normal. If food containing high concentrations of tyramine and dopamine is consumed by patients on MAOIs, there may be an acute hypertensive episode which may result in an intracranial haemorrhage. The effect on blood pressure wears off spontaneously within 1–2 hours and is best treated with repeated i.v. injections of the short acting alpha-adrenergic receptor antagonist phentolamine. Foods containing appreciable amounts of tyramine and dopamine are cheeses, marmite, liver, game birds, pickled herrings and broad beans. Some wines and beers taken in large quantities may also be dangerous.

MAOIs also enhance the responsiveness to adrenaline, noradrenaline and alpha-adrenergic agonists (e.g. phenylephrine) as well as amine releasing drugs such as amphetamine and ephedrine. Such agents are commonly contained in nasal decongestants, local anaesthetics and bronchodilators and many are available without prescription. Patients on MAOIs should be warned against buying drugs over the counter.

Interactions due to alterations in drug metabolism or responsiveness Patients on MAOIs who receive pethidine may have an exaggerated response and develop coma, hypotension and depressed respirations, or symptoms of dysphoria. This reaction is due to impairment of pethidine metabolism by liver microsomal enzymes, which are inhibited by MAOIs, and accumulation in the plasma of the parent compound or an active metabolite. Other drugs may also be affected in the same way. This may account in part for the exaggerated response that occasionally occurs in patients on MAOIs who are being treated with other drugs including CNS depressants such as ethanol, major and minor tranquillisers and antimuscarinic agents, L-dopa, hypotensive agents of all types, insulin and oral hypoglycaemic agents. Factors other than altered drug metabolism may also be involved in these examples of enhanced drug responsiveness due to MAOIs.

CLINICAL USE

Indications The modest benefit that commonly results from treatment with MAOIs seldom justifies the risks of their potentially dangerous food and drug interactions. As a result, these agents are very seldom used by doctors other than psychiatrists and are used much less than the tricyclic antidepressants.

Administration MAOIs are administered orally once or twice a day, usually becoming effective in 1–2 weeks. They are usually continued for a period of weeks to months as long as the depressive reaction is thought to last. Patients should be advised to avoid the foods, drinks and drugs outlined above and if the patient is incapable of taking such precautions, these drugs are best not

prescribed. As the effects of these agents may persist for two weeks or more after the last dose, these precautions should continue for this period.

Prescribing of MAOIs in conjunction with tricyclic antidepressants is not generally recommended as there is no convincing clinical trial evidence of the efficacy of this combination to justify the risk of the potentiated CNS depressant effects of the tricyclic compounds. Not withstanding this, some psychiatrists are convinced of the efficacy of this combination and commonly use it.

Choice of preparation The amphetamine-like MAOIs increase motor activity and are agents of choice in retarded patients. Otherwise, there seems little to choose between agents.

DRUGS IN THE TREATMENT OF MANIC STATES

Hypomania is a common affective disorder that occurs mostly as part of a manic depressive psychoses. Drug therapy is used in the management of acute manic episodes when the major tranquillisers either alone or with lithium carbonate are the drugs of choice and in chronic prophylaxis when lithium carbonate is the treatment of choice.

Lithium Carbonate

ACTION Lithium ions, usually prescribed as the carbonate, reduce physical and mental activity in patients with hypomania and mania. Lithium is of little benefit as a sedative in anxiety of psychotic states and it is not useful in the treatment or prophylaxis of depressive illness. Chronic administration may reduce the incidence and severity of recurrent manic episodes.

MODE OF ACTION Lithium ions (Li^+) have similar physicochemical properties to sodium and potassium ions. In the body Li^+ is distributed more evenly than Na^+ and K^+ and shares some of the biological properties of extracellular Na^+ and intracellular K^+. It affects many physiological systems, probably due to its ability to impair two basic cellular mechanisms. It impairs ion transport across cell membranes tending to replace Na^+ both inside and outside cells. It also inhibits one or more steps in the adenylcyclase system, reducing cyclic AMP production. The relationship between these effects and lithium's therapeutic effect has not been established.

DRUG FATE Lithium is readily absorbed from the bowel and reaches a peak plasma concentration at 30 minutes. It diffuses in and out of cells more slowly than sodium ions so that it takes longer for equilibration of extra and intracellular lithium to occur. It is distributed in total body water and is eliminated by renal excretion. Fifty–60% of lithium in the glomerular filtrate is absorbed in the proximal tubule but in the rest of the tubule, it is handled independently of sodium and its excretion is unaffected by aldosterone. The plasma half-life is 24 hours, the rate of elimination being limited by the rate it

diffuses out of cells and renal excretion is reduced in renal failure. Triampterine increases renal lithium clearance but thiazides cause a small reduction.

ADVERSE EFFECTS Lithium interferes with some basic cell functions and produces, in consequence, a large number of side effects. Tremor is common, nausea, vomiting and diarrhoea being symptoms of mild overdose which are followed by drowsiness, ataxia, nystagmus, confusion and convulsions in severe overdosage. Endocrine effects include water diuresis with excess thirst through impairment of the effect of antidiuretic hormone on the renal tubule, hypoglycaemia through an insulin-like effect, perhaps mediated through ACTH antagonism, and hypothyroidism, which occurs in approximately 5% of lithium treated patients, through thyroid stimulating hormone antagonism. T wave abnormalities on the ECG are common, but are rarely of clinical importance.

CLINICAL USE

Administration Lithium carbonate is given daily or twice daily and it may take 5–7 days to control manic symptoms. Treatment is continued indefinitely in patients with recurrent hypomania or mania. The effects of the drug are related to its plasma concentration and this should be monitored during therapy (therapeutic range 0·6–1·5 mEq/l), especially in patients with impaired renal function when accumulation of lithium occurs, unless the dose or the dose frequency is reduced.

Preparation

	Dose g/24 h
Lithium carbonate	0·9–1·8

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Chapter 16

Anti-Parkinsonian Drugs

Parkinson's disease is characterised by three cardinal symptoms, hypokinesia, rigidity and tremor. The degree to which any of these symptoms contributes to the patient's disability varies, but in general the most disabling is the hypokinesia.

There are several known causes for Parkinson's disease, including that induced by drugs (phenothiazines, butyrophenones and reserpine) but in the great majority of cases the cause is unknown and the disorder is described as idiopathic Parkinson's disease. The objective of drug therapy in this condition is to relieve the symptoms. There is no evidence that any drug in current use prevents the progress of the disease.

Pathophysiology of Parkinson's Disease

Parkinsonism results from disordered function of the corpus striatum and connecting pathways. The corpus striatum is part of a highly complex polysynaptic nerve network which provides 'feed back' mechanisms between basal ganglia, subthalamic region, cortex and globus pallidus. These pathways are concerned with the adjustment of voluntary movements, mainly by modulating corticospinal activity. The efferent pathways between corpus striatum and corticospinal tract are largely unknown.

Stimulation of striatal neurones by implanted electrodes results in the development of many of the features of parkinsonism. Striatal neurones are stimulated by cholinergic neurones, situated principally in the cortex and subthalamic region, which project on to the corpus striatum. They are inhibited by dopaminergic neurones, with cell bodies in the substantia nigra, which also project on the corpus striatum. Parkinson's disease is thought to develop as a consequence of a reduction in the inhibitory dopaminergic input to the corpus striatum. This may be due to degeneration of the nigrostriatal tract, as in idiopathic Parkinson's disease; to depletion of dopamine stores in dopaminergic nerve terminals by reserpine; or to blockade of dopamine receptors in the corpus striatum by phenothiazines or butyrophenones. Reduction in inhibitory input to the corpus striatum results in relatively greater cholinergic excitatory input and an increase in impulse traffic arising in the corpus striatum.

L-Dopa

ACTION L-dopa (Levo Dopa) is the most effective agent in the treatment of Parkinson's disease producing an improvement in 70–90% of patients who can tolerate it. The hypokinesia and rigidity respond well but the tremor is improved

only in a minority of patients. L-dopa is effective in all types of parkinsonism but the degree of improvement achieved varies widely and is usually better in younger patients with milder symptoms who can tolerate higher doses. The maximum benefit afforded by L-dopa occurs usually in the first two years of therapy. Thereafter the beneficial effects begin to wear off and after five years many patients experience the same functional disability as before starting therapy. The mechanism for this progressive decline in the effectiveness is not understood but it probably represents progression of the disease process.

Mode of action L-dopa that crosses the blood brain barrier is converted to the active metabolite dopamine (DA) by dopa decarboxylase (L-aromatic amino acid decarboxylase) present in some neurones of the corpus striatum (Fig. 1).

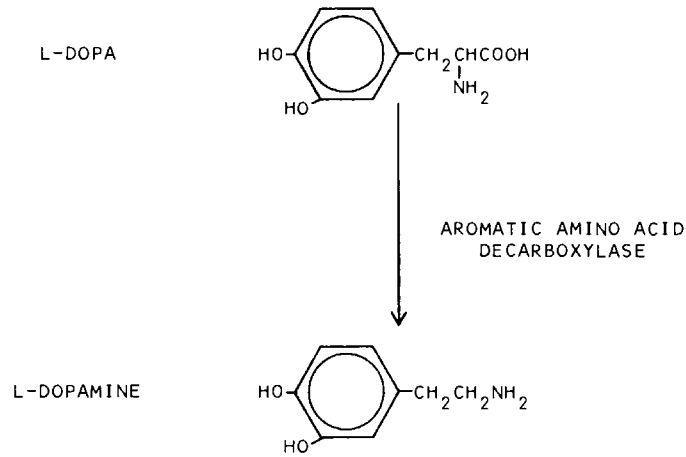

FIG. 1 Conversion of L-dopa to L-dopamine

Administration of L-dopa increases the concentration of dopamine in the corpus striatum which, in turn, inhibits striatal neurones. Dopamine is not effective as an anti-parkinsonian therapy itself as, owing to its high water solubility, insufficient drug can diffuse across the blood brain barrier at maximally tolerated systemic doses.

DRUG FATE L-dopa is readily absorbed from the small intestine by an active carrier mechanism specific for aromatic amino acids and peak plasma concentrations of the unmetabolised drug are achieved by 1–2 hours. Absorption is delayed by factors that delay gastric emptying (e.g. antimuscarinic drugs). L-dopa is rapidly metabolised and negligible amounts of unchanged drug are excreted in the urine. It is metabolised by dopa-decarboxylase which, as well as being present in neurones of the corpus striatum, is present in the gut wall, liver, kidney and the capillaries of the blood-brain barrier. As a consequence, the drug is rapidly converted to dopamine which attains a plasma concentration

higher than that of L-dopa and only a small proportion (circa 1%) of ingested L-dopa reaches the brain. Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) also participate in L-dopa metabolism. Over 30 metabolites have been identified in the urine but homovanillic acid (HVA) accounts for 80–90% of the total drug excreted. A very small proportion of dopamine is metabolised to noradrenaline. The plasma concentration of L-dopa declines with a half-life of 1–3 hours.

ADVERSE EFFECTS Side-effects are common and are frequently dose-limiting. Dopamine and dopamine agonists are central emetics acting on the vomiting centre which is outside the blood-brain barrier and therefore accessible to systemic dopamine. Nausea and vomiting occur early if large initial doses are used. They may be avoided by starting with small frequent doses (2–4 hourly), increasing the dose every 4–6 days, and by prescribing the drug with food.

Postural hypotension A fall in the erect systolic and diastolic BP is a common finding and in a small proportion of patients causes episodes of light-headedness and fainting. The mechanism for this effect is not known.

Cardiac dysrhythmias There is an increased frequency of ventricular ectopics and of both supraventricular and ventricular tachydysrhythmias in patients on L-dopa. This has been attributed to dopamine which, as a beta-receptor agonist, has a positive inotropic and chronotropic effect on the heart. It can be prevented by beta-receptor blocking agents, and other antidysrhythmic drugs. Although there is no convincing evidence that L-dopa exacerbates heart disease, patients with heart disease should be carefully monitored for the cardiac effects of the drug.

Involuntary movements Paradoxically, L-dopa, which is prescribed for a disorder of involuntary movement, may itself cause involuntary movements described as dyskinesia or dystonic movements. These most commonly involve the muscles of the face and lips, e.g. grimacing, chewing, tongue protrusion, but may also involve the limbs. They are dose related and in patients who do not derive benefit from moderate doses, are often dose limiting.

Psychotic episodes Mental disturbances occur quite commonly. Behaviour may be frankly psychotic with hallucinations and delusions or there may be an alteration of personality or a change in mood of which depressive episodes are the most common. Depression is common in parkinsonian patients not on treatment and the contribution of this drug to depression occurring in such patients can only be assessed by stopping the drug.

'On—off' effect Nearly half the patients treated with L-dopa experience episodes when there is a sudden return of severe hypokinesis which lasts from 30 minutes to 6 hours and is followed by an equally rapid improvement. Such episodes are occasionally experienced by untreated parkinsonian patients. They are unusual in the early stages of L-dopa therapy, becoming more

frequent after 1–2 years on the drug. They cannot be wholly explained on the basis of fluctuating plasma concentrations of dopamine and are more common in patients on high doses.

Miscellaneous L-dopa may cause a rise in plasma uric acid and cholesterol concentrations and a Coombe's positive haemolytic anaemia. Prolonged use results in a rise in growth hormone and a decrease in glucose tolerance.

DRUG INTERACTIONS

Extra cerebral dopa decarboxylase inhibitors Inhibitors of L-aromatic amino acid decarboxylase that do not penetrate the blood-brain barrier, e.g. alpha methyldopa hydrazine (carbidopa) and benserazide, increase the plasma half life of L-dopa several fold and hence the proportion of an oral dose that reaches the brain. Given in conjunction with L-dopa, they reduce the dose requirement by 3–5 fold and the incidence of nausea from 80 to 15%. The vomiting centre is outside the blood brain barrier and dopa decarboxylase inhibitors probably prevent emesis by decreasing the concentration of dopamine in the circulation and hence at receptors on the vomiting centre. They reduce the incidence of cardiac dysrhythmias but have little effect on the other side effects. As yet, no serious adverse effects have been reported to alpha methyldopa hydrazine or benserazide. Alpha methyldopa hydrazine is well absorbed, is cleared from the plasma mostly by metabolism with a $t_{\frac{1}{2}}$ of 1–2 hours and approximately 20% of an oral dose is excreted in the urine as unchanged drug.

Methyldopa inhibits L-aromatic amino acid decarboxylase both centrally and peripherally but at therapeutic doses does not reliably enhance or antagonise L-dopa's therapeutic effect.

Antagonists Reserpine, the phenothiazines (least with thioridazine) and the butyrophenones antagonise L-dopa through the mechanisms described on page 208.

Pyridoxine Pyridoxal phosphate is a cofactor to L-aromatic amino acid decarboxylase and hence enhances the rate of L-dopa degradation, decreasing the proportion of an oral dose that diffuses into the CNS. It therefore increases the dose requirement of L-dopa. Pyridoxine is contained in most multi-vitamin preparations and patients should be warned against taking these while on L-dopa. It does not antagonise the effect of L-dopa in conjunction with carbidopa.

CLINICAL USE L-dopa is the drug of first choice in all forms of parkinsonism other than that induced by a phenothiazine or butyrophenone in psychotic or mentally disturbed patients. In such patients it may exacerbate psychotic symptoms. Used alone, treatment is started with 250 mg three times a day after meals. The dose is increased every 3–7 days to a maximum of 2–6 g/day in divided doses according to the clinical response and the incidence of adverse effects. Therapy may be started with carbidopa or benserazide in combination

with L-dopa as this combination reduces the incidence of nausea and vomiting and the dose requirement. If patients on L-dopa only are changed to the fixed dose combination, the dose of L-dopa should be reduced by 75%. An antimuscarinic agent used in combination with L-dopa adds some benefit in approximately half the patients and is particularly effective when parasympathetic symptoms such as sialorrhoea and hyperhydrosis are prominent.

Failure to respond A sizeable proportion of parkinsonian patients either derive little benefit from L-dopa or do not tolerate the adverse side effects. Alternative therapy is now available in the form of a number of dopaminergic agonists, e.g. bromocriptine and norpropylapomorphine. These agents have a direct effect on dopamine receptors and are independent of L-aromatic amino acid decarboxylase which is often depleted in parkinsonian patients. Norpropyl apomorphine is an analogue of the dompamine receptor agonist apomorphine but causes less nausea than apomorphine. It is not available for clinical use in the UK and will not be discussed.

Bromocriptine (2-bromo-α-ergocryptine)

This drug is an analogue of the ergot alkaloids ergotoxin. It is a dopamine agonist and this is probably the basis of its therapeutic effect (*see* Chapter 11).

In Parkinson's disease Bromocriptine has similar therapeutic and adverse effects to L-dopa and is sometimes useful in patients who continue to deteriorate on L-dopa. It has a longer duration of action (6–8 hours) and may be given 1–3 times a day either alone or in combination with L-dopa. On-off phenomena are less frequent than with L-dopa, perhaps because of its longer $t_{\frac{1}{2}}$. The average daily dose is 30–60 μg/day. Its place in the therapy of Parkinson's disease is not as yet established pending the results of adequate clinical trials, but it seems to have no major advantages over L-dopa.

Amantadine

Amantadine was developed as an antiviral agent capable of preventing influenza due to A_2 influenza virus, supposedly acting by preventing viruses penetrating cells. During a clinical trial as a prophylactic agent against this virus its anti-parkinsonian activity was discovered.

ANTI-PARKINSONIAN EFFECT Like L-dopa, amantadine improves hypokinesia and rigidity in a high proportion of patients and has some slight beneficial effect on the tremor. The degree of improvement however is much less than with L-dopa and tends to wear off after a few weeks. It probably acts by releasing dopamine from dopamine nerve terminals which accounts for the rapidity with which tolerance develops to its effect.

DRUG FATE Amantadine is orally active and over 90% is excreted unchanged in the urine.

ADVERSE EFFECTS Side-effects are quite common and consist of dry mouth,

blurred vision, ankle oedema and difficulty in micturition. Central effects, restlessness, insomnia and nightmares, drowsiness, hallucinations and occasionally myoclonic convulsions are often dose limiting.

CLINICAL USE Amantadine is not as effective as L-dopa and does not enhance the responsiveness to that drug. It is, however, cheaper and easier to administer as it is possible to initiate treatment with a maintenance dose. It is used when L-dopa is not available or when it is not tolerated. It may also be used for periods of weeks only to give additional symptomatic relief. The dose should be reduced in patients with impaired renal function.

Antimuscarinic Agents

Atropine has been used in the treatment of Parkinson's disease for over one hundred years. Synthetic antimuscarinic agents have now taken the place of atropine, notably trihexyphenidyl, benztropine, procyclidine and orphenidrine, and until the advent of L-dopa in the 1960s, were the only effective drug therapy. Although there are a large number of these agents there are few significant differences in their therapeutic or adverse effects (*see* Chapter 10).

ANTI-PARKINSONIAN EFFECT Used alone, antimuscarinic agents give some symptomatic relief to a majority of parkinsonian patients but the extent of benefit is much less than that due to L-dopa. The rigidity is improved more than the tremor, though tremor is often helped in mild cases, but hypokinesia is seldom affected. Hyperhydrosis and sialorrhoea, which are not uncommon symptoms of Parkinson's disease, are particularly improved. All types of Parkinson's disease may derive some benefit from antimuscarinic agents, but they are especially effective in the treatment of drug-induced parkinsonism and are given prophylactically with large doses of phenothiozines, thioxanthenes or haloperidol.

ACTION The beneficial effect of antimuscarinic agents in Parkinson's disease is assumed to be due to competitive antagonism of acetylcholine released from excitatory cholinergic nerve terminals in the corpus striatum, so reducing impulse traffic arising from the corpus striatum. Quaternary antimuscarinic agents are ineffective as they do not reach central cholinergic receptors in effective concentrations.

ADVERSE EFFECTS These are fully described in Chapter 10. The most common serious adverse effects in parkinsonian patients, most of whom are elderly, are confusion and acute psychoses, glaucoma and urinary retention.

CLINICAL USE Antimuscarinic agents are the drugs of first choice in the treatment and prophylaxis of drug induced parkinsonism. They are also indicated when hyperhydrosis and sialorrhoea are a prominent feature of the disease. When used in conjunction with L-dopa they may give some therapeutic benefit, but this can only be established empirically. They should not be

withdrawn suddenly from patients on L-dopa as this may cause an acute exacerbation of symptoms.

Miscellaneous Drugs

Before L-dopa many drugs were claimed to have some beneficial effect in Parkinson's disease, including several antihistamines with antimuscarinic activity, MAO inhibitors, tricyclic antidepressants, amphetamine and various minor tranquillisers. The therapeutic benefit of most of these agents has not been established in this condition.

Preparations

	Dose	*Dose interval (h)*
L-dopa	125 mg–2 g	6–8
Amantadine	0·1–0·2 g	12–24
Antimuscarinic agents	(*see* Chapter 10)	
Carbidopa L-dopa	25 mg 100–250 mg	8–24
Benserazide L-dopa	25–50 100–200	8–24

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Chapter 17

Anticonvulsants

A convulsion (or epileptic fit) is the clinical manifestation of an abnormal spread of nerve impulses in the brain. It is initiated by a local disorder of nerve cell function and is entirely non specific. In the majority of cases the nature of the abnormality is unknown. Epilepsy may be a symptom of a physical injury (e.g. trauma, cerebral tumour) or chemical injury (e.g. hypoglycaemia, withdrawal from barbiturates or ethanol) to the brain and it is logical to investigate the cause of the convulsions at the same time as administering drugs to treat them.

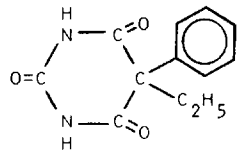
For the purposes of considering drug therapy, convulsions may be classified as cortical or subcortical according to whether the abnormal focus of nerve impulses is located in the cerebral cortex or in deeper structures, as most anticonvulsants are specific to one or other of these types of epilepsy. Cortical epilepsy includes grand mal, focal motor (Jacksonian) epilepsy and temporal lobe (psycho-motor) epilepsy, and subcortical epilepsy includes petit mal, myoclonic and akinetic seizures. Status epilepticus is a state in which the patient does not recover consciousness between recurrent grand mal convulsions. Petit mal status can also occur but is rare.

Anaesthetics and most hypnotics and minor tranquillisers have anticonvulsant properties when given in dosages sufficient to induce sleep. Epilepsy, however, is a chronic condition and drugs are taken to prevent attacks so that only those capable of suppressing fits at subhypnotic doses are of value clinically.

DRUGS FOR CORTICAL EPILEPSY

In cortical epilepsy there is a focus of high frequency neuronal discharges at or close to the cerebral cortex. In grand mal epilepsy these abnormal neuronal discharges activate brain stem reticular structures and cause a massive response which reaches both hemispheres through the ascending diffuse thalamic projections, to cause a convulsion. A grand mal seizure is characterised by a sudden loss of consciousness with or without an aura, a tonic phase, a clonic phase and a period of confusion followed by sleep. In focal motor epilepsy the abnormal focus is close to the motor cortex and clonic movements are localised to one side of the body or one part of one side of the body. In temporal lobe epilepsy (TLE) or psychomotor epilepsy the abnormal focus is in the region of the temporal lobe and symptoms may be gastrointestinal or psychic in nature. Both focal motor and temporal lobe epilepsies may be followed by a grand mal attack.

Phenobarbitone



Phenobaribitone, which has been used as an anticonvulsant since the turn of the century, is effective at suppressing or decreasing the frequency of grand mal and focal motor seizures in 60–70% of patients and in approximately 50% of patients with temporal lobe epilepsy. It sometimes increases the frequency of petit mal attacks and may exacerbate the restlessness of children with diffuse brain damage. Its anticonvulsant effect is enhanced by phenytoin, the actions of these drugs being additive rather than synergistic.

Phenobarbitone depresses all aspects of epileptic activity including the aura and the abnormal epileptic focus on EEG. As with other anticonvulsants, it probably acts at central synapses, but there is little knowledge of how it selectively depresses abnormal neuronal discharges. Methylphenobarbitone and methylbarbitone are other barbiturates used as anticonvulsants that are metabolised to phenobarbitone. They have no advantages over phenobarbitone. Other barbiturates also have anticonvulsant properties but only at hypnotic doses, and as their duration of action is shorter than that of phenobarbitone they are less suitable for maintenance therapy.

DRUG FATE Phenobarbitone is readily absorbed from the bowel and is distributed in total body water, 40–50% of drug in the blood being bound to plasma proteins. It is slowly metabolised by liver microsomal enzymes, partly by paraphenyl hydroxylation. Twenty–40% of a dose is excreted in the urine unchanged and the amount increases with an increase in urinary pH.

Clearance of phenobarbitone from the plasma follows first order kinetics in the therapeutic concentration range (10–25 μg/ml) and the half-life varies between 70–140 hours for adults and is slightly shorter (40–70 hours) for children. The maximal effect of any dose in adults therefore will not be evident for 2–3 weeks from starting therapy.

ADVERSE EFFECTS The adverse effects of phenobarbitone are similar to those of other barbiturates (*see* Chapter 13). It is well tolerated as an anticonvulsant, the commonest side effect being drowsiness which seldom lasts more than 2–3 weeks. It may also cause depression, particularly in the elderly. In children, especially those with severe brain damage, it may cause restlessness and hyperkinesis. Tolerance to the anticonvulsant effect does not develop as it does to the hypnotic effect.

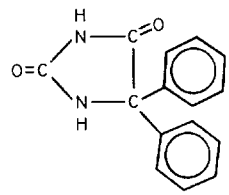
Overdose effects are similar to those of other barbiturates; dysarthria, ataxia and nystagmus attributed to cerebellar disturbance occurring initially and unconsciousness and respiratory depression at higher doses.

Enzyme induction Phenobarbitone is the most potent enzyme-inducing drug in clinical use. It may decrease the half-lives of other drugs administered

concurrently that are metabolised by microsomal enzymes. Phenytoin is such a drug and there is some evidence that the steady-state plasma concentration achieved when a given dose of phenytoin is given with phenobarbitone is lower than that achieved when the drug is given alone. Osteomalacia with a raised alkaline phosphatase and rarely hypocalcaemia may occur in patients on phenobarbitone, phenytoin or primidone. It is most common in inactive epileptics who are rarely exposed to sunlight (*see* Chapter 34). It is probable that this adverse effect is dependent on the enzyme-inducing properties of these drugs, as microsomal enzymes also hydroxylate the active metabolites of vitamin D, 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol to inactive metabolites and this process is expedited by these drugs.

CLINICAL USE Phenobarbitone is a drug of first choice in the prophylaxis of cortical epilepsy. It may be given alone or in combination with phenytoin, the rational basis for combined therapy being that the two drugs have additive anticonvulsant effects, but slightly different side effects. A starting dose of 30–60 mg/day need only be given once per day as the long half-life means that over 24 hours there will be an 8–25% fall only in plasma phenobarbitone concentration.

Phenytoin (Diphenylhydantoin)



Phenytoin was introduced in 1938 and is the most effective of the hydantoin anticonvulsants. It is very similar to phenobarbitone in being most effective against grand mal epilepsy, less effective in temporal lobe epilepsy and often exacerbating petit mal epilepsy. It is effective alone, but is commonly used in conjunction with phenobarbitone.

There are differences in the actions of phenobarbitone and phenytoin. In animals, phenobarbitone raises the threshold to convulsions induced by both an electric shock and by the convulsant pentylene tetrazol, while phenytoin raises the threshold to electro-convulsions only. Phenytoin may prevent a convulsion without abolishing the aura or the epileptic focus on EEG and it is ineffective against barbiturate withdrawal fits which respond readily to phenobarbitone. In nerve-muscle preparations and at autonomic ganglia, phenytoin prevents post tetanic potentiation whereby high frequency discharges facilitate the passage of impulses across synapses. If this occurs at central synapses, it would account for the ability of phenytoin to prevent the spread of impulses from an abnormal focus and hence prevent the maximal seizural activity that causes the tonic phase in a grand mal seizure. Phenytoin prevents sodium accumulation in neurones which occurs during convulsions and it has been proposed that it stabilises nerve

terminals by expediting sodium extrusion fron neurones, hence raising the transmembrane potential.

DRUG FATE Phenytoin is rapidly absorbed from the bowel and is approximately 90% bound to plasma albumin. It achieves a concentration in the CSF equivalent to that of free drug in the plasma. In the brain the highest concentrations are found in the cerebellum. Its volume of distribution is slightly greater than that of total body water.

Phenytoin is hydroxylated by liver microsomal enzymes. The main metabolite is 5-phenyl-5-hydroxyphenylhydantoin which is glucuronidated and excreted in the urine where it accounts for 45–70% of an oral dose. Less than 10% of a dose is excreted in the urine as unchanged phenytoin. At therapeutic plasma concentrations (10–20 μg/ml) phenytoin is cleared from the plasma in accordance with first-order kinetics, the mean $t_{\frac{1}{2}}$ being 20–25 hours, with a range of 7–40 hours. At higher concentrations the half-life increases, due to inhibition of phenytoin hydroxylating enzymes by the drug itself, so that relatively small increases in dose may cause much larger increases in drug plasma concentration and clinical evidence of overdosage (Fig. 1). A small number of individuals have phenytoin half-lifes 3–4 times the normal value.

ADVERSE EFFECTS Cerebellar signs with dysarthria, ataxia and nystagmus develop at plasma phenytoin concentrations of 30μg/ml and greater. Drowsiness is not a prominent side-effect. At higher plasma concentrations nystagmus

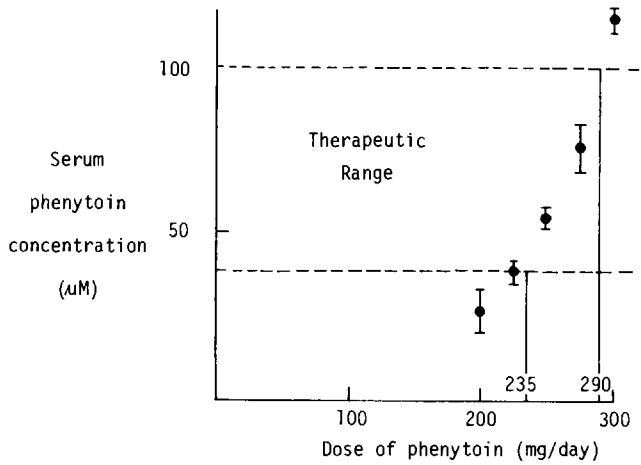


FIG. 1 Serum phenytoin concentration in 25-year-old male epileptic receiving phenytoin at several different daily doses. The horizontal dotted lines represent the upper and lower limits of the therapeutic range. A dose of 235 mg/day would produce a serum concentration at the lower limit and one of 290 mg a concentration at the upper limit of the normal range. (From Richens, A. (1974), Drug estimations in the treatment of epilepsy. *Proc. Roy. soc. Med.* **67**, 1228.)

occurs on frontal gaze and patients may become confused and develop psychotic behaviour.

Gum hypertrophy This occurs in 15–20% of patients at therapeutic doses and is due to hypertrophy and hyperplasia of gum connective tissue. It is usually dose dependent but is also related to poor oral hygiene and may be associated with coarsening of facial features. If troublesome, a gingevectomy may be indicated.

Table 1

Therapeutic range of plasma concentrations of some anticonvulsant drugs

Drug	*Therapeutic range μg/ml*
Phenobarbitone	10–25
Phenytoin	10–20
Carbamazepine	6–12
Sodium valproate	less than 50
Clonazepam	15–50
Ethosuximide	40–100

Folic acid deficiency Phenytoin, and to a lesser extent phenobarbitone and primidone, may cause a macrocytosic and megaloblastic anaemia and a fall in RBC-folic acid concentration. This occurs in subjects on a normal folic acid diet and is corrected by folic acid replacement, even when phenytoin is continued. How phenytoin causes folic acid deficiency is uncertain, but there is evidence that the highly alkaline sodium phenytoin impairs folic acid absorption and that phenytoin and other anticonvulsants, have steric similarities to folic acid and compete with it for enzyme sites in its intermediary metabolism.

Teratogenic effects Fetal abnormalities occur 2–3 times more frequently than normal in babies born to mothers who were taking maintenance doses of phenytoin during the first trimester of pregnancy and appreciably more frequently than in babies born to mothers on phenobarbitone only.

Miscellaneous effects Hirsuitism occurs quite commonly and may be troublesome in women. Rashes, a serum sickness-like syndrome, a systemic lupus erythematosus-like syndrome, hepatocellular damage and haematological abnormalities are rare adverse effects.

Drug interactions Metabolism of phenytoin is impaired by chloramphenicol, PAS and isoniazid, sulthiame and dicourmarol and these drugs, if administered concurrently, may cause phenytoin accumulation. Phenobarbitone and carbamazepine enhance the rate of phenytoin metabolism.

CLINICAL USE Phenytoin alone, or more commonly with phenobarbitone, prevents or reduces the frequency and severity of grand mal epilepsy in up to

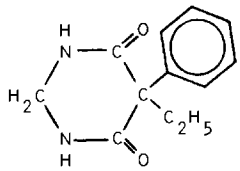
70% of patients, but is less effective in temporal lobe epilepsy. It may be given no more frequently than 12 hourly in most patients and in some a once daily regime may be effective. A low dose (100–200 mg/24 hours for adults) is used initially increasing by small increments (50–100 mg/24 hours) until the fits are controlled or the patient becomes ataxic.

Other uses

1. Cardiac dysrhythmias. Phenytoin is effective at treating and preventing ventricular dysrhythmias whatever the cause and all dysrhythmias due to digoxin overdosage (*see* Chapter 22).
2. Trigeminal neuralgia. Phenytoin is effective at preventing or ameliorating the facial pain of trigeminal neuralgia, but is less effective than carbamazepine.

Other hydantoins Ethoin and methoin are hydantoins with similar actions to phenytoin. They are seldom used as they are no more effective than phenytoin and adverse effects are more common. Methoin may cause bone marrow depression and severe skin rashes.

Primidone



Primidone is an analogue of phenobarbitone in which the carbonyl group of the urea moiety has been replaced by 2 hydrogen atoms. It has a similar spectrum of anticonvulsant activity to phenobarbitone, and is 1/3–1/5 as potent on a weight basis. There is a widely held clinical view, not supported by clinical trial data, that primidone is more effective than phenobarbitone and phenytoin in temporal lobe epilepsy. Occasionally it may also be of value in myoclonic and akinetic seizures.

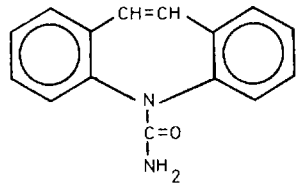
DRUG FATE Primidone is readily absorbed from the bowel. It is partially oxidised to phenobarbitone, the amount of primidone required to achieve a given phenobarbitone-plasma concentration being five times that of phenobarbitone itself. During maintenance therapy the phenobarbitone concentration is 1·5–3 times that of primidone as primidone has a short half-life of 5–10 hours. The other main metabolite phenyl ethyl malonamide (PEMA), also has anticonvulsant activity. It is present in the plasma in higher concentrations than primidone itself.

ADVERSE EFFECTS Adverse effects are very similar to those of phenobarbitone. Drowsiness and visual symptoms are prominent and wear off over 2–3 weeks.

CLINICAL USE Primidone is used without much justification as a drug of first

choice in temporal lobe epilepsy, the apparent difference between itself and phenobarbitone presumably being due to the anticonvulsant properties of primidone itself. In other types of cortical epilepsy primidone is usually administered when maximally tolerated doses of phenobarbitone and phenytoin have proved ineffective.

Carbamazepine



Carbamazepine is chemically similar to the diabenzazepine imipramine. It is an effective anticonvulsant in all forms of cortical epilepsy, including temporal lobe epilepsy, and in grand mal attacks is as effective as phenytoin or phenobarbitone.

DRUG FATE Carbamazepine is well absorbed from the bowel and is cleared from the plasma by hepatic metabolism. The half-life in adults is 24–26 hours but is shorter in children. Its main metabolite, 10,11-epoxycarbamazepine, also has anticonvulsant activity. Carbamazepine is an enzyme inducing agent and shortens the half-lifes of phenytoin and warfarin.

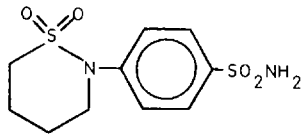
ADVERSE EFFECTS Nausea, vomiting and giddiness are quite common, dry mouth, ataxia and confusion being other minor side-effects. Serious adverse reactions are rare and include bone marrow depression, jaundice and retention of urine.

CLINICAL USE

Cortical epilepsy Carbamazepine used alone or in addition to other drugs, is a drug of first choice in this form of epilepsy, being less likely to cause a depression than phenobarbitone and safer after over dosage.

Trigeminal neuralgia Carbamazepine is the most effective drug at preventing or ameliorating the episodic, stabbing facial pains that characterise this condition. It is used in doses similar to those used in cortical epilepsy.

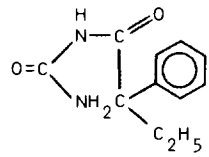
Sulthiame



This drug is a sulphonamide with weak diuretic and carbonic anhydrase inhibitory activity. It is most effective in the control of grand mal and temporal lobe epilepsy. In children it is often of value in hyperkinetic states and in myoclonic seizures.

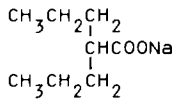
Sulthiame is orally active, 60% is excreted unchanged in the urine. When administered concomitantly with phenytoin it may inhibit the metabolism of the latter. Adverse effects are common and include drowsiness, ataxia, confusional and psychotic states.

Phenylethylacetylurea (Pheneturide)



This drug is a less toxic derivative of phenacemide. It is most effective in cortical epilepsy including temporal lobe epilepsy. Adverse effects are common and may be serious. They include ataxia, affective and behavioural disorders and psychotic episodes, rashes and bone marrow depression. Pheneturide is only used in severely affected epileptics when less toxic drugs have failed. It is said to improve mood and alertness in retarded epileptics.

Sodium Valproate



This agent is unrelated chemically to other anticonvulsants and was being used as a solvent for other drugs when its anticonvulsant properties were observed. It has a broad spectrum of anticonvulsant activity being effective against grand mal and petit mal seizures. In a proportion of patients, it is effective against all types of seizures, but is less effective against temporal lobe epilepsy, focal motor epilepsy and myoclonic seizures than in grand mal and petit mal.

Sodium valproate is administered orally in a dose 20–50 mg/kg/day. It achieves a peak plasma concentration at 1–2 hours and is cleared from the plasma by metabolism with a half-life of 8–10 hours. Adverse effects are seldom serious. Drowsiness, ataxia, anorexia, nausea and vomiting are the most common. Increased motor activity occurs in some children and occasionally a temporary loss of hair.

Sodium valproate has been most widely used in children with cortical and subcortical epilepsy that has not responded to other drugs. It is also of value in some adults suffering from poorly controlled cortical epilepsy. It is often combined with either phenytoin or carbamazepine.

Benzodiazepines All the benzodiazepines have anticonvulsant activity. Diazepam is the drug of choice in status epilepticus (*see* below) and chlordiazepoxide is occasionally of value in addition to first line drugs in grand mal epilepsy. Clonazepam is the most potent anticonvulsant of the benzodiazepines and is effective against cortical and subcortical epilepsy, especially myoclonic seizures. It is cleared from the plasma by metabolism with a $t_{\frac{1}{2}}$ of 25–30 hours. Its place in clinical management is currently being evaluated but its low toxicity

in high doses relative to those of phenobarbitone and phenytoin makes this drug a potentially useful anticonvulsant agent and it is proving particularly effective in status epilepticus.

DRUGS IN STATUS EPILEPTICUS

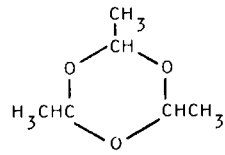
In status epilepticus the patient does not recover consciousness between phases of tonic and clonic convulsions and if the tonic phase is sufficiently long to cause cerebral anoxia, irreversible brain damage may result and the patient may die. The objective of drug therapy therefore is to prevent brain damage by stopping the fits. As the patient is already unconscious it is not necessary only to use drugs that control convulsions at non-hypnotic doses.

Benzodiazepines Diazepam is effective at stopping grand mal seizures when given i.v. in anaesthetic doses. Clinical experience suggests that it is as effective as paraldehyde, phenobarbitone and phentyoin at doses that do not cause as much depression of the respiratory centre. There are conformational similarities between diazepam and phenytoin but otherwise there is little understanding of its mode of anticonvulsant action.

Diazepam is given as a bolus i.v. dose of 5–20 mg and followed by an infusion of 0·5–2·0 mg/min until fitting stops. At these doses the most common adverse effects are hypotension and respiratory depression, patients with pre-existing CO_2 retention being at special risk of the latter. In practice, most cases of status epilepticus are on maintenance doses of anticonvulsants and adverse drug effects in such cases are probably the result of additive effects of multiple drug therapy.

Chlormethiazole Chlormethizole is a derivative of the thiazole nucleus of aneurine (vitamin B_1). It is an anticonvulsant with CNS depressant properties. It has a short duration of action with a plasma half-life of 50 minutes, most of an i.v. dose being excreted in the urine in 3 hours. In status epilepticus it is often effective at doses (0·5–0·7 g/h by continuous infusion) that cause only a slight depression of respiration in cases not responding to diazepam. Chlormethiazole is an effective hypnotic and minor tranquilliser when it is administered orally (0·5–6 g/24 h) and is commonly used in ethanol withdrawal states. Adverse effects are few and include excessive sneezing and coughing.

Paraldehyde



Paraldehyde is a polymer of acetaldehyde with hypnotic properties similar to those of chloral hydrate and has been in clinical use since the 1880s. Before the advent of the benzodiazepines it was commonly used in status epilepticus 5–10 ml i.m. controlling fits in 10–20 minutes.

Paraldehyde is a liquid with a pungent odour that decomposes to acetaldehyde and acetic acid on exposure to light. It must be administered by glass syringe as it causes irreversible changes in plastic. It is rapidly absorbed when taken orally, part is metabolised by the liver, but most of the drug is excreted unchanged by the lungs.

Adverse effects are the pungent odour exhaled, by the patient; a tissue irritant effect and given i.m., sterile abscesses and sciatic nerve damage occasionally occur. It should never be given i.v. as it may cause pulmonary haemorrhages.

Paraldehyde is only used in status epilepticus when diazepam or chlormethiazole have failed or are not available. It is occasionally used as a hypnotic or as a sedative in ethanol withdrawal or in manic states. However, as it is liable to abuse like other CNS depressants and as it has a narrow therapeutic index and may be lethal when used in attempted suicide, it is seldom, if ever, the drug of first choice in any of these conditions.

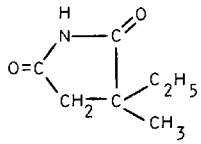
Anaesthesia In rare instances diazepam, phenobarbitone and phenytoin and chlormethiazole fail to stop fitting in status epilepticus. When this occurs anaesthesia with thiopentone and curarisation with positive pressure respiration is usually effective.

DRUGS IN SUBCORTICAL EPILEPSY

Subcortical epilepsy alone is much less common than cortical epilepsy, petit mal and myoclonic seizures being the most frequent clinical forms. Petit mal and myoclonic seizures result from damage to primitive brain structures and are disorders of childhood, onset being rare after the age of 15. These disorders regress spontaneously by adulthood in a proportion, but the majority develop grand mal epilepsy.

In petit mal there are recurrent lapses of consciousness leasting a few seconds only, without alteration of posture, that are associated with a 3 per second spike and wave discharge on the EEG. In myoclonic seizures clonic movements of the jaw and arms accompany the lapses of consciousness and there is a concurrent poly spike and wave pattern on the EEG. Although subcortical epilepsy may prevent normal social activities it does not usually cause brain damage or loss of life and petit mal status is rare.

Ethosuximide



Ethosuximide is the most effective of a number of succinimides in the control of petit mal epilepsy, abolishing or decreasing fit frequency and severity in 60–70% of patients. When petit mal coexists with cortical epilepsy, as it does more often than not, ethosuximide may exacerbate the cortical epilepsy.

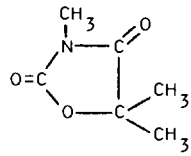
DRUG FATE Ethosuximide is readily absorbed from the bowel. It is cleared from the plasma by metabolism, which occurs more rapidly in children in whom the mean plasma half-life is 30 hours, than in adults in whom it is 60 hours. Very little unchanged drug is excreted in the urine.

ADVERSE EFFECTS Nausea, vomiting, anorexia and colic occur in 10–15% of patients. Leucopenia occurs in a small proportion and rarely aplastic anaemia.

CLINICAL USE Ethosuximide is generally the drug of first choice in petit mal and myoclonic seizures, being as effective as trimethadione, but having a lower incidence of serious adverse effects. If grand mal epilepsy coexists agents for this condition should be used concurrently.

Methosuximide is less effective than ethosuximide in petit mal, but occasionally is of value in temporal lobe epilepsy. Periorbital oedema, nephrotic syndrome and bone marrow depression are occasional adverse effects.

Trimethadione (Troxidone)



Trimethadione was the first effective agent in the treatment of petit mal and like ethosuximide is capable of controlling fits in 60–70% of cases. It exacerbates grand mal but may be of some value in temporal lobe epilepsy. Trimethadione is rapidly absorbed and has a plasma half life of 15–20 hours. It is demethylated to dimethadione which has a half-life of several days and anticonvulsant properties. Dimethadione achieves a plasma concentration approximately 20 times that of trimethadione within 2–3 weeks of starting therapy.

ADVERSE EFFECTS Drowsiness occurs early in therapy but wears off within 2–3 weeks. Blurring of vision to bright light (hemeralopia) is a common side effect due to an adverse effect of the drug on the retina and rarely this may progress to cause a scotoma. These effects are reversible on stopping the drug.

Severe, infrequent adverse effects are rashes, including exfoliative dermatitis, nephrotic syndrome, hepatocellular damage and bone marrow depression.

CLINICAL USE Trimethadione is seldom used as a drug of first choice in petit mal in view of the severity of potential adverse effects.

Paramethadione is occasionally effective in petit mal when trimethadione has failed. Visual symptoms are less common but bone marrow depression more frequent.

Acetazolamide Acetazolamide is a sulphonamide, a potent carbonic anhydrase inhibitor (*see* Chapter 21) and a diuretic. It is also an effective agent in the control of petit mal and is used by some clinicians in preference to ethosuximide.

Carbonic anhydrase is present in the brain, in RBCs, the renal cortex and the

gastric mucosal. Inhibition of the enzyme causes a rise in intracellular CO_2 and hydrogen ions, a fall in intracellular sodium and a rise in extracellular sodium. The anticonvulsant effects of acetazolamide seem to be related to its effect on sodium ions disposition in the CNS rather than the metabolic acidosis or the diuresis it induces.

Acetazolamide is tightly bound to carbonic anhydrase and its effects outlast the presence of free drug in the plasma as the latter is rapidly excreted mostly unchanged in the urine.

ADVERSE EFFECTS These are common to all sulphoamides (*see* Chapter 35) including rashes, bone marrow depression and renal lesions. Diuresis occurs during the first few days of therapy as does a metabolic acidosis (*see* Chapter 21). In patients with hepatocellular failure hepatic encephalopathy may be precipitated by acetazolamide.

CLINICAL USE Acetazolamide is mostly used alone or in combination with ethosuximide when the latter has proved ineffective. Its beneficial effects seem to be short lived as patients commonly relapse on this drug. In conjunction with primidone it may be of value in infantile spasms and akinetic seizures.

ANTICONVULSANT THERAPY

With all types of epilepsy, treatment is started with a low dose of a drug that is likely to be effective and that has a low incidence of severe adverse effects. The dose should be increased after an interval of no less than five times the half life of the drug or active metabolite, which ever is the longer, to allow the full effect of any dose to become evident and dose increases continued until fits are controlled or side effects become intolerable. If one drug does not give adequate control, a second may be instituted and the dose increased as for the first drug. Drugs judged on clinical grounds to be ineffective should be withdrawn slowly, as withdrawal of anticonvulsants is the commonest precipitating factor in status epilepticus.

Drug-plasma concentration determinations Anticonvulsants are type I drugs (*see* Chapter 4), their anticonvulsant effect being closely related to their plasma concentration. Monitoring the drug plasma concentration of anticonvulsants is of use:

1. in determining the patient's compliance with therapeutic instructions. Patient compliance is often poor in epileptic clinics and this can best be assessed by comparing the drug plasma concentration when a patient is under close surveillance with that as an out-patient.
2. to establish in each patient the drug plasma concentration at which good control is established.
3. to determine whether a particular clinical state is due to too large or too small a dose of anticonvulsant.

Preparations

Drug	*Adult dose**	*Dose interval (h)*
Phenobarbitone	30–350	24
Phenytoin	100–300	8–12
Primidone	250–750	12–24
Carbamazepine	100–200	12–24
Sulthiame	50–200	8–12
Pheneturide	200–400	8–12
Sodium valproate	20–50 mg/kg/24h	8–12
Ethosuximide	250–750	12–24
Trimethadione	300–900	12–24
Acetazolamide	500–1000	8–12

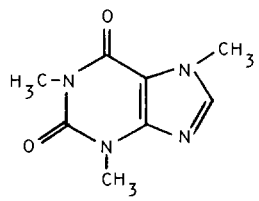
*Doses for children are generally higher on a mg/kg basis than for those of adults.

CNS STIMULANTS

Central nervous system stimulant drugs increase neuronal activity at all levels of the CNS. Though caffeine, which is used for its CNS stimulant effect, is probably the most widely used of all drugs, unlike CNS depressants, CNS stimulants have no established place in therapeutics and will be considered only briefly.

Methylxanthines Caffeine, theobromine and theophylline are all methylxanthines and all have CNS stimulant effects. Although it has no place in drug therapy caffeine will be considered because of its widepread use in the community. Theobromine will not be discussed as it is not used clinically and is much less widely consumed than caffeine. Theophyline is considered in Chapter 35.

Caffeine (Trimethylxanthine)



ACTION *CNS stimulation*—caffeine in doses of 50–100 mg, such as are contained in a cup of tea or coffee, stimulates cerebrospinal activity, increases wakefulness, improves concentration and the capacity for work. There are large differences in the effects produced by caffeine on individual subjects. Those who habitually drink tea and coffee obtain pleasure from its stimulant effect and complain of tiredness and drowsiness in its absence, while abstainers usually dislike its effects complaining of jitteryness and insomnia after caffeine-containing beverages. Caffeine stimulates medullary centres and increases their

sensitivity to CO_2, but stimulates ventilation only in doses considerably higher than those in conventional beverages.

Caffeine has a direct stimulant effect on skeletal muscle probably by releasing calcium from the sarcoplasmic reticulum into the myoplasm and this may contribute to its ability to increase the capacity for physical work.

The effects of caffeine on the heart, smooth muscle and kidney are similar to those of theophyline but it is less effective on a weight basis. Both drugs increase the basal metabolic rate to a small degree.

DRUG FATE Caffeine is quite rapidly absorbed from the bowel. It is oxidised and partially de-alkylated by the liver and is excreted as mono and dimethylxanthine and mono-dimethyl uric acid. As with other methylxanthines, it is not metabolised to uric acid and therefore is not contra-indicated in gout. Less than 10% is excreted unchanged in the urine.

ADVERSE EFFECTS Restlessness, jitteryness, palpitations, gastrointestinal symptoms and insomnia are prominant symptoms of overdosage and are usually more prominent in children than adults. As most colas contain both caffeine and theobromine, children may ingest appreciable doses of methylxanthines. It does not exacerbate epilepsy and causes convulsions only at doses 100 times those in a cup of tea or coffee.

Cardiac tachydysrhythmias may be precipitated or exacerbated by caffeine. Symptoms of a peptic ulcer may also be exacerbated but there is no convincing evidence that caffeine causes peptic ulcers. There is no correlation between coffee and tea drinking and the incidence of myocardial infarction.

Caffeine is remarkable for its apparently low degree of chronic toxicity (*see* Chapter 18).

Drug interactions Caffeine antagonises the effects of CNS depressants in a non-specific manner.

Other CNS stimulants

There are a number of CNS stimulants that increase neuronal activity in many parts of the CNS, increasing the level of consciousness, the rate of respiration and the BP. These agents (Table 2) have been used to stimulate respiration in circumstances in which it is depressed, e.g. post anaesthesia, barbiturate overdosage, chronic obstructive airways disease etc.

Table 2
Examples of drugs used to stimulate respiration

Nikethamide	Bemigride
Amiphenazole	Pentylenetetrazol
Ethamivan	Doxapram
Picrotoxin	Methyl phenidate

These drugs are non-specific in their effects and do not act at the same receptors as CNS depressants such as barbiturates or ethanol. All may cause convulsions in doses within the therapeutic range, although clinical experience with doxapram indicates that it causes convulsions only at doses well above those recommended for therapeutic purposes.

ADMINISTRATION AND ADVERSE EFFECTS All these agents have to be given i.v. to achieve a therapeutic effect and they are given as repeated bolus injections or by continuous infusion. They all have a short duration of action, their effect on respirations usually wearing off in 30 minutes after a bolus injection. Convulsions may occur at doses within or close to the therapeutic range and exacerbate the degree of respiratory depression during the post-ictal period. Less serious side effects are hypertension and tachydysrhythmias, anxiety, sweating, skin irritation, muscle tremors and gastrointestinal symptoms and these may be dose-limiting if the drugs are given by continuous infusion.

CLINICAL USE There is little to choose between the respiratory stimulants although doxapram usually causes fewest side effects when given by continuous infusion and is less liable to cause convulsions.

Drug overdose Respiratory stimulants were commonly used in the 1930s and 1940s in the treatment of barbiturate poisoning but the mortality of patients who were treated with these drugs was shown to be higher than those treated conservatively. They now have no place in the management of overdosage of CNS depressant drugs.

Chronic respiratory failure Respiratory stimulants only increase the rate and depth of ventilation in a minority of patients in chronic respiratory failure and the effect is short lived. They increase oxygen consumption and CO_2 production by increasing the work of breathing and often cause no net change in pO_2 and pCO_2. They are of most use in patients whose level of consciousness rises sufficiently after their administration to enable them to cough and by so doing, increase airway

Preparations

Drug	*Dose*	*Route*	*Dose interval*
Aminophylline	250–500 mg	i.v.	bolus
	0·9 mg/kg/h		infusion
	360 mg	per rectum	8 h
Choline theophylline	400–600 mg/24h	Oral	8 h
Theophylline sodium glycinate	1200–3600 mg/24h	Oral	6–8 h
	Adult dose		
Doxapram	10–30 mg		bolus
	2–3 mg/min		infusion

patency. However, in most instances of severe respiratory failure not responding to therapy with antibiotics, physiotherapy and bronchodilators, positive pressure respiration is used in preference to respiratory stimulants.

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Chapter 18

Drugs of Addiction

Drug addiction (or dependence) arises, when as a result of giving a drug, forces, physiological, biochemical, social or environmental, are set up which predispose to continued drug use. Drugs of addiction are the most commonly consumed of all foreign compounds and while they include useful therapeutic agents such as narcotic analgesics and hypnotics, their therapeutic and prophylactic uses will not be considered in this chapter.

The commonly used drugs of addiction all affect mood or behaviour and are taken to increase or maintain the sense of well-being of the addicted person. The response to these drugs, as to others, varies between individuals and whether or not a given person becomes dependent on a drug depends on the characteristics of the individual as well as the pharmacological properties of the drug. In this chapter, only the pharmacological properties of drugs liable to produce addiction (i.e. having a high abuse liability) will be considered.

The major drugs of addiction are shown in Table 1.

Table 1

CNS depressants	*CNS stimulants*	*Hallucinogens*
Ethanol	caffeine	cannabis
Hypnotics	tobacco	LSD
Narcotic analgesics	sympathomimetics	mescaline
	cocaine	

All drugs of addiction induce a sense of 'psychological dependence' in susceptible individuals. Drugs that cause physical changes on withdrawal, other than craving or changes in mood, after a period of prolonged, repeated use are described as drugs that induce 'physical dependence'. A component in the compulsion to repetitive use of these drugs is the desire to prevent the physical withdrawal syndrome. The difference between 'psychological' dependence and 'physical' dependence is probably apparent rather than real, resulting from the incapacity to detect physical changes in the CNS coincident with craving.

CNS DEPRESSANTS

Ethanol Ethanol is one of the oldest drugs known to man and has been used as a therapeutic agent in all manner of conditions at various times, but now has no place in therapy.

ACTION

Sedative Ethanol is a CNS depressant which, like the barbiturates, affects the ascending reticular formation at concentrations lower than those depressing neurones in other parts of the brain.

In moderate doses, ethanol causes release from inhibitions and has an apparent stimulating effect, increasing friendly behaviour, garrulousness and occasionally aggression, depending on the personality and mood of the individual. Anxiety is relieved but intellectual functions such as memory and ability to do mental arithmetic, are impaired. Similarly, the ability to perform skilled tasks such as driving a motor car is impaired, except in a few repressed individuals in whom small amounts of ethanol, by relieving anxiety, improve performance.

In large doses, the effects of ethanol are similar to those of the barbiturates. There are signs of cerebellar dysfunction, dysarthria, ataxia and nystagmus, gross impairment of intellectual and motor skills and depression of respiration and eventually unconsciousness.

Other actions

1. Vasodilatation of the vessels of the skin causes flushing and a sense of warmth and is due to depression of the vasomotor centre. Coronary vasodilatation does not occur.

2. Increased gastric acid. By a direct effect on antral mucosa, ethanol stimulates release of histamine and gastrin, causing an increase in gastric acid secretion. High concentrations, such as are present in spirits, have irritant effects and cause gastritis in heavy drinkers.

3. Diuresis. Ethanol depresses antidiuretic hormone secretion and causes a marked diuresis. There is an increase of 22 mOsm/l in plasma osmolality for every 100 mg/100 ml of plasma ethanol.

DRUG FATE Ethanol has a molecular weight of 46 and, like urea, is a small polar molecule that readily diffuses across cell membranes. It is rapidly absorbed from the gastrointestinal tract, including the buccal mucosa and stomach, but absorption is most rapid from the small intestine. After ingestion, the highest concentrations occur in organs with the highest blood flow, e.g. CNS, myocardium and kidneys, but it is rapidly distributed to other organs and has a volume of distribution equivalent to total body water.

Metabolism Ethanol is removed from the plasma principally by metabolism by the enzymes ethanol dehydrogenase and acetaldehyde dehydrogenase, nicotinamide adenine dinucleotide (NAD) being the hydrogen acceptor in both reactions (Fig. 1).

Ethanol is cleared from the plasma by zero-order kinetics, i.e. the amount removed per unit of time is constant and independent of the plasma concentration. The rate-limiting factor in this metabolic process is the supply of NAD. There are considerable interindividual differences in the rates of ethanol clearance from the plasma and the average value is 10 ml (7·9 g) per hour.

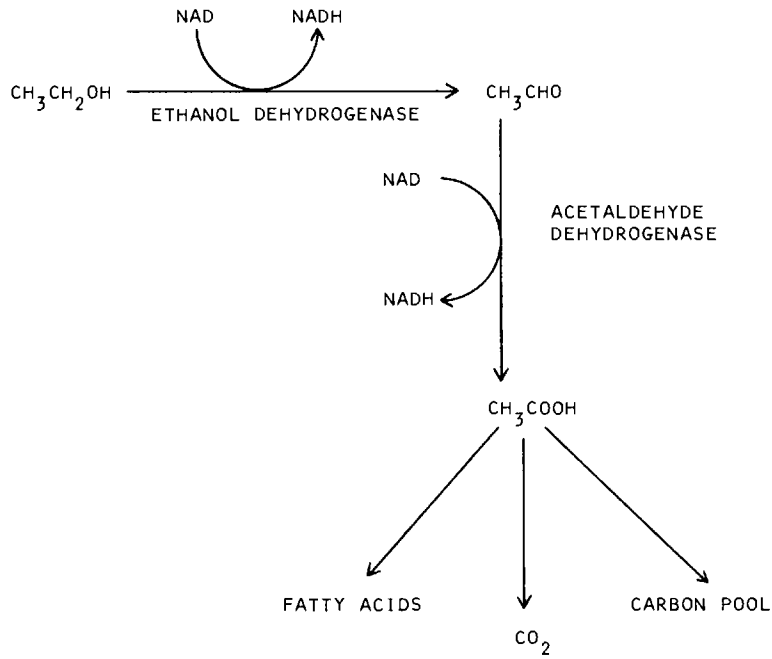

FIG. 1 The removal of ethanol from the plasma by metabolism.

Acetaldehyde is rapidly removed from the blood by both hepatic and extrahepatic acetaldehyde dehydrogenases and is present in the plasma at only one thousandth the concentration of ethanol.

Excretion After moderate doses, 2% or less of the dose is excreted unchanged in the urine, in which the concentration is similar to that in the plasma.

Plasma concentration The effects of ethanol are related to the plasma concentration and these are shown in Table 2, assuming a volume of distribution of 42 l and a clearance rate of 7·9 g/h.

Table 2

Plasma mg%	*Concentration millimoles/l*	*Effect*	*Plasma clearance time (h)*
500	110	deeply comatose	25
200	44	moderately intoxicated	10
100	22	mildly intoxicated	5

There are considerable differences in the response of different individuals to ethanol, habitual drinkers tolerating higher doses than those not habitulated, so that the lethal concentration in the plasma may vary between 200–600 mg/100 ml.

The amount of ethanol in common alcoholic beverages is shown in Table 3.

Table 3

Alcoholic beverage	*Ethanol concentration per 100 ml*	*Usual measure (mls)*		*Amount(g)*
beer	2·8–4·4 g	473 (pint)	=	13–21
wine	7·5	700 (bottle)	=	53
fortified wine	15·0	700 (bottle)	=	105
spirits	42·0	700 (bottle)	=	294
		20 (1/6 gill)	=	8·4

The concentration is also a determinant of the effect of ethanol as the more concentrated the ethanol, the greater the amount absorbed per unit of time and the higher the CNS concentration and the greater the effect on the CNS.

TOLERANCE Tolerance to the CNS effects of ethanol develops rapidly so that the plasma concentration necessary to achieve a given effect increases during the course of an evening's drinking. Habitual heavy drinkers are far less affected by a given plasma level of ethanol than are non-drinkers, tolerance being due to changes in the neuronal response to ethanol rather than to more rapid metabolism of ethanol by dependent individuals.

ADVERSE EFFECTS

Acute overdose Nausea and vomiting occur usually in those who are not habitual drinkers after moderate or large doses. Hangover symptoms of headache, anorexia, nausea and malaise are time-honoured consequences of an acute overdose of ethanol.

High doses of ethanol may be fatal, causing coma and respiratory depression. Inhalation of vomit causing inhalation pneumonia is also a common terminal event in cases of acute poisoning. Ethanol is now frequently ingested with other drugs in patients admitted to hospital with self-poisoning and in drug-induced suicides.

ETHANOL DEPENDENCE The use of ethanol in social situations as a means of lessening tensions between people and increasing conviviality, is time-honoured in most cultures. In western societies, although the patterns of ethanol ingestion vary widely between countries, most adults drink ethanol-containing beverages regularly on social occasions and there are very many who drink large quantities

(90–100 g or more) per day. In the USA there are estimated to be at least 5 million such people and in the UK the number is 400 000 and is probably growing.

CHRONIC TOXICITY The chronic toxic effects of ethanol are responsible for approximately 10 000 admissions per year to hospitals in the UK. Ethanol is an important cause of motor accidents and there are 30 000 arrests for drunken driving per year in the UK.

The clinical conditions that may be caused by chronic ethanol ingestion are shown in Table 4. In some of these dietary deficiency, associated with a high ethanol intake (ethanol having a high calorie content), is the main cause of the syndrome. For example Korsakoff's psychosis, Wernicke's encephalopathy and peripheral neuropathy, are all due in part to thiamine (B_1) deficiency.

Table 4

Gastrointestinal tract	cirrhosis
	pancreatitis
Nervous system	dementia
	peripheral neuropathy
	Wernicke's encephalopathy
	Korsakoff's psychosis
	cerebellar syndrome
	myopathy
Cardiovascular system	cardiomyopathy

There are large interindividual differences in susceptibility to the chronic toxic effects of ethanol. The amounts that must be consumed chronically per day to cause these effects in a significant proportion of drinkers are large, the generally accepted upper limit of safety being 50–75 g/day which is equivalent to three pints of beer, a bottle of wine or three double portions of spirits.

Cirrhosis of the liver is probably the most common morbid consequence of chronic ethanol ingestion, fatty changes often occurring before cirrhosis. High doses over a short period of time may cause an acute hepatocellular jaundice.

The nervous system is susceptible to the deleterious effects of ethanol, dementia and a peripheral neuropathy being the most common syndromes due to chronic ethanol abuse. The cardiomyopathy usually presents as congestive cardiac failure but there are no pathognomonic clinical features and the prognosis in patients who do not stop drinking, as in the case of cirrhosis, is poor.

WITHDRAWAL After prolonged ingestion of large amounts of ethanol, sudden withdrawal is followed within 24–48 hours by delirium tremens (DTs) characterised by agitation, a coarse tremor, restlessness and hallucinations, usually visual and tactile, which terrify the patient. Convulsions occur but are not invariable. Withdrawal symptoms usually persist for a few days and respond to sedation with a phenothiazine, chlormethiazole or any minor tranquilliser.

Barbiturates Until the introduction of the benzodiazepines, barbiturates were amongst the most widely consumed drugs for their sedative and hypnotic effects. In 1972 there were ten million prescriptions for these drugs in the UK where they accounted for 1–2% of all prescriptions.

There are still a large number of patients dependent on one to two barbiturate sleeping tablets per night and who do not increase their dose with time. But there is a much smaller number who have a strong desire to continue the drug, have a tendency to increase the dose, who become tolerant of the drug effects and who develop pronounced symptoms on withdrawal. Such patients commonly administer barbiturates intravenously alone or in conjunction with narcotic analgesics or other drugs.

TOLERANCE Tolerance to the sedative and hypnotic effects of barbiturates develops over a few days. A small proportion of barbiturate users increase their dose regularly to obtain the optimal effect and, as a consequence, finish up taking 1–3 g per day. The signs of overdosage are often obvious—impaired judgement, mood swings, irritability, child-like uninhibited behaviour and dysarthria, ataxia and nystagmus.

WITHDRAWAL Chronic ingestion of 800 mg/day or more will, on cessation, be followed within 8–35 hours by a physical withdrawal syndrome characterised by anxiety, dizziness, muscle twitchings, visual distortions, nausea, vomiting and weight loss, orthostatic hypotension and insomnia. Grandmal convulsions occur in 70–80% of cases and an acute psychosis, identical to delirium tremens in 60–70% of cases. Symptoms may persist for 1–7 days. In general, the longer the duration of action of the drug, the later the onset of withdrawal symptoms, withdrawal symptoms after the long-acting phenobarbitone sometimes not occurring for several days after stopping the drug.

ACUTE OVERDOSE Barbiturates are still the most commonly used drugs in suicide due to drugs and are still widely used in non-fatal self-poisonings. They have a narrow therapeutic index and as little as 5–10 times the usual hypnotic dose may be fatal.

CHRONIC TOXICITY There are no chronic toxic effects of barbiturates analogous to those of ethanol.

Other hypnotics All hypnotics and minor tranquillisers may induce dependence and cause physical withdrawal syndromes similar to those of barbiturates and ethanol. Benzodiazepines are no exceptions but their abuse liability is probably less and the withdrawal syndrome not so severe.

Narcotic analgesics In the UK in 1974, there were approximately 2000 registered narcotic analgesic addicts. This number had doubled since 1959, while there had also been a change from predominantly morphine dependence to predominantly heroin dependence. The numbers dependent on these drugs

in the USA is very much larger, more than 50 000, and in both communities there are many people, mostly teenagers, who use these drugs occasionally.

ACTION Apart from the analgesic, anti-tussive and constipating actions discussed in Chapter 19, morphine and related narcotic analgesics have a euphoriant effect and cause a feeling that all drives to satisfy the needs of the individual are themselves satisfied. These actions are thought responsible for the high abuse liability of these compounds and have been heavily stressed in the past. However, it has become evident recently that, although all habitual users of these drugs become tolerant of their effects and suffer physical withdrawal symptoms, not all have an increased sense of well-being on the drugs and many can give them up spontaneously. Only a very small proportion of the US troops in Vietnam who were dependent on heroin continued to be dependent on returning to the USA.

The first dose of a narcotic analgesic i.m. causes nausea, vomiting, pallor, sweating and itching. There is a fall in respiratory rate and blood pressure, body temperature, the conjunctivae become injected and the eyes droop. Appetite is suppressed and sexual drive reduced and the patient becomes drowsy and inactive and may drop into an intermittent sleep. After an intravenous dose, dizziness occurs within seconds and vasodilatation of the skin and mucous membranes and the patient experiences a feeling very like a sexual orgasm, but referred to the lower abdomen rather than genitalia, which lasts for seconds only.

The narcotic analgesic dependent patient on a maintenance dose may be normal in appearance apart from a persistent meiosis. Constipation is usually persistent, appetite is poor and the desire for sexual intercourse negligible. Women may develop amenorrhoea.

TOLERANCE The emetic effect of narcotic analgesics wears off after 1–2 doses. The euphoriant, analgesic and respiratory depressant effects are also diminished which causes the morphine-dependent patient to increase the dose to achieve the same desired effect and in this way tolerance to very large doses (up to 5 g/24 h) may be achieved within a few weeks. No tolerance develops to the meiosis or the spasmogenic effect causing constipation. There is cross tolerance between the narcotic analgesics and some degree of tolerance to other CNS depressants such as barbiturates, ethanol and general anaesthetics. Tolerance is reversible, the normal degree of sensitivity being achieved 2–3 weeks after withdrawal.

The mechanism of tolerance is not established but is not due to a greater rate of drug metabolism by dependent individuals.

WITHDRAWAL Abstinence after a period of taking a narcotic analgesic regularly for two weeks or more will cause a sterotyped withdrawal syndrome. The signs and symptoms caused by withdrawal are similar for all drugs in the group but are more severe the shorter the duration of the drug's effect. Thus they are most severe after heroin and least severe after methadone.

The stages of withdrawal from morphine are:

0–12 h	normal
12–18 h	yawning, sweating, rhinorrhoea, lacrimation and restless sleep.
18–36 h	the above persist. The patient wakes, pupils are dilated, waves of gooseflesh pass over the patient who feels cold. Muscle twitching occurs and muscle pains are severe.
36–72 h	symptoms more pronounced reaching a peak at 48–72 h. Retching and diarrhoea occur and there is a rise in blood pressure and temperature.
3–10 days	symptoms decline to zero. Weight loss may amount to several kilograms.

Symptoms are not as severe as other narcotic analgesics and do not occur for 3–4 days after stopping methadone, but they may last for several weeks.

Treatment Withdrawal symptoms respond within minutes to administration of morphine, heroin or methadone. As the severity of the withdrawal syndrome is less on methadone, patients are frequently changed to a dose of this drug, equivalent to that of the heroin they were taking and are then withdrawn from this slowly over a period of days to weeks. During the withdrawal period, care of diet and fluid and electrolyte balance is important as well as psychiatric management.

ACUTE POISONING Though tolerance to many of the effects of narcotic analgesics develops rapidly in habitual users, acute overdoses either accidental or deliberate are common and sometimes fatal. It is fairly common for patients who have stopped habitual use of heroin and, in consequence, lost their tolerance to it, to readminister heroin at the relatively high doses to which they were accustomed after habitual use and suffer severe overdose effects.

CHRONIC TOXICITY Narcotic analgesic addicts administer their drugs intravenously, often mixing them with barbiturates and, inadvertently, with contaminants such as talc (magnesium trisilicate) and quinine. Apart from the physical changes from acute overdosage or withdrawal, there is a high morbidity and mortality in such patients due to serum hepatitis, bacterial endocarditis (often of the tricuspid and pulmonary valves) superficial ulcers, pneumonia, acute pulmonary oedema in the presence of normal left ventricular function, dementia and convulsions. The chronic toxic effects of narcotic analgesics are not only due to the direct actions of the drugs themselves, but also to the means of their administration and the life style commonly adopted by chronic abusers.

CNS STIMULANTS

Caffeine Caffeine in the form of tea, coffee and cocoa is probably the most widely used of all drugs and is remarkable for its freedom from adverse effects.

In the western world, nearly all adults and many children take caffeine in one form or another at least once per day and some take it 10–15 times. Yet caffeine in this form has a trivial degree of acute toxicity, it does not cause allergic reactions and there are no established chronic toxic effects. Tolerance does not develop to its analeptic effect and there is no physical withdrawal syndrome.

ACTION In common with other xanthines, caffeine stimulates all parts of the CNS, especially the cortex (*see* Chapter 17). At doses common in a cup of tea or coffee (65–100 mg) it alleviates drowsiness and facilitates thought and it is this analeptic effect that is responsible for the dependence that it induces.

ADVERSE EFFECTS High doses of caffeine cause insomnia, anxiety, restlessness and tachydysrhythmias. These are seldom pronounced in adults but may be so in children. There are no withdrawal symptoms, although headaches have been attributed to caffeine withdrawal.

Tobacco Tobacco was introduced to Europe in the 16th century and until the 20th century was smoked in a pipe or as cigars by a small proportion of the population only. In the 20th century, the popularity of the habit has soared and cigarettes have become by far and away the most common form in which tobacco is smoked. In 1968 in the UK 66% of adult males and 21% of adult females smoked, the equivalent figures for the USA in 1970 being 40–50% and 30–40% respectively.

Despite this long history, the chronic toxic effects of tobacco smoking were not remarked on until 1938 and not established until 1950.

CONSTITUENTS OF TOBACCO The biological effects of tobacco are partly attributable to nicotine and carbon monoxide and partly to carcinogens and irritants present in tobacco smoke.

ACTION Dependence on tobacco is mediated partly by the actions of the chemical constituents of inhaled smoke and partly by the ritual of smoking. Nearly a thousand chemicals have been isolated from tobacco and only those with known effects are considered here.

1. Nicotine Between 0·4–3·0 mg of nicotine is absorbed after smoking one cigarette depending on the rate of smoking and on how much smoke is inhaled. The peak arterial nicotine concentration varies from 40 ng/ml for inhalers to 25 ng/ml for non-inhalers. There are large interindividual differences in plasma concentration of nicotine achieved and these are dependent on differences in smoking method. The half-life of nicotine in plasma is about 30 minutes and cotinine is the main metabolite. Nicotine is an important factor in determining dependence on tobacco smoking as cigarettes with a high nicotine content are

more popular than those with a lower content and feelings of craving can be alleviated by intravenous nicotine.

The subjective effects of smoking vary between individuals, but most smokers say that smoking either makes them more alert or calms them down. The effects on the CNS in man are not well established, but in animals it may cause arousal or sedation depending on the animal, the dose administered and the state of the animal before administration.

Nicotine stimulates and then depresses autonomic ganglia. This probably accounts for the increase in the plasma concentration of catecholamines, the increase in pulse rate, cardiac output, BP and peripheral resistance and in plasma free fatty acids that follow the inhalation of tobacco smoke. Nicotine also stimulates the release antidiuretic hormone and increases platelet adhesiveness.

2. *Carbon monoxide* Carbon monoxide accounts for 400 parts/million of air inhaled into the lungs from a cigarette and by forming the relatively stable carboxy-haemaglobin, causes a 10% reduction in haemaglobin available for oxygen carriage. While such a reduction is of little importance for normal people, for patients with reduced cardiopulmonary function, anaemia or severe arterial disease, such a reduction may be critical.

3. *Carcinogens* Tobacco smoke contains a number of agents that can either initiate cancer, e.g. polycylic hydrocarbons, nitrosamines, and radioactive isotopes (e.g. polonium), or promote tumour growth once initiated, e.g. volatile phenols, non-volatile fatty acids and N-alkyl heterocyclic compounds. These agents and possibly others in tobacco smoke, are probably responsible for the strong statistical link between cigarette smoking and several cancers, notably cancer of the bronchus. The incidence of bronchial carcinoma, squamous cell, oat cell and undifferentiated types, but not adenocarcinoma, is higher in smokers than non-smokers and is higher in cigarette than pipe and cigar smokers. The risk of developing cancer of the bronchus increases with the number of cigarettes smoked and with their 'tar' content, and in males in the UK who smoke 40 a day is 25–30 times that of non-smokers. The risk is probably lower in females than male smokers and is lower in both sexes in the USA than in the UK. Lung cancer is commoner in smokers living in the town than those living in the country. Ex-smokers have a lower risk of developing lung cancer than smokers and the risk declines with time after stopping smoking.

There is a statistical link between cigarette smoking and other cancers. The incidence of cancer of the oral cavity, larynx, oesophagus, urinary bladder and pancreas is higher in cigarette smokers than non-smokers as is the incidence of cancer of the stomach and kidney, although the relationship in the latter two cases is less statistically significant.

4. Irritants Tobacco smoke contains a number of tissue irritants including ammonia, volatile acids and phenols, aldehydes and ketones and these probably account for many of the deleterious effects of tobacco smoke on the bronchial mucosa and may be major factors in the pathogenesis of chronic obstructive airways disease. Cigarette smoking causes an increase in bronchial mucous secretion, impairs the function of mucosal cilia and reduces the phagocytic activity of pulmonary macrophages, thus reducing the rate that bacteria and particulate matter are cleared from the lungs. After both acute and chronic use, cigarette smoking increases airways resistance and decreases exercise tolerance.

The incidence of chronic obstructive airways disease (chronic bronchitis) is higher in smokers than non-smokers and the incidence of death from this disease for males smoking 25 cigarettes a day or more is approximately six times that for non-smokers. Chronic bronchitis is one of the most common chronic disabling diseases in the UK and accounts for many millions of working days lost per year, the great majority of these being lost by cigarette smokers. The incidence of attacks of acute bronchitis declines on stopping smoking and the rate of decline in lung function with age slows considerably.

Apart from cancers of the bronchus and other organs mentioned above and chronic obstructive airways disease, smoking has been implicated as one of a number of high risk factors in coronary artery disease, the incidence of sudden death and death due to myocardial infarction being substantially higher in smokers than non-smokers. The incidence of both gastric and duodenal ulcers is also substantially higher in smokers than non-smokers and in patients with gastric ulcers at least, stopping smoking increases the rate of healing of the ulcer.

Other conditions occurring more commonly in smokers than non-smokers include cirrhosis of the liver, hypertensive heart disease, influenza, pneumonia, suicides and accidents.

When all these conditions are considered together, cigarette smoking probably contributes as a causative factor to over one third of all deaths in the UK and to a high proportion of disabilities through ill health.

Cocaine Cocaine is now quite commonly used as a drug of dependence in the UK, mostly in combination with other drugs.

After i.v. administration cocaine induces a profound sense of physical and mental power and an increase in self-esteem. Fatigue and hunger are eliminated and there are signs of increased activity of the sympathetic nervous system. The ecstatic feeling that cocaine gives only lasts a few seconds and addicts may take repeated intravenous doses over quite short periods.

Acute toxicity Causes paranoid delusions, auditory and tactile hallucinations and signs of increased CNS activity with increased tendon jerks and eventually convulsions. Addicts may act out paranoid delusions and become violent.

There is no physical withdrawal syndrome caused by stopping cocaine and it does not cause chronic toxic effects.

Cocaine is rarely taken alone, but may be taken by addicts in conjunction with heroin, ethanol or barbiturates.

Sympathomimetic amines Only those sympathomimetic amines with pronounced CNS stimulant effects have a high abuse liability, e.g. amphetamine and methylphenidate.

Amphetamines were first used as analeptics and as anorectic agents, but their widespread use was associated with dependence which developed in a high proportion of those using the drug. There are now several thousand amphetamine addicts in the UK, amphetamines usually being taken in conjunction with barbiturates or other hypnotics.

Amphetamines induce a state very similar to that induced by cocaine. They are usually taken orally but may be injected. The effects they produce, though less intense than those of cocaine, last longer and are enhanced by barbiturates.

Acute toxicity The acute overdose effects of amphetamine are similar to those of cocaine. It may cause an acute psychotic state indistinguishable from an acute schizophrenic episode. In subjects not accustomed to the drugs, amphetamines cause hypertension due to release of catecholamines from sympathetic nerve terminals, but this effect wears off with repeated use.

Tolerance Tolerance develops to the euphoriant effects of amphetamines so that addicts gradually increase their daily dosages and may end up consuming hundreds of milligrams per day, whereas the smallest dose that causes detectable CNS stimulation is 10 mg.

Withdrawal There is no abstinence syndrome caused by amphetamines, although there is an increase in REM sleep, similar to that caused by withdrawal from barbiturates.

Chronic toxicity There are no chronic toxic effects of amphetamines and related sympathomimetic amines.

HALLUCINOGENS

Cannabis Cannabis (marihuana, hashish) is derived from the flower tops of the female hemp plant, the most active ingredient being tetrahydrocannabinol. Cannabis is usually smoked as cigarettes (pot) but may be smoked in a pipe or be swallowed.

ACTION As with other drugs that affect mood or behaviour, the effects of cannabis vary widely between individuals. One to two cigarettes usually cause a dreamy state of altered awareness. The taker is often drowsy, but has an increased sense of well-being and an inner happiness and experiences a free flow of ideas. There is an increased acuity for sound and often an altered perception of sound and bodily image. The appetite may be increased and sleep enhanced.

Acute toxicity High doses of cannabis cause hallucinations and an acute

psychosis indistinguishable from that due to LSD, hence the classification of cannabis as an hallucinogen. Like tobacco, cannabis causes no harmful physical effects in high doses over short periods. Nausea may occur and the irritant properties of cannabis smoke causes a burning at the back of the throat. There is a slight tachycardia and the conjunctivae become injected.

Tolerance Tolerance does not occur although some addicts gradually increase their daily intakes.

Withdrawal Craving is unusual on stopping cannabis and there are no physical withdrawal effects.

Chronic toxicity There are no established chronic toxic effects of cannabis.

LSD Lysergic acid diethylamide (LSD) and mescaline are the most widely used agents whose principle effects are to cause an alteration in perception.

LSD is taken orally and after as little as 10–25 μg and within 20–30 minutes there is an alteration of mood, usually elation or dejection, followed by vivid visual and occasional tactile hallucinations and a state of confusion in which the patient may be disorientated in time and place. Occasionally a paranoid or anxiety state may be caused by the drug. The effect usually lasts 2–3 hours but it may be followed by a prolonged depressed state.

Acute toxic effects There are no harmful physical effects of a large dose of LSD. However, the depressed state that may follow ingestion of LSD may be sufficiently severe to precipitate an attempt at suicide.

Tolerance and withdrawal Tolerance does not develop to the hallucinogenic effects of LSD and there are no physical withdrawal symptoms.

Chronic toxicity There are no established chronic toxic effects of LSD.

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Chapter 19

Analgesics and Non-steroidal Anti-inflammatory Agents

Analgesics are drugs used to relieve pain. As pain is a very common symptom of disease and trauma, analgesics are amongst the most widely used drugs, many preparations being available without prescription. There are several groups of drugs with analgesic activity and they can be classified in terms of the other effects they have. The possession of antipyretic activity is often used as a basis for the classification of weak analgesics, but as the therapeutic benefit of lowering the body temperature in the presence of a fever has not been established, in Table 1 the anti-inflammatory activity of these drugs is used

Table 1

Analgesics and anti-inflammatory agents

	Narcotic analgesics	*Analgesics with anti-inflammatory activity*	*Analgesics with no anti-inflammatory activity*	*Anti-inflammatory agents with little or no analgesic activity*
e.g.	Morphine	Salicylates*	Paracetamol*	Indomethacin*
	Codeine	Propionic acid* derivatives	Phenacetin*	Phenylbutazone*
	Heroin	Anthranilic acid* analogues		Gold
	Pethidine			Chloroquine
	Methadone			Penicillamine
	Dextroprop-oxyphene			
	Pentazocine			

* denotes antipyretic activity

instead for this purpose. The close relationship between the analgesic effect of some drugs and their ability to suppress inflammation is evidence of the central part that the inflammatory process plays in the pathogenesis of many diseases and in the causation of painful syndromes.

NARCOTIC ANALGESICS

The term narcotic analgesic is a generic name for all analgesics derived from, or

with actions similar to, the opium alkaloids. They are so named because of the hypnotic qualities of the naturally occurring members of this group, although it is not a prominent side effect of the less potent synthetic members. The narcotic analgesics are classified here in terms of whether they are naturally occurring (opium alkaloids), semi-synthetic or wholly synthetic. The chemical structure of some of the more commonly used narcotic analgesics is shown in Fig. 1. There are many similarities between the pharmacological activities of the three groups and in view of this, only the pharmacology of the parent compound morphine will be considered in detail and the other agents contrasted with it.

Opium Alkaloids

The opium alkaloids contain morphine and codeine as well as a number of pharmacologically active compounds with no analgesic properties, e.g. the smooth muscle relaxant papaverine. Morphine, which is present in higher concentrations than codeine, accounts for the analgesic activity of opium alkaloids. Both morphine and codeine are now only prescribed in their purified forms.

Morphine

ACTIONS

Analgesic Morphine is capable of relieving the most severe forms of pain that occur clinically and is most effective against continuous pain. It is less effective against spasmodic short-lasting pain such as renal colic or trigeminal neuralgia. It alters the psychological response to pain in pain-producing situations so that although a stimulus may be recognised as painful, the patient does not react to it in the same way. Morphine also raises the pain threshold although this effect is not as consistent as that on the reaction to pain.

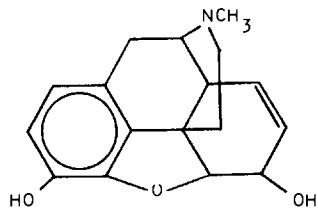
Analgesia is usually associated with some drowsiness, dizziness and a feeling of well-being described as euphoria. There is no alteration in the response to other sensory stimuli and no cerebellar syndrome with ataxia and dysarthria, as occurs with the minor tranquillisers and ethanol. Meiosis occurs at analgesic doses probably medicated by a central mechanism.

Anti-tussive Morphine suppresses the cough reflex by an action on the cough centre in the medulla and this action is independent of its depressant effect on respirations.

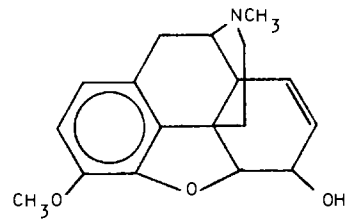
Constipating Morphine increases the tone of the smooth muscle of the gastrointestinal tract and decreases propulsive bowel movements and the amplitude of mixing contractions. This action is the basis of its use in the treatment of diarrhoea (see Chapter 30).

DRUG FATE Morphine is absorbed from the bowel but, owing to rapid metabolism during its first passage through the liver, is much less effective administered via this route than when given parenterally. Like most bases it is concentrated in the tissues, highest concentrations being achieved in the liver and kidney.

OPIUM ALKALOIDS

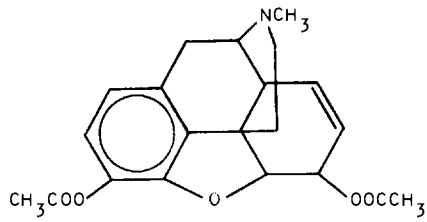


MORPHINE



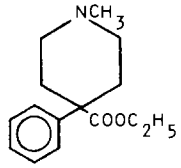
CODEINE

SEMI-SYNTHETIC NARCOTIC ANALGESICS

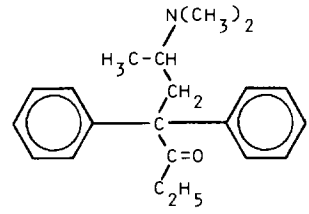


HEROIN (DIACETYLMORPHINE)

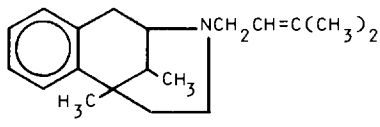
SYNTHETIC NARCOTIC ANALGESICS



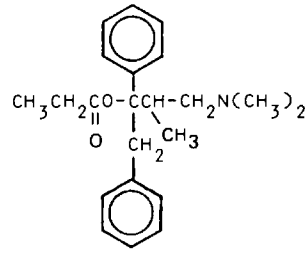
PETHIDINE



METHADONE



PENTAZOCINE



DEXTROPROPOXYPHENE

FIG. 1 Chemical structures of some commonly used narcotic analgesics.

Relatively small amounts reach the central nervous system owing to poor diffusion of morphine through the blood brain barrier. Morphine receptors are located in many areas, the main sites being the medial thalamus, the solitary nucleus, the area postrema and the amygdala in the brain and the substantia gelatinosa in the spinal cord. Morphine readily crosses the placental barrier, the peak effect on the fetus occurring 4–6 hours after its administration to the mother. Infants of mothers who are morphine addicts often have a pronounced withdrawal reaction during the first few days as neonates if they are not breast-fed. As appreciable morphine is excreted in breast milk, breast-fed infants of morphine addicts suffer withdrawal symptoms on weaning.

Morphine is conjugated with glucuronic acid. It also undergoes oxidative dealkylation by hepatic microsomal enzymes to normorphine which has similar pharmacological effects to morphine but is much less potent. Sixty–90% of an oral dose is excreted in the urine in 24 hours, mostly as conjugates, very little being excreted as unchanged drug. A small amount is present in the faeces as a consequence of biliary excretion.

The analgesic effect of morphine after i.m. administration is maximal within 30–60 minutes and declines from peak effect with a half-life of 2–3 hours, and there is no increase in its rate of metabolism in morphine addicts. In liver disease there is often an increased responsiveness to the CNS effects of this drug, but there is no evidence that it is metabolised more slowly.

ADVERSE EFFECTS

Nausea Morphine stimulates the chemoreceptor trigger zone in the medulla and very commonly causes nausea and vomiting at analgesic doses. This occurs more commonly in ambulant patients than in those at rest and usually only after the first dose if repeated doses are given. Tolerance to the emetic effect is ascribed to the depressant effect that repeated doses of morphine have on the vomiting centre.

Respiratory depression Morphine decreases both the rate and depth of respirations by a depressant effect on the respiratory centre. At therapeutic doses it may exacerbate or precipitate respiratory failure in patients with obstructive airways disease and impaired ventilation. After an acute overdose the respiratory rate may fall below 5/min and respiratory failure is nearly always the cause of death.

Hypotension It causes slight hypotension due partly to a direct vasodilator effect and partly to its ability to cause histamine release. Occasionally hypotension may be severe and life threatening in patients with an impaired cardiac output, e.g. after a myocardial infarct.

Tolerance Tolerance develops quite rapidly to the analgesic, euphoriant and respiratory depressant effects of morphine. In patients with severe pain treated with repeated doses, the dose requirement may increase up to 20 times the original dose within a few weeks of starting therapy. There is no tolerance to the meiotic effect or to the spasmogenic effect that causes constipation.

Drug abuse and dependence Morphine has a high liability to abuse (*see* Chapter 18) which is the major factor limiting its clinical use.

Drug interactions Many of the central effects of morphine (including analgesia) can be enhanced by phenothiazines. Phenothiazines antagonise the emetic effects of morphine and these drugs are commonly used together.

Monoamine oxidase inhibitors, and to a lesser extent the tricyclic antidepressants and phenothiazines, enhance the depressant effects of morphine on respiration and BP.

CLINICAL USE

Pain Morphine (or another potent narcotic analgesic) is commonly used in the treatment of severe pain of short duration (2–4 days or less) e.g. post-operative pain, pain of childbirth or that accompanying a myocardial infarct. It has no place in the management of conditions such as rheumatoid arthritis which are associated with chronic pain. In terminal malignant disease when this is associated with pain or anxiety, morphine is useful as an increasing dose requirement does not carry the long term implications it does in non-fatal conditions. In such cases, the daily dose requirement can be kept down by early adequate analgesia, the co-administration of a phenothiazine and other analgesics and by sympathetic management of the patient.

Pulmonary oedema Morphine causes relief of dyspnoea in acute pulmonary oedema within minutes of its administration i.m. or i.v. As it has no direct effect on the bronchi or lungs this is most probably partly a central effect and partly due to a morphine-induced fall in venous return and peripheral resistance. As a sizeable proportion of patients with a myocardial infarct or in pulmonary oedema have chronic obstructive airways disease, it is wise to determine the arterial blood gas tensions before administering morphine or heroin and to withhold these drugs if the pCO_2 is raised.

Cough and diarrhoea As codeine is as effective an anti-tussive and anti-diarrhoea agent as morphine, morphine is only used for the relief of these symptoms during a terminal illness.

Codeine Codeine is the only other opium alkaloid used in clinical practice. It has a similar spectrum of activity to morphine but is much less potent as an analgesic, 60 mg codeine being equivalent to 10 mg of morphine. It produces no euphoria and has a low abuse liability.

Codeine is active orally and has a similar duration of action to morphine. Approximately 10% is dealkylated to morphine. It is usually taken in the form of the phosphate to suppress a cough or to treat diarrhoea or abdominal colic. It is seldom used alone as an analgesic but is included in many proprietary preparations in combination with other analgesics, e.g. aspirin and paracetamol, as there is clinical evidence of synergism between codeine and these analgesics.

Diphenoxylate is a synthetic analogue of codeine that is as effective in relieving diarrhoea and causes a similar range of side effects (*see* Chapter 30).

Semi-Synthetic Narcotic Analgesics

Heroin (diacetyl morphine) Heroin has an identical spectrum of pharmacological effects to morphine but is twice as potent on a weight basis. It is very rapidly deacetylated by the liver and enters the brain mostly as 6-monoacetyl morphine. It has a more rapid onset of action than morphine when given i.v., probably because of its more rapid diffusion through the blood-brain barrier. It is this reason, as well as its greater potency, which causes it to be preferred by addicts as the intensity of the drug effect after i.v. administration is closely related to the rate of onset of effect (*see* Chapter 18). It also has a shorter duration of action and because of this the withdrawal syndrome starts earlier than that of morphine and is more severe.

Heroin has no clearly established advantages over morphine although there is a widely held clinical impression that it causes less nausea and hypotension at equipotent doses.

Other agents Dihydromorphine, methyl-dihydromorphinone, desmorphine and oxymorphone are all similar to morphine.

Dihydrocodeine and dihydrocodeinone are intermediate in potency and abuse liability between morphine and codeine and their pharmacological actions are similar to these agents.

Apomorphine This drug is a derivative of morphine. It is a dopamine receptor agonist and a potent emetic acting by stimulation of the chemoreceptor trigger zone. Given i.m. vomiting occurs within 20 minutes and apomorphine is as effective as ipecacuanha at inducing vomiting. It has been used instead of gastric aspiration in the treatment of self-poisoning but there is always the danger that the patient will aspirate vomit or that the response will be excessive.

In Parkinson's disease, apomorphine ameliorates the tremor, rigidity and akinesis at doses that induce profound vomiting but a derivative, norpropylap-morphine, produces the same effect with less nausea and vomiting. The place of this agent in the management of parkinsonism is not established (*see* Chapter 16).

Pethidine Pethidine was synthesised in 1939 and initially investigated for anti-histamine and antimuscarinic properties but its pharmacological actions are similar to those of morphine. It is less potent on a weight basis than morphine but in equianalgesic doses causes a similar degree of respiratory depression. It is active by mouth and is removed from the plasma by hepatic metabolism. It is demethylated to norpethidine which is then hydrolysed and conjugated, the conjugates being excreted in the urine. It has a plasma half-life of 3–4 hours but this increases to 7–8 hours in patients with hepatic cirrhosis. Its abuse liability is similar to that of morphine. An acute overdose is similar in clinical presentation to that of atropine with mydriasis, tachycardia and psychotic symptoms being prominent.

Methadone Although structurally quite different from morphine, methadone

has a very similar spectrum of pharmacological effects. It is orally active, an oral dose having one-third to one-half the activity of a parenteral dose. After a single i.m. dose methadone has the same rate of onset and duration of action as morphine. However, after repeated doses, e.g. in addicts, the offset of its effects is much slower and hence the withdrawal syndrome is much less severe. It has a relatively high abuse liability, although less than that of heroin and morphine, and it is used as replacement therapy in the management of morphine and herion addiciton (*see* Chapter 18).

Dextropropoxyphene Propoxyphene is very similar to methadone chemically (*see* Fig. 1). It is a racemic compound, like methadone, only the dextro-form having analgesic properties. It is approximately half as potent as codeine on a weight basis. Dextropropoxyphene is effective against mild and moderately severe pain. It is orally active and is demethylated by the liver, the plasma half-life ranging from 1·5–4·0 hours.

The adverse effects of dextropropoxyphene are very similar to those of codeine, nausea and vomiting being the most common. It has a low abuse liability but over dosage causes loss of consciousness and respiratory depression especially when taken in conjunction with ethanol. Dextropropoxyphene is commonly prescribed in a fixed dose combination with other analgesics, e.g. paracetamol or aspirin, such combinations being amongst the most widely prescribed drugs. There is little convincing evidence that dextropropoxyphene has any advantages over codeine.

Pentazocine Pentazocine is derived from the morphinan and benzomorphan series of which levorphanol and phenazocine are also members. Neither of the latter agents have any advantage over morphine but pentazocine, which is 3–6 times less potent than morphine, has a much lower abuse liability. It is effective at relieving severe pain clinically. It is not subject to legislative controls and does not exhibit cross tolerance with other narcotic analgesics.

Pentazocine is active orally, an oral dose being one-third to one-half as effective as an i.m. dose, the peak effect occurring after 30–60 minutes. It is removed from the plasma by hepatic glucuronic acid conjugation. The concentration of the parent drug in plasma declines with a half-life of around 2 hours, which correlates well with decline of its analgesic effect. Less than 10% is excreted unchanged in the urine.

As with other narcotic analgesics, pentazocine may cause dizziness, drowsiness, nausea, meiosis and respiratory depression. Hypotension does not occur, rather it may cause an increase in systemic and pulmonary artery pressure. There is a higher incidence of mental symptoms such as auditory hallucinations euphoria and dysphoria than with other narcotic analgesics and these side effects are the principal limitation to its use. It may be used orally or i.m. instead of morphine or heroin in relief of severe pain. More commonly, however, it is used in the relief of acute or chronic pain that has not responded to less potent

analgesics. As its abuse liability is low, it is suitable for chronic administration although a small percentage of patients become dependent on it.

Narcotic Analgesic Antagonists

Nalorphine is a partial agonist of morphine-receptors. It is a potent analgesic, though less so than morphine, has anti-tussive activity and causes respiratory depression, meiosis and constipation. However, at analgesic doses it causes dysphoria, confusion and hallucinations which preclude it from clinical use as an analgesic.

If nalorphine is administered with or shortly after morphine it reverses its analgesic, respiratory depressant and the narcotic effects. After an acute overdose of morphine, nalorphine (15 mg i.v.) causes the patient to regain consciousness and reverses the respiratory depression within 1–2 minutes. It has a shorter half-life than morphine (2–3 hours) and repeated doses are usually required until the respiratory depressant effects of morphine have worn off. The assumption is that nalorphine competes for the same central receptor sites as morphine and as it is only a partial agonist, causes less of a pharmacological effect, e.g. respiratory depression. Nalorphine antagonises most narcotic analgesics but is less effective against pethidine.

Nalozon is a pure morphine-receptor antagonist, i.e. it occupies the same receptors as morphine but has no morphine-like actions. It is a safer drug to use in the treatment of a narcotic analgesic overdose than nalorphine as it does not depress the respiratory centre but it too has a shorter $T_{\frac{1}{2}}$ than morphine so that more than one dose may be necessary.

Both nalorphine and naloxon precipitate acute withdrawal symptoms in narcotic addicts.

Preparations

	Adult analgesic dose (mg)	*Route*
Morphine	10	i.m.
Codeine	16–32	Oral
Heroin	5	i.m.
Pethidine	75–150	Oral or i.m.
Methadone	5–10	Oral or i.m.
Dextropropoxyphene	32·5–65	Oral
Pentazocine	50–100	Oral or i.m.
Naloxon	0·4–1·2	i.v.

ANTIPYRETIC ANALGESICS

The analgesics with antipyretic activity are amongst the oldest drugs in clinical use. Aspirin, the most widely used of these agents, derived from studies on the analgesics and antipyretic activity of willow bark preparations (*Salix alba*) which

has been known for centuries. The active component of willow bark, a glycoside called salicin, was isolated in the 19th century and the derivatives sodium salicylate and acetyl salicylate (aspirin) were synthesised later in the same century.

The antipyretic analgesics differ from the narcotic analgesics in several ways, but the most important clinically are that they have no hypnotic effect, are generally ineffective against severe pain and have a low abuse liability.

The antipyretic analgesics can be classified on the basis of their anti-inflammatory activity.

Agents with Anti-Inflammatory Activity

Salicylates Salicylic acid, the parent compound of the group, is a potent local irritant as are its carboxylic acid esters, e.g. methyl salicylate (Fig. 2). The gastric irritant properties of these compounds preclude them from use as systemic analgesics but they are useful as counter-irritants and as keratolytics in the treatment of skin conditions (Chapter 41). The phenolic ester, acetyl salicylate, is less irritant and is the most widely used salicylate. Other forms suitable as systemic analgesics are sodium and potassium salts of salicylic acid and salicylamide.

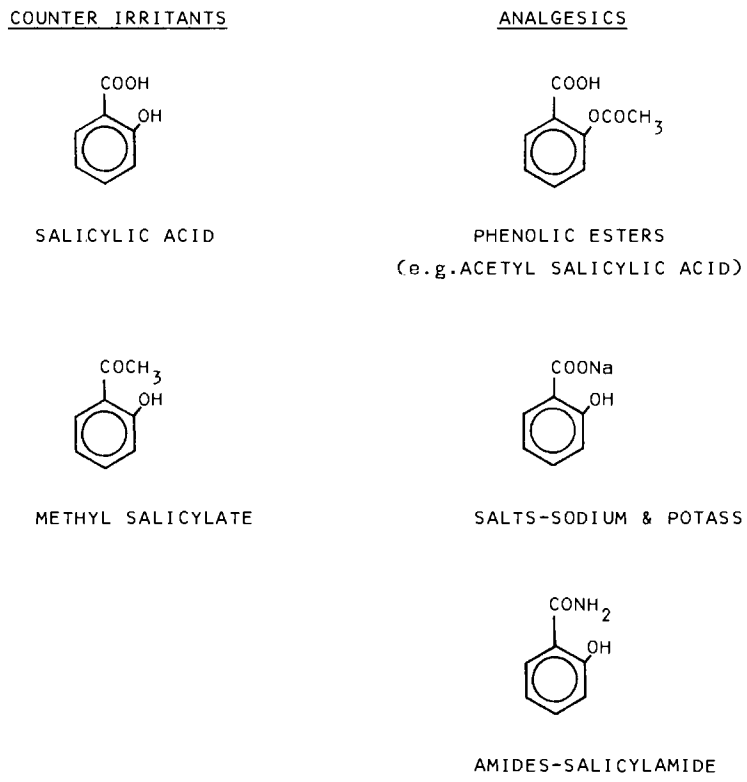


FIG. 2 Salicylates.

There are only minor differences in the pharmacological properties of the different salicylates used for their systemic effects. Since acetyl salicylate is the most widely used salicylate the clinical pharmacology of this agent only will be considered in detail.

ACTIONS

Analgesia Aspirin is capable of relieving mild and moderate pains but is ineffective against severe pain. It is more effective against prolonged pain than against spasmodic pains. Tolerance does not develop to its analgesic effect and, unlike the narcotic analgesics, there are no associated central effects such as drowsiness or impairment of intellectual function and no modalities of sensation other than pain are affected.

The mechanisms whereby aspirin relieves pain are obscure. There is a central site of action which is probably within the thalamus, as spinal pain fibres terminate there. In conditions in which pain is associated with inflammation there is also a peripheral component (*see* below) due to the anti-inflammatory effect of aspirin.

Antipyresis Aspirin rapidly lowers an elevated body temperature by an action on the hypothalamus which results in a net increase in heat loss by sweating and peripheral vasodilatation. Heat production is also enhanced but to a lesser degree than heat loss. The fall in body temperature probably contributes to the symptomatic relief aspirin has in minor febrile illnesses. It has little effect on the normal temperature in therapeutic concentrations.

Anti-inflammatory action All types of inflammation are suppressed by high concentrations of aspirin, the maximum effect usually being achieved with plasma concentrations of 200–300 mg/l. Clinical conditions in which the anti-inflammatory activity of aspirin contributes to its therapeutic effect include rheumatoid arthritis and other connective tissue disorders, other forms of arthritis such as psoriatic arthropathy and Reiter's syndrome, and rheumatic fever.

Platelet inhibition Aspirin increases the bleeding time by inhibiting the normal function of platelets. It prevents platelets adhering to connective tissue surfaces and impairs their release of adenine diphosphate (ADP). ADP release increases platelet stickiness and by preventing ADP release, aspirin inhibits platelet aggregation. This effect on platelet function lasts up to seven days after a single 300 mg tablet.

The therapeutic implication of this action is that aspirin will be effective in preventing the formation of arterial thrombi. Its ability to prevent myocardial infarction and strokes is currently being evaluated.

MODE OF ACTION Aspirin inhibits the biosynthesis of prostaglandins by irreversibly acetylating the enzyme cyclo-oxygenase that converts arachidonic acid to endoperoxides, the latter being the precursors of the prostaglandins, thromboxane and prostacyclin. This action is probably responsible, at least in part, for the anti-inflammatory, antipyretic and antiplatelet actions of aspirin

and other non-steroidal anti-inflammatory drugs, as prostaglandins are thought to play an important part in the genesis of inflammation, in the pyretic response through prostaglandins produced in the CNS and in the function of platelets.

DRUG FATE Aspirin (pKa 3·5) is absorbed from the stomach and small bowel largely in the unionised form. The unionised form is poorly soluble in water and much of the aspirin in the stomach is in the solid state. Absorption occurs with a half time of 15 minutes at therapeutic doses but is often greatly delayed, due to slow passage of drug from the stomach, after an overdose. Buffered forms of aspirin and other salicylates, are as well absorbed as aspirin and absorption from salicylate suppositories is similar to that of oral aspirin.

Aspirin is loosely bound to plasma albumin, the percentage varying between 40–70% at therapeutic concentrations (300 mg/l or less). Binding is rapidly reversible and salicylates compete for the same binding sites as other acidic drugs e.g. sulphonamides and phenylbutazone (*see* Chapter 9).

Acetyl salicylic acid is rapidly hydrolysed to the equipotent analgesic, salicylic acid, by esterases present in the bowel wall, plasma, liver and kidney. The half life in the plasma is 15 minutes for aspirin and 4 hours for salicylate at therapeutic doses. The highest concentration of salicylate occurs in the liver and kidney but as salicylates diffuse slowly across the blood-brain barrier, the concentration in the brain is less than 10% of that in the plasma. Diffusion across the blood-brain barrier is facilitated by a fall and retarded by a rise in blood pH.

Salicylate is metabolised by liver microsomal enzymes to the glycine conjugate salicyluric acid which accounts for 80% of a therapeutic dose excreted in the urine. Other metabolites are the phenolic glucuronide and the salicylacyl glucuronide. This process follows first-order kinetics at plasma concentrations in the usual therapeutic range 100–300 mg/l but at higher concentrations the supply of glycine is insufficient and a progressively greater proportion is excreted as the glucuronide or as unchanged drug. The half-life of the drug in the plasma increases and the plasma concentration time curve veers towards zero-order kinetics.

Salicylate is partly excreted unchanged in the urine. At urine pH 5, the renal clearance of salicylate is only 5–10% that of creatinine, but this rises sharply at pH values over 7 and at a urinary pH of 8 is 1·5–2·0 times that of creatinine. This is utilised in the treatment of salicylate overdose, the rate of drug excretion being increased several fold by alkalinisation of the urine (*see* Chapter 40).

ADVERSE EFFECTS Despite the fact that salicylates, especially aspirin, are amongst the most commonly consumed drugs, the incidence of serious adverse effects is very low. In contrast to most narcotic analgesics the abuse liability is also very low.

Gastrointestinal haemorrhage Therapeutic doses of aspirin quite commonly cause epigastric discomfort and invariably a 4–6 fold increase in gastrointestinal blood loss. This usually amounts to a blood loss of 3–4 ml per tablet per day in

normal subjects. It enhances blood loss from gastrointestinal lesions, especially from peptic ulcers. There is an increased incidence of serious gastrointestinal bleeding and gastric ulceration in patients who ingest four or more aspirin tablets per day regularly, but the incidence of both of these effects in such patients is still low. All salicylate preparations, including buffered aspirin and slow release preparations have these effects on the gastrointestinal tract. The mechanism whereby salicylates cause gastrointestinal bleeding is not established. Salicylates cause changes in the integrity of the gastric mucosa when applied directly to the mucosa. In experimental animals, aspirin causes bleeding from established gastrointestinal lesions when given i.v. and it is possible that its effect on platelet aggregation may contribute to its ability to enhance bleeding from established peptic ulcers.

Nephropathy Despite the fact that aspirin is nephrotoxic to many animal species and causes an increase in urinary casts in man, chronic ingestion of aspirin alone very rarely causes renal damage of clinical importance.

Drug interactions: anticoagulants Severe gastrointestinal haemorrhage may occur in patients on anticoagulants who receive salicylates (*see* Chapter 33).

Salicylate overdose Salicylate overdose occurs as a result of self-poisoning and less commonly as the result of using high therapeutic doses, e.g. in rheumatic fever. Aspirin is amongst the most common agents taken in self-poisoning and in the accidental poisoning of children. The mortality is appreciable, being 3–7% in children and 1–2% in adults. Patients admitted after a salicylate overdose are conscious and may be euphoric and garrulous. They usually complain of tinnitus and nausea and often have a purpuric skin as high doses of aspirin have an anti-vitamin K action and increase prothrombin time. The respiratory rate is increased due to stimulation of the respiratory centre by salicylate with a resultant respiratory alkalosis. Later, a metabolic acidosis develops, this effect being more common in children than adults. Indeed the occurrence of an acidosis in adults is indicative of severe poisoning and carries a poor prognosis. The temperature is quite commonly raised and patients are often dehydrated.

The cause of death in aspirin poisoning is usually respiratory failure but the mechanism is obscure. There is no close relationship between plasma aspirin concentration on arrival in hospital and mortality. In most instances active therapy to expedite excretion of the drug is initiated at plasma concentrations greater than 500 mg/l (3·6 mM) (*see* Chapter 40).

Miscellaneous effects Sensitivity reactions to aspirin such as skin rashes and anaphylaxis do occur but are rare. In some asthmatic patients aspirin precipitates attacks while in a small number of patients it relieves asthma. Salicylates compete with uric acid for sites of active transport in the proximal renal tubule. At low doses (2·6 g/24 h or less) they cause a fall in uric acid excretion by inhibiting its secretion and at higher doses an increase in uric acid excretion by inhibiting its reabsorption.

CLINICAL USE

Analgesic agent Aspirin is one of the most widely used of all analgesics in the treatment of mild and moderate pain.

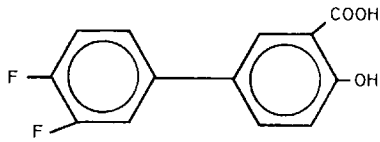
Anti-inflammatory agent Aspirin is the drug of first choice in the treatment of rheumatoid arthritis and related connective tissue disorders associated with pain. Similarly, in rheumatic fever it is most effective in relieving the arthralgia and in improving the patients sense of well-being, but it has little if any effect on the course of the disease. The dose required in these conditions is established empirically, being gradually increased until symptoms are alleviated or until tinnitus occurs. The upper dose limit for adults is around 17 g/day. For therapeutic purposes the upper limit for the plasma salicylate concentration is 300 mg/l.

Antipyretic agent In minor febrile illnesses salicylates relieve the symptoms of fever, muscle pains and headache. On this account they are included in a large number of proprietary preparations designed as treatment for minor ailments.

Anti-thrombogenic agent Aspirin is not effective at preventing venous thrombosis. It is of established value in reducing the incidence of transient episodes of blindness due to platelet emboli arising from atheromatous plaques on the major vessels (amaurosis fugax). There is some evidence to suggest that the incidence of myocardial infarction is less common in subjects who habitually ingest aspirin. The role of aspirin in preventing coronary artery disease is currently being investigated in a prospective controlled clinical trial.

Methyl salicylate (oil of wintergreen) is used in skin disease as a keratolytic agent and as a counter-irritant (*see* Chapter 41).

Diflunisal



This new salicylate has analgesic anti-inflammatory and antipyretic activity. It is a cyclo oxygenase inhibitor and is approximately ten times as potent an analgesic as aspirin on a weight basis although it is no more effective at maximally recommended doses. It does not appreciably affect platelet function at analgesic doses. Diflunisal is orally active and is over 98% protein bound in the plasma. It undergoes glucuronide conjugation by the liver, little unchanged drug being excreted in the urine. The $t_{\frac{1}{2}}$ tends to increase with the dose, the range being 7–11 hours in subjects with normal renal function. Adverse effects to this new drug are not fully evaluated. It causes less gastrointestinal blood loss than aspirin after single equianalgesic doses, but there is not adequate data on its gastrointestinal effects after chronic dosage to justify its use in patients with peptic ulceration. It enhances the effects of oral anticoagulants.

Propionic Acid Derivatives Ibuprofen, ketoprofen, fenoprofen and naproxen are propionic acid derivatives with pharmacological properties similar to those

of aspirin. They are more potent analgesics, but are less potent anti-inflammatory agents. As with other classes of analgesics with anti-inflammatory properties, the greater the anti-inflammatory potency, the greater the ability to cause gastrointestinal erosions and to relieve the pain of inflammatory joint disease. Thus ibuprofen is less effective in rheumatoid arthritis than other members of the class but causes fewer gastrointestinal side effects. These agents are generally as effective as aspirin and are well tolerated. They cause fewer gastrointestinal side effects but are all capable of causing gastrointestinal bleeding. They all displace warfarin from protein binding sites and hence enhance its anticoagulant effect.

Anthranilic Acid Derivatives Mefenamic and flufenamic acid are anthranilic acid derivatives with pharmacological effects similar to those of aspirin. They are no more effective than aspirin. Diarrhoea is a common side-effect and they may cause dyspepsia and gastrointestinal bleeding. Skin rashes occur more commonly than with aspirin.

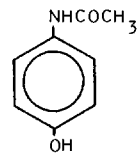
Antipyrine (Phenazone) Antipyrine is a pyrazolone derivative and has analgesic, anti-inflammatory and antipyretic activity. Its actions are more like those of aspirin than phenylbutazone and it is used clinically as an analgesic. It has no advantages over aspirin and is seldom used alone in the UK but is quite commonly administered in combination with the hypnotic chloral as dichloralphenazone.

Antipyrine is rapidly absorbed from the gut. It has an apparent volume of distribution similar to that of total body water and undergoes hydroxylation by hepatic microsomal enzymes. It has been frequently used by investigators of drug metabolism in man by virtue of the ease with which it can be measured in the plasma. It has a mean half-life of 10–12 hours but there are large interindividual differences in the rate of its metabolism.

Adverse effects are few, skin rashes being the most common. It does not have the bone marrow depressant effects of its cogener, aminopyrine, which is now not available in the UK or USA.

Agents with no anti-inflammatory activity

Paracetamol (Acetoaminophenol)



Paracetamol, like phenacetin, was introduced into medicine in the 19th century as the result of an investigation into the antipyretic and analgesic properties of coal tar. However it was not used as an analgesic until the 1960s but is now amongst the most commonly used analgesics.

ACTIONS

Analgesia Paracetamol is very similar to aspirin in its ability to relieve pain.

It is less effective than aspirin when pain is due to inflammation as it lacks anti-inflammatory activity.

Antipyresis Like aspirin, paracetamol lowers body temperature by increasing heat loss.

DRUG FATE Paracetamol is weakly acidic (pKa 9·5). It is absorbed rapidly from the stomach and to a greater extent from the small bowel, reaching a peak plasma concentration by 30–60 minutes. Only 25% is bound to plasma proteins and it has an apparent volume of distribution equal to that of total body water. It is conjugated in the liver with glucuronic acid and sulphate. A small proportion is first oxidised and conjugated with glutathione to form a mercapturic acid (*see* Chapter 3).

The plasma half-life of paracetamol in patients with normal liver function is 2 hours and very little is excreted unchanged in the urine.

ADVERSE EFFECTS Paracetamol is well tolerated at therapeutic doses and it does not cause gastrointestinal haemorrhage. Hypersensitivity reactions, usually rashes, occur occasionally. Its abuse liability is low. The major drawback to paracetamol is that it has a narrow therapeutic index, as little as 7·5 g (15 tablets) taken as an overdose being capable of causing severe liver damage.

Overdosage 5–10% of cases of self-poisoning admitted to hospital in the UK have taken a paracetamol overdose and the fatality rate of these patients is 2–3%. Patients are conscious on admission and are often nauseated and vomiting. If severely affected they develop jaundice in 24–48 hours with a rise in aspartate transaminase and prothrombin time. The peak effect in patients that eventually recover usually occurs by 72 hours and thereafter a slow resolution of the jaundice occurs. There is an increase in the plasma half-life of paracetamol in patients who sustain liver damage and a poor prognosis is usually associated with a drug half-life greater than 4 hours or a bilirubin value greater than 700 μmol/l (400 mg%) by the third day.

Liver histology shows centrilobular necrosis similar to that caused by carbon tetrachloride. Enzyme-inducing agents such as phenobarbitone enhance paracetamol toxicity in animals while compounds containing sulphydryl groups, methionine, cysteine and cysteamine prevent it. This suggests that a metabolite of paracetamol is responsible for its hepatoxic effect (*see* Chapter 3). For the use of cysteamine and methionine in treatment *see* Chapter 40.

Nephrotoxicity Phenacetin, the parent compound of paracetamol, was withdrawn from the UK market in 1978 as chronic ingestion may cause chronic renal failure with renal papillary necrosis and interstitial nephritis. Not withstanding this, despite extensive use for long periods, paracetamol has only very rarely been implicated in the causation of renal papillary necrosis.

Methaemaglobinaemia Paracetamol may cause methaemaglobinaemia but is much less potent in this respect than was phenacetin (*see* below).

CLINICAL USE

Analgesia Paracetamol alone or in combination with other analgesics, e.g. dextropropoxyphene, is used clinically for the treatment of mild and moderate pain. Its antipyretic activity may contribute to the symptomatic relief it gives in febrile illnesses. It is not a drug of first choice in painful conditions associated with inflammation, e.g. rheumatoid arthritis, as it lacks anti-inflammatory activity.

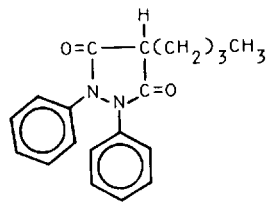
Preparations

Drug	*Oral analgesic adult dose (g)*	*Dose interval*
Acetyl salicylic acid (aspirin)	0·325–1·0	4–6
Paracetamol	0·5–1·0	4–6
Ibuprofen	0·2–0·4	8
Naproxen	0·25–0·75	12
Flufenamic acid	0·2	8

NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

In this section, a number of agents whose principal pharmacological action is to suppress inflammation, will be considered. These are mostly used in the treatment of rheumatoid arthritis, related connective tissue diseases and other arthroses but they are only used when aspirin or one of the other mild analgesics have failed to give adequate symptomatic relief. The anti-inflammatory activity of glucocorticoids is considered in Chapter 27.

Phenylbutazone



Phenylbutazone is a pyrazolone derivative whose pharmacological activity was discovered when it was used as a solubilising agent for the chemically related analgesic aminopyrine.

ACTIONS

Anti-inflammatory Phenylbutazone is a potent anti-inflammatory agent with weak analgesic and antipyretic activity. It is effective in relieving the symptoms of ankylosing spondylitis when chronic therapy may be justified by the severity of the symptoms. In rheumatoid arthritis, other connective tissue

diseases and arthroses, it is often effective in relieving symptoms but does not affect the natural history of the diseases themselves. Because of its greater toxicity it is only used when aspirin alone or a propionic acid derivative have failed to give adequate symptomatic relief.

Uricosuric At therapeutic doses phenylbutazone impairs the reabsorption of uric acid by the proximal renal tubule. It competes with uric acid for anion binding sites and thus increases the renal clearance of uric acid. It is not used as a uricosuric agent but its sulphoxide derivative sulphinpyrazone which is a more potent uricosuric agent, is (*see* below).

In acute gout, phenylbutazone is most effective at rapidly relieving the acute pain (*see* below).

DRUG FATE Phenylbutazone is rapidly absorbed from the bowel. In the plasma more than 98% of the drug is bound to plasma albumin and it may be displaced from these binding sites by other acidic drugs, e.g. warfarin, sulphonylureas and sulphonamides (*see* below).

Phenylbutazone is cleared from the plasma by metabolism, very little of the unchanged drug being excreted in the urine. It undergoes aromatic parahydroxylation, by liver microsomal enzymes, to form the active metabolite oxyphenbutazone. The alkyl side chain also undergoes hydroxylation. Oxyphenbutazone has similar pharmacological and pharmacokinetic properties to phenylbutazone and is marketed as an anti-inflammatory agent in its own right. There are considerable interindividual differences in the rates of phenylbutazone metabolism, the mean half-life in subjects with normal hepatic function being 72 hours. In patients with severe liver disease, the rate of metabolism is often reduced. As phenylbutazone is a potent enzyme-inducing agent it increases the rate of its own metabolism and that of other drugs metabolised by liver microsomal enzymes e.g. warfarin.

ADVERSE EFFECTS

Bone marrow depression Phenylbutazone may cause an aplastic anaemia, an agranulocytosis or a thrombocytopenia. The incidence is dose-related and rises sharply at doses in excess of 600–800 mg/day. Above these doses, plasma albumin binding sites are saturated and any increase in drug concentration causes a disproportionate increase in free drug. Similarly, the incidence of bone marrow depression is highest in patients who metabolise the drug slowly. This serious adverse effect is uncommon with doses less than 600 mg/day. Nonetheless, phenylbutazone is one of the drugs most commonly implicated as a cause for myelosuppression in the UK and is second only to chloramphenicol in this regard in the USA.

Gastric ulceration Epigastric discomfort, nausea and diarrhoea are common side effects of phenylbutazone. It may also cause gastric ulceration, ulcers typically being large, often asymptomatic and located in the antral region where they may be mistaken for malignant ulcers.

Fluid retention Salt and water retention and an increase in the extracellular

fluid volume commonly occur in subjects on phenylbutazone and may cause pulmonary oedema in patients with impaired cardiac or renal function. This effect is due to an action on the renal tubule and is independent of mineralocorticoids.

Others Rashes, serum sickness and hepatitis are rare adverse effects presumed to have an immunological basis.

Drug interactions

1. Anticoagulants. Phenylbutazone enhances the anticoagulant effect of warfarin and related oral anticoagulants by displacing these drugs from plasma albumin and tissue binding sites. It also increases the rate at which they are metabolised by increasing their availability to drug metabolising enzymes and by its enzyme inducing effect. Patients on anticoagulants should not be treated with phenylbutazone as the ulcerogenic effect of this drug and its displacement of warfarin from plasma protein binding sites greatly increases the probability of patients developing a massive gastrointestinal haemorrhage.
2. Sulphonylureas. The hypoglycaemic action of these drugs may be enhanced by phenylbutazone by displacement from plasma albumin.
3. Others. By its enzyme inducing effect phenylbutazone may decrease the clinical effectiveness of drugs such as phenytoin, tolbutamide and barbiturates which are metabolised by liver microsomal enzymes. There are few convincing clinical examples of this type of interaction.

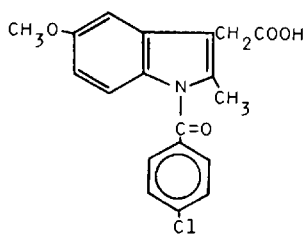
CLINICAL USE

Ankylosing spondylitis Phenylbutazone is the drug of choice for relieving the pain and reducing the stiffness of this condition.

Other arthroses The potentially serious adverse effects of phenylbutazone results in it being used only as an alternative to, or in addition to, salicylates in such common conditions as rheumatoid arthritis.

Gout Phenylbutazone is as effective as indomethacin and colchicine at relieving the pain and inflammation of acute gout (*see* below).

Indomethacin



Indomethacin, though differing in chemical structure from phenylbutazone, is very similar in its pharmacological actions. It is a potent anti-inflammatory and antipyretic agent, but has no analgesic effect other than that due to suppression of inflammation. It has no uricosuric effect. Indomethacin is the most potent inhibitor of prostaglandin synthesis known, an effect shared by all anti-

inflammatory agents, and it is possible that, as with aspirin, its anti-inflammatory effect is secondary to this effect.

DRUG FATE The drug is rapidly absorbed from the gut and in the plasma is over 90% bound to albumin. It is mostly excreted as hepatic metabolites. A small proportion of a dose is excreted in the urine as unchanged drug by active tubular secretion and this process is inhibited by probenecid which causes an accumulation of unchanged drug in the plasma. Indomethacin is also excreted in the bile and undergoes an entero-hepatic circulation, part of a dose being excreted unchanged in the faeces. Its plasma half-life is 2–3 hours.

ADVERSE EFFECTS Indomethacin causes intolerable side effects in at least 20% of patients, although its adverse effects are usually less serious than those of phenylbutazone.

CNS effects Headaches and light-headedness occur in a high proportion of patients. Affective disorders and acute psychotic episodes may also be precipitated by this drug in subjects with no history of psychiatric illness.

Gastrointestinal Epigastric pain, gastric ulceration and haemorrhage occur with a frequency similar to that of phenylbutazone and it also causes gastric ulcers which have clinical and radiological similarities to those caused by phenylbutazone (*see* above).

Bone marrow depression may occur but is much less frequent than with phenylbutazone. A peripheral neuropathy is another rare adverse effect.

CLINICAL USES These are very similar to those of phenylbutazone. It is usually less effective than phenylbutazone in ankylosing spondylitis and is ineffective in osteoarthrosis except in osteoarthrosis of the hip in which it commonly gives symptomatic relief. In gout it is used in acute attacks but not as a prophylactic agent.

Indomethacin is administered by mouth or rectally from which route it is well absorbed, although rectal ulceration is a rare complication.

Colloidal gold salts Gold salts, of which sodium aurothiomalate is the most commonly used, can relieve the pain and incapacity of active rheumatoid arthritis. In contrast to aspirin, phenylbutazone and indomethacin, the beneficial effects of gold take 6–12 weeks to develop and are associated with a fall in erythrocyte sedimentation rate (ESR) and in the rheumatoid factor. Furthermore, on existing animal models of this disease it has no anti-inflammatory activity although this may reflect the inadequacy of the models. It is most effective in the early stages of the disease but does not affect its clinical or radiological course. It is of no established benefit in other inflammatory joint diseases.

The mechanisms whereby gold relieves the inflammation are not established. It was first used in the treatment of rheumatoid arthritis in the 1920s when the disease was thought to be the consequence of tuberculosis as its antituberculous activity *in vitro* had been clearly demonstrated by Koch. It has a high affinity for

sulphydryl groups in tissues. It inhibits a number of enzymes responsible for the biosynthesis of connective tissue and is toxic to mycoplasma organisms which have been implicated as possible causative organisms in rheumatoid arthritis.

DRUG FATE Gold salts are inactive orally but are well absorbed after i.m. administration. They are highly bound to tissue proteins and are present in the highest concentration in the liver, kidney and spleen. Gold salts are excreted in the urine, no more than 10–15% of a weekly dose being excreted so that they accumulate in the tissues throughout the period of their administration. The chelating agent dimercaprol expedites its excretion and is used for this purpose in the management of toxic reactions.

ADVERSE EFFECTS Adverse reactions to gold occur in up to 20% of cases and may be life-threatening.

Skin eruptions Pruritis, stomatitis, purpura and dermatitis including exfoliative dermatitis may occur.

Bone marrow depression Neutropenia, thrombocytopenia and aplastic anaemia occur in a small proportion of cases and may be fatal. An eosinophilia is quite common and often occurs before signs of bone marrow depression.

Nephropathy Albuminuria commonly precedes development of the nephrotic syndrome or chronic renal failure.

Other serious adverse effects that occur less frequently are hepatitis and a peripheral neuropathy.

CLINICAL USE Gold salts are most commonly used in the treatment of early, active rheumatoid arthritis, that has not responded to aspirin or aspirin-like analgesics, phenylbutazone or indomethacin. It is often preferred in this situation to glucocorticoids as it usually causes fewer serious adverse effects.

Therapeutic regimes vary but commonly an initial small dose (10 mg) is given s.c. in an attempt to identify patients who will develop adverse skin reactions. A weekly dose of 25–50 mg is given i.m. until symptomatic relief is achieved when the dose may be reduced or left unchanged. The duration of therapy is not universally agreed but as relapse inevitably follows cessation of the drug, many clinicians continue therapy indefinitely or until adverse reactions develop.

Chloroquine and hydroxychloroquine Chloroquine and hydroxychloroquine in high doses (200 mg/day) have anti-inflammatory activity similar to that of gold salts and are effective at relieving symptoms in rheumatoid arthritis, discoid and systemic lupus erythematosus. Chloroquine is administered orally and like gold salts, accumulates in the tissues. Its therapeutic effect is not evident for several weeks and continues, in patients who respond, only for the duration of therapy.

The principal adverse effect of chloroquine used in high doses, apart from those described in Chapter 36, is a retinopathy which usually does not occur unless the patient has received 300–500 mg/day for at least one year. Early reversible signs of this are retinal macular deposits which are followed, if the drug is not discontinued, by macular oedema and irreversible visual impairment. This course of events can be prevented in most instances by 3–6 monthly examination of the retina and cessation of therapy with the development of retinal changes. Occasionally retinal changes occur months after stopping the drug.

D-penicillamine The chelating agent penicillamine (*see* Chapter 41) is an effective anti-inflammatory agent in the treatment of rheumatoid arthritis. It is similar to gold salts in that it is most effective in early active rheumatoid arthritis, its symptomatic relief takes some weeks to develop and is associated with a fall in the ESR and rheumatoid factor and that it does not affect the course of the disease. Its adverse effects too are similar and occur in around 30% of cases. Nausea, vomiting and diarrhoea are the most frequent but skin rashes, proteinuria and bone marrow depression may also occur and rarely a reversible myasthenia gravis-like syndrome. A regular blood count and urine test for protein should be undertaken during chronic therapy.

DRUGS IN THE TREATMENT OF GOUT

Uric acid is the main metabolic product of purine metabolism in man and in normal subjects 20% of that elaborated in the body is excreted in the urine, the rest undergoing further metabolism. Uric acid is filtered by the glomerulus and 98–99% of that in the glomerular filtrate is actively reabsorbed by the proximal tubule. There is also active secretion into the proximal tubule which accounts for 80–90% of the uric acid in the urine.

In gout, there is hyperuricaemia and an increase in the total uric acid pool. This is due to an increase in uric acid synthesis in approximately a third of cases, a decrease in its renal excretion in another third and a combination of both these defects in a further third. Uric acid is poorly water-soluble and the clinical manifestations of the disease, an acute arthropathy, tophaceous gout (tophi are soft tissue swellings caused by uric acid crystals and the inflammatory response to them) and a uric acid nephropathy, are consequences of precipitation of urates in the tissues. Gout probably results from several different metabolic disorders and it is only rarely that there is a clinically detectable cause such as an increase in uric acid production as in myeloproliferative disorders and after cytotoxic drug therapy or a reduction in uric acid excretion due to diuretic therapy or low-dose salicylate administration.

Drugs used in the treatment of gout act in one of three ways (Fig. 3). They either diminish the inflammatory response to uric acid crystal formation in the tissues (site 1), expedite uric acid excretion in the urine by preventing its tubular reabsorption (site 2) or they reduce its synthesis (site 3).

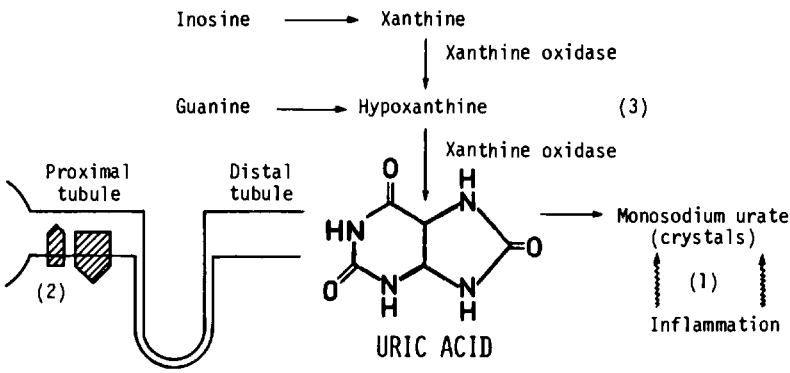
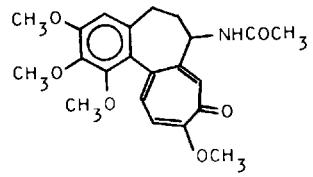


FIG. 3 Sites of action of drugs used in gout:
(1) Impairment of the inflammatory response to urate crystals: phenylbutazone, idomethacin, colchicine, (corticosteroids);
(2) Impairment of active reabsorption of urate by proximal renal tubule: probenecid, sulphinpyrazone (phenylbutazone);
(3) Inhibition of xanthine oxidase and hence of urate synthesis: allopurinol.

Drugs that Impair the Inflammatory Response to Urate Crystals

Colchicine



Colchicine is an alkaloid derived from the autumn crocus (*Colchicum autumnale*) and its effectiveness at relieving the acute pain of certain types of joint pain has been known since the 6th century AD.

ACTIONS Colchicine causes rapid relief of pain in acute attacks of gout, within 1–2 hours of starting treatment. It has no analgesic properties and does not relieve pain in other inflammatory joint diseases. Its therapeutic effectiveness is probably related to its ability to reduce polymorphonuclear leukocyte motility in response to urate deposition. In concentrations higher than those achieved clinically, colchicine inhibits mitosis in metaphase. This is the basis of its use *in vitro* in chromosome counting, but is not responsible for its action in gout.

DRUG FATE Colchicine is rapidly absorbed from the gut and is present in highest concentrations in the liver, kidney, spleen and intestine. It is deacetylated by the liver and undergoes enterohepatic circulation. Most of an oral dose is excreted as metabolites in the urine, less than 30% being excreted as

unchanged drug. A small amount is excreted as unchanged drug in the faeces. Its plasma half-life is around 2 hours.

ADVERSE EFFECTS

Gastrointestinal Diarrhoea is a common and often dose-limiting side-effect. Nausea and colic are also common. In high doses, colchicine may cause bloody diarrhoea. Bone marrow depression is a rare consequence of chronic therapy.

CLINICAL USE

Therapy Colchicine is as effective as phenylbutazone and indomethacin at relieving the pain and inflammatory changes of acute gout. An initial dose of 0·5–1·0 mg is administered and is followed by 0·5–1·0 mg every 1–2 hours until symptoms subside or diarrhoea and nausea supervene.

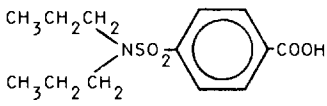
Prophylaxis Colchicine in small doses (0·5–2·0 mg/day) is effective at preventing recurrent attacks of gout in patients with chronic gout but is rarely used now for this purpose. It is useful during initiation of therapy with uricosuric agents and allopurinol that may precipitate acute attacks.

Mediterranean fever Colchicine in similar doses to those used in the prophylaxis of gout, reduces the frequency and severity of the acute attacks of polyserositis that characterise this condition. Its ability to prevent the development of amyloidosis is still being evaluated.

Indomethacin and Phenylbutazone These agents are equally effective at relieving the pain of acute attacks and are more commonly used for this purpose than colchicine. Their potentially serious adverse effects preclude their use as prophylactic agents in chronic gout.

Uricosuric Agents

The sites of active reabsorption of uric acid in the proximal tubule are not specific for uric acid but are shared by many other anions. Uricosuric agents, probenecid, phenylbutazone and sulphinpyrazone and high dose salicylates (more than 4 g/day) are anions that competitively inhibit the active tubular reabsorption of uric acid and hence cause an increase in its renal excretion, a fall in plasma concentration and a decrease in the size of the uric acid pool. Other anions, e.g. thiazides, frusemide and ethacrynic acid and low dose aspirin, competatively inhibit uric acid tubular secretion and hence cause an increase in plasma uric acid and occasionally an acute attack of gout.

Probenecid 

Probenecid was used initially to inhibit the tubular secretion of penicillin and so to prolong its plasma half-life which it may do by a factor of three. It is now only

rarely used for this purpose in view of the cheapness and ready availability of the penicillins.

In hyperuricaemia and in chronic gout, probenecid causes a fall in plasma uric acid concentration and mobilises tissue stores of uric acid and decreases the size of tophi.

DRUG FATE Probenecid is orally active and is over 85% bound to albumin in the plasma sharing the same sites as the barbiturates. The drug is cleared from the plasma principally by hepatic metabolism, only 5–15% being excreted as unchanged drug. A glucuronide conjugate is the major metabolite, the remainder being oxidised by microsomal enzymes. The plasma half-life of the unchanged drug is 4–12 hours.

ADVERSE EFFECTS

Acute gout Acute attacks of gout, which commonly occur when there is a rapid change in the plasma uric acid concentration, may be precipitated by probenecid and other uricosuric agents and can be prevented by the prophylactic administration of small doses of colchicine.

Uric acid stones An increase in urinary uric acid concentration may precipitate uric acid stone formation or an acute uric acid nephropathy. This may be prevented by maintaining an alkaline urine with sodium bicarbonate or potassium citrate which increase uric acid solubility in the urine.

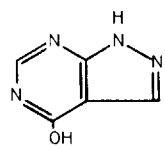
Rashes and other hypersensitivity reactions occur in a small percentage of cases.

CLINICAL USE Probenecid is used in chronic gout or when gout is precipitated by drugs that reduce uric acid excretion, e.g. thiazide diuretics.

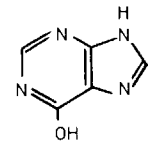
Sulphinpyrazone The sulphoxide derivative of phenylbutazone, sulphinpyrazone, is a potent uricosuric agent. At uricosuric doses, it lacks the anti-inflammatory activity of phenylbutazone. It is similar in its disposition and pharmacokinetics to phenylbutazone and is as effective a uricosuric agent as probenecid, causing a similar incidence of adverse effects. In addition to precipitating acute attacks of gout and uric acid stone formation, it is a gastric irritant and may cause epigastric discomfort and rarely gastrointestinal haemorrhage. Its uricosuric action is antagonised by salicylates. Sulphinpyrazone is an alternative uricosuric agent to probenecid and there is no cross sensitivity between these drugs.

Myocardial infarction Sulphinpyrazine is an anti-platelet drug, prolonging platelet survival and preventing their adhesion and aggregation at doses (800 mg/day) that do not affect the bleeding time. In prospective clinical trials in the secondary prevention of myocardial infarction, it was found to significantly reduce the cardiac death rate.

Allopurinol



ALLOPURINOL



HYPOXANTHINE

Allopurinol is a hypoxanthine analogue that was synthesised during the search for agents that decreased the rate of metabolism of another hypoxanthine analogue, the cytotoxic agent 6-mercaptopurine (*see* Chapter 38). It inhibits the enzyme xanthine oxidase which is involved in the conversion of hypoxanthine to xanthine and later, of xanthine to uric acid (Fig. 1). It thus acts as an anti-metabolite to hypoxanthine and xanthine causing an increase in the plasma and tissue concentrations of these purines and an increase in their concentration in the urine. In patients with gout, allopurinol causes a fall in the plasma uric acid concentration, a decrease in the size of tophi and in the uric acid pool and a fall in the uric acid concentration in the urine.

DRUG FATE Allopurinol is orally active. It is cleared from the plasma by hepatic metabolism being converted to a number of metabolites of which alloxanthine (oxpurinol) is the most important. Allopurinol has a plasma half-life of 2–3 hours but this is exceeded by alloxanthine ($t_{\frac{1}{2}}$ 15–30 hours) which therefore accumulates during chronic administration. Alloxanthine is also a xanthine oxidase inhibitor and contributes to the therapeutic effect of allopurinol. It is excreted unchanged or as its riboside in the urine.

ADVERSE EFFECTS

Acute gout As with the uricosuric agents, during the early months of treatment when the uric acid concentration is falling, allopurinol may increase the frequency of acute attacks of gout.

OTHERS Allopurinol is very well tolerated. Mild rashes and gastrointestinal upsets are the commonest adverse effects. There is as yet no evidence that the presence of crystals of hypoxanthine and xanthine in the tissues caused by allopurinol is detrimental to patients.

Drug interactions Allopurinol inhibits the oxidation of 6-mercaptopurine to inactive metabolites by xanthine oxidase and hence increases its concentration in the plasma and its myelosuppressive effect. It also suppresses purine synthesis as well as uric acid formation and may therefore enhance the myelosuppressive effects of other cytotoxic agents, e.g. cyclophosphamide.

CLINICAL USE Allopurinol is the drug of choice in the treatment of hyperuricaemia when there is impaired renal function, uric acid stone formation

or an acute uric acid nephropathy. It is also an alternative to uricosuric agents in chronic gout.

Preparations

Drug	*Adult dose (mg)*	*Route*	*Dose interval (h)*
Phenylbutazone	100–200	Oral	8–12
Indomethacin	25–50	Oral	8–12
Sodium aurothiomalate	25–50	i.m.	Weekly
Chloroquine	200	Oral	24
D-penicillamine	125–500	Oral	8–12
Colchicine	0·5–1·2	Oral	1–2
Probenecid	250–500	Oral	12
Sulphinpyrazone	100–200	Oral	12
Allopurinol	100–200	Oral	8–12

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Chapter 20

Cardiac Glycosides

Since their introduction in the 18th century, cardiac glycosides have played an essential part in the treatment of cardiac failure and disorders of cardiac rhythm. Cardiac glycosides are derived from a variety of plants of which digitalis, the foxglove, is the most widely used. *Digitalis purpura* in the dried form (d. folia) provides the main source of digitoxin and *D. lanata* is the main source of digoxin. Ouabain is derived from *Strophanthus gratus*. A variety of other plants including squill (*Urginea maritima*) also contain cardiac glycosides but are not now used clinically.

CHEMICAL STRUCTURE There is a structure common to all cardiac glycosides and consisting of three components, a steroid nucleus to which a polysaccharide moiety is attached at the C3 position (hence the generic name) and a lactone moiety in the C17 position. The structure of digoxin is shown in Fig. 1.

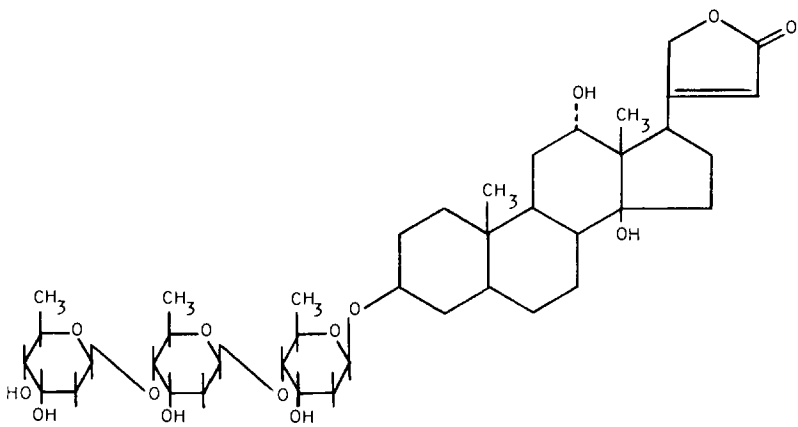

FIG. 1 Digoxin

Digitoxin is less polar than digoxin and is the most lipid soluble of the cardiac glycosides, whereas ouabain is more polar.

The only cardiac glycoside preparations used clinically are powdered digitalis leaf (digitalis folia) of which the principle component is digitoxin and the purified preparations digoxin, digitoxin and ouabain. Deslantoside has one more glucose molecule than digoxin but its clinical pharmacology is identical to digoxin. The therapeutic and adverse effects of these various cardiac glycosides are identical but they differ in their pharmacokinetic characteristics.

ACTIONS

Positive inotropic Cardiac glycosides cause an increase in the force of contraction of the myocardium of the failing heart and a shift in the curve relating left ventricular work to left ventricular filling pressure (i.e. left atrial pressure) upwards and to the left. They increase the speed of contraction of both the failing and non-failing heart. In patients with pulmonary oedema or congestive cardiac failure secondary to left ventricular failure, cardiac glycosides cause a fall in ventricular-end diastolic pressure, an increase in cardiac output and a decrease in heart size. These changes are associated with a shortening of the QT interval on ECG indicating a decrease in the myocardial refractory period.

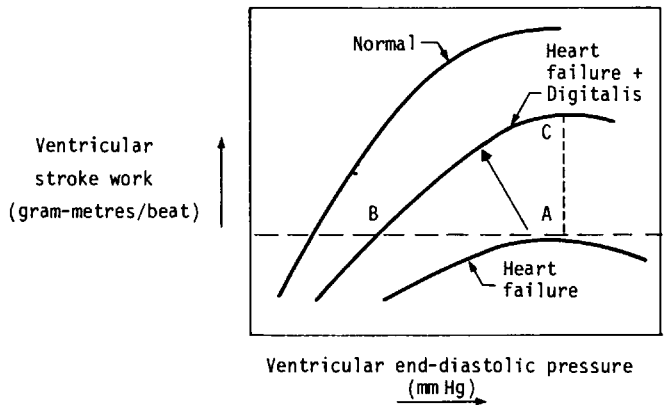

FIG. 2 *Frank-Starling* principle: effects of digitalis on ventricular function. In heart failure, work capacity of myocardium at any given end-diastolic volume or pressure is diminished. Digitalis shifts this abnormal ventricular function curve upward and to the left, indicating drug increases cardiac contractility.

Antidysrhythmic Cardiac glycosides slow the heart and may be used for this purpose in the treatment of all types of supraventricular tachycardia other than those caused by cardiac glycoside overdosage. The principle mechanisms involved are:

1. An increase in vagal tone. Cardiac glycosides cause an increase in vagal tone by a direct action on the dorsal nucleus of the vagus in the medulla. ACh released from the vagal nerve terminals acts principally on the sino-atrial (SA) node and atrial muscle, as the parasympathetic innervation of the ventricles is, for all practical purposes, non-existent. It hyperpolarises the SA node by enhancing K^+ conductance, slows conduction in the node and conducting tissue and increases the refractory period. These changes result in a decrease in rate of AV depolarisation and hence in atrial-driven ventricular contractions.

2. A direct SA node blocking action similar to that caused by ACh but evident in the fully atropinised patient.

3. A decrease in heart rate to within physiological limits increases cardiac output and adds to the positive inotropic effect of these drugs. In left ventricular failure, there is often an increase in sympathetic tone due to cerebral anoxia. By increasing arterial blood oxygen concentration cardiac glycosides reduce sympathetic tone and this is a third mechanism whereby they slow the heart rate.

Cardiac glycosides also convert the unstable rhythm atrial flutter to the more stable atrial fibrillation. This is due to its principle effect on the atria, namely to cause an increase in the rate of atrial repolarisation and hence a decrease in refractory period. There are minor differences in the refractory period of different parts of the atria after digitalisation. This results in different parts depolarising at different times causing an increase in the frequency, but a decrease in the amplitude of impulses arriving at the A–V node.

OTHER EFFECTS

Diuretic In high doses cardiac glycosides impair renal tubular reabsorption of sodium and chloride, but the diuretic effect at therapeutic concentrations is mainly secondary to an increase in renal perfusion and glomerular filtration rate.

Vasoconstriction When sympathetic tone is high secondary to hypoxaemia, these drugs cause vasodilatation due to the decrease in sympathetic tone. They do also have a direct vasoconstrictor effect which may contribute to the occasional precipitous increase in blood pressure following digitalisation.

BIOCHEMICAL CHANGES The subcellular change most consistently correlated with actions of cardiac glycosides is inhibition of myocardial sodium- and potassium-dependent ATPase, that provides energy for the active transport of Na^+ and K^+ across the myocardial membrane. This results in a net increase in intracellular Na^+ and a fall in intracellular K^+. The increase in intracellular Na^+ increases the exchangeable calcium fraction in the myocardium, either by displacing calcium ions from intracellular binding sites or by increasing calcium influx. This increase in calcium ions available for the contractile elements of the myocardium enhances myocardial contractability.

Whether Na^+ and K^+ ATPase inhibition is responsible for the positive inotropic effects of cardiac glycosides remains in dispute but it is widely accepted that it is responsible for the electrophysiological changes associated with digoxin toxicity (*see* below).

DRUG FATE As there are differences in the fate of the different cardiac glycosides, only that of the most widely used agent, digoxin, will be described in detail, digitoxin and ouabain being contrasted with it. Some details of the pharmacokinetics of these drugs are shown in Table 1.

Digoxin is partially absorbed from the bowel, 45–80% of an oral dose reaching the systemic circulation. The peak plasma concentration after an oral

Table 1

Comparison of some pharmacokinetic characteristics of cardiac glycosides given orally

Glycoside	*% oral dose absorbed*	*time to onset min*	*time to peak min*	*beta phase $t_{\frac{1}{2}}$ h*	*route of elimination*
Ouabain	less than digoxin	5–10	30–120	20–25	R + B
Digoxin	45–80	15–30	90–300	35–45	R
Digitoxin	95–100	25–120	240–720	120–170	M

R = renal excretion
B = biliary excretion
M = metabolism

dose is achieved in 1–2 hours, the greater the rate of dissolution of the tablet and the smaller the digoxin particle size, the sooner is the peak plasma concentration achieved and the higher its value. Differences in these properties between different brands of digoxin, and sometimes between batches of a given brand produced by different manufacturing processes, account for differences in the peak plasma concentrations achieved after administration of a given weight of digoxin prepared by different manufacturers. However, such differences seldom cause major differences in the proportion of a dose absorbed. Similarly, if digoxin is taken with food, there is a delay to peak plasma concentration and a reduction in that peak but little reduction in the proportion of the drug absorbed.

Only 20–30% of digoxin in the plasma is protein bound. It is concentrated in the tissues, achieving a peak myocardial concentration 10–30 times that in the plasma 15–30 minutes after attainment of the peak plasma value. Uptake of digoxin by the myocardium is enhanced by hypokalaemia and reduced by hyperkalaemia. Digoxin rapidly diffuses into the brain and across the placental barrier.

Less than 10% of an oral dose of digoxin is cleared from the plasma by metabolism, 80–90% of absorbed drug is excreted unchanged in the urine by glomerular filtration, the excretion rate being similar to that of creatinine and 10% is excreted in the faeces as a result of bilary excretion. Digoxin plasma clearance rates fall with that of creatinine in renal failure, but show no change in hepatocellular failure when renal function is normal.

PHARMACOKINETICS After administration of digoxin as a bolus i.v., the plasma concentration time curve declines biphasically, the initial or alpha phase with a $t_{\frac{1}{2}}$ of 30–60 minutes and the beta phase with a $t_{\frac{1}{2}}$ of 35–45 hours, i.e. the amount of digoxin present in the body falls by 31–37%/24 hours. The initial peak plasma concentration is 10–15 times that at the beginning of the beta phase. Digoxin is highly concentrated in the tissues and has an apparent volume of distribution of 4–6 l kg. After tablet ingestion, the biphasic decline in the plasma concentration is less pronounced than after an i.v. bolus injection and

the peak plasma concentration is only 2–3 times that at the beginning of the beta phase. There is a delay of approximately 1 hour between the attainment of peak myocardial digoxin concentration and development of peak inotropic effect. It takes 5–7 days before the maximal effect of a given dose of digoxin develops in patients with normal renal function and a similar time for the full effect of a change in dose to develop.

Digitoxin The differences between digoxin and digitoxin can largely be accounted for by the greater lipid solubility of the latter drug. Nearly all an oral dose of digitoxin is absorbed. It has a volume of distribution similar to that of digoxin and 90–95% of the drug in the plasma is bound to albumin. Very little digitoxin is excreted unchanged in urine or faeces, the drug being converted to more polar metabolites by liver microsomal enzymes and approximately 10% is converted to digoxin. The rate of digitoxin metabolism and the proportion converted to digoxin is increased by enzyme-inducing agents such as phenobarbitone. Digitoxin does not accumulate in the plasma in either renal or liver cell failure but the plasma concentration fluctuates with fluctuations in plasma protein concentrations.

There is a longer delay between achievement of peak plasma concentration and development of peak effect with digitoxin and the beta phase $t_{\frac{1}{2}}$ is 5–7 days so that it takes approximately one month for a steady state plasma concentration to develop after initiating therapy or changing dosage.

Ouabain As ouabain is more polar than digoxin, its absorption is more variable and is incomplete. It has a smaller volume of distribution as it is confined chiefly to the extracellular space and very little drug is bound to plasma proteins in the blood. Most of the drug is excreted unchanged, 50–60% of absorbed drug being excreted in the urine, the remainder in the faeces. It has a more rapid onset of action than digoxin and a shorter half-life, the beta phase of the plasma concentration time curve having a $t_{\frac{1}{2}}$ of 20–25 hours.

ADVERSE REACTIONS Cardiac glycosides have a narrow therapeutic index. Adverse effects, other than rashes and gynaecomastia which are rare, are mostly construed as overdose effects and occur in 10–30% of patients.

Gastrointestinal effects Centrally mediated anorexia and nausea are common early symptoms of overdosage, vomiting and diarrhoea occurring at higher doses.

Nervous system effects A large number of symptoms have been attributed to effects of cardiac glycosides on the nervous system. Fatigue, muscle weakness and visual symptoms such as blurred vision, photophobia and spots before the eyes are common and in high doses a retrobulbar neuritis may develop. Dizziness, headaches, neuralgic pains, psychogenic symptoms such as excessive dreaming and restlessness have also been attributed to these drugs.

CVS effects In high doses, these drugs cause depression of the SA node,

impaired AV node conduction, a fall in resting potential of the AV node and His-Purkinje system, a decrease in velocity and amplitude of the action potential, a decrease in impulse conduction rate and eventually an increase in diastolic depolarisation. These changes predispose to the development of ectopic pacemakers in atria, AV node and His-Purkinje system and to re-entrant tachydysrhythmias (*see* Chapter 22).

In therapeutic doses, cardiac glycosides cause ST wave depression, a decrease in amplitude of the T wave, a prolongation of the PR interval and a shortening of the QT interval. In higher doses, all manner of rhythm disturbance may occur, ventricular ectopic beats and first degree heart block being the most common. Atrial tachycardia with variable AV block and pulsus bigeminus (coupling) are widely recognised as indicative of toxicity, but are no more common than other rhythm disturbances. All types of heart block, all types of tachycardia and ectopic beats arising from foci anywhere in the heart may occur and occasionally prove fatal, so that ECG evidence alone is seldom sufficient to diagnose digoxin toxicity. Factors predisposing to the development of adverse cardiac effects include hypokalaemia, hypoxaemia and acidaemia which are common in patients with cor pulmonale, severe heart disease and renal failure. A recent myocardial infarct is not a contra-indication to the use of cardiac glycosides as they probably do not increase the incidence of cardiac dysrhythmias after an infarct.

TREATMENT OF OVERDOSAGE Potassium replacement, preferably orally, is the first step in therapy and oxygen therapy if pO_2 is 60 mmHg or less. Phenytoin, lignocaine and beta blockers such as propranolol have all been successful in the treatment of digoxin toxicity. Phenytoin reverses the electrophysiological abnormalities induced by cardiac glycosides and has proved effective clinically, 200–250 mg being given as a bolus i.v. and followed by an oral maintenance dose until signs of digoxin toxicity have abated. Hypotension is an occasional adverse effect during bolus infusion of this drug. Lignocaine is as effective, but more commonly causes AV blockade and this effect is much more common with either procainamide or quinidine. A centrally induced increase in sympathetic tone may be caused by high doses of cardiac glycosides and some of their cardiac dysrhythmic effects have been attributed to this effect. This may account in part for the effectiveness of beta blocking drugs in treating digoxin toxicity, although occasionally they may exacerbate the AV blockade. Beta-blockers do not antagonise the positive inotropic effects of cardiac glycosides at therapeutic doses.

DRUG INTERACTIONS

Diuretics All renal diuretics other than those impairing sodium reabsorption by the distal tubule only (*see* Chapter 21) may cause hypokalaemia and hence predispose patients to the development of the adverse cardiac effects of cardiac glycosides. Hypomagnesaemia also predisposes patients to such effects and may be induced by thiazide diuretics and frusemide.

Absorption of cardiac glycosides is impaired by drugs that increase bowel motility and increased by drugs that decrease motility, e.g. antimuscarinic agents. Absorption is also reduced by cholestyramine and this drug reduces the $t_{\frac{1}{2}}$ of digitoxin by binding the drug in the bowel and reducing the reabsorption of drug excreted in the bile. Enzyme inducing agents shorten the half-life of digitoxin (*see* above).

CLINICAL USE

Atrial fibrillation and supraventricular tachycardias Cardiac glycosides are unique amongst the anti-dysrhythmic drugs in that they slow the heart while having a positive inotropic effect. On this account, they are usually drugs of first choice in the management of supraventricular tachycardias of all types, but are of less value in ventricular tachydysrhythmias (Chapter 22).

Left ventricular failure and congestive cardiac failure Studies on patients with pulmonary oedema have established the positive inotropic effect of cardiac glycosides in this situation. Less certain however is their place in the management of chronic congestive cardiac failure as the initial increase in cardiac output may not be maintained during chronic therapy. Although they are very widely used in congestive cardiac failure there is no clinical trial evidence establishing their value in addition to, or as an alternative to, diuretic therapy and salt restriction. In view of the high incidence of adverse effects in patients treated with cardiac glycosides, it is reasonable to use these agents in congestive cardiac failure only when diuretics have failed to be effective.

Cor pulmonale In this condition in which congestive cardiac failure is secondary to pulmonary hypertension, cardiac output is usually normal or raised and is not increased by cardiac glycosides. As these drugs do not increase pO_2 or improve tissue perfusion they are only likely to benefit the small number of patients with severe cor pulmonale in whom the cardiac output is low.

AGENT AND DOSE Digoxin is now by far the most widely used of the cardiac glycosides in the UK and although there is no sound clinical evidence demonstrating its advantages over ouabain or digitoxin, there are obvious advantages in having uniformity of practice.

The long half-life of digoxin and to a greater extent, digitoxin, determines drug administration. For non-urgent cases, therapy may be initiated with a maintenance dose and the full effect of the dose evaluated after approximately five half-lifes, i.e. in 1–2 weeks for digoxin or 2–4 weeks for digitoxin. In urgent cases, in which the drug effect is required as soon as possible, a loading dose is given so that a therapeutic plasma and tissue concentration can be established quickly. If an adequate loading dose is given in one dose, adverse CNS and cardiac effects may occur, so the dose is spread over 24–48 hours depending on the urgency of the clinical situation. For instance, with digoxin, the loading dose is normally 4–6

times the maintenance dose and a typical dose schedule is 0·5 mg orally 8 hourly for three doses, then 0·25 mg daily. However, there is no universal digitalising dose. The range of maintenance doses observed in clinical practice (0·0625–1·0 mg/24 hour) attests the range of interindividual differences in response to the drug and the need to evaluate each patient individually and to monitor drug effects.

MONITORING THERAPY Before initiating therapy, renal function and electrolyte status should be evaluated. The therapeutic and adverse effects are monitored frequently during the loading dose and much less frequently once the appropriate dose is established. Symptoms of anorexia and nausea are useful as early signs of overdosage, and the pulse rate and regularity of cardiotoxic effects. If overdosage is suspected, an ECG and plasma digoxin concentration may be helpful and a plasma potassium concentration should also be determined.

PLASMA DIGOXIN CONCENTRATION MONITORING The plasma concentration of cardiac glycosides can be measured using a radioimmunoassay method. Studies comparing drug effect with plasma digoxin concentrations at 'steady state' (i.e. 8–24 hours after a dose in patients who have been on a daily dose for at least 2 weeks) have shown that therapeutic effects usually occur at concentrations of 1–2 ng/ml and that adverse effects become progressively frequent at values of 2 ng/ml and more. The scatter of values around the means however is large, standard deviations for mean therapeutic and mean toxic doses being 50–100% the mean values. For instance, some patients judged to be suffering from adverse effects may have plasma values of 1 ng/ml or less while others well controlled yet free from adverse effects may have plasma values of 3 ng/ml or more. The relatively poor correlation between plasma concentration and drug effects has severely limited the clinical usefulness of the assay, but it is obviously of value in establishing patients' compliance and as one of a number of pieces of evidence in determining whether a patient is receiving too little or too much of the drug. It may also be of value in establishing an appropriate dose in individual patients, in treating patients with renal failure and in the investigation of novel events in patients receiving digoxin.

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Chapter 21

Diuretics

Diuretics are drugs that increase urine flow rate. Drugs may produce a diuresis indirectly by altering renal haemodynamics or directly by an action on the renal tubule, and in this chapter only diuretic drugs with a direct action will be considered.

All diuretics with a direct action on the renal tubule impair the reabsorption of either sodium or chloride or both, at one or more sites along the renal tubule. To understand the effects of such drugs it is necessary first to consider the principal sites of sodium and chloride reabsorption by the renal tubule (Fig. 1).

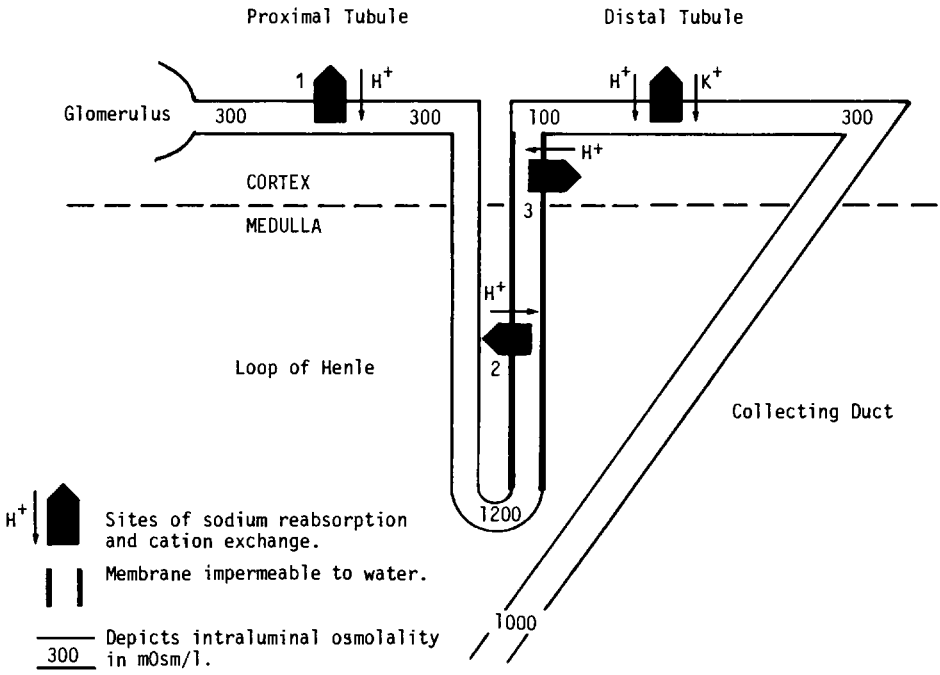


FIG. 1 Principal sites of sodium and chloride reabsorption by the renal tubule.

Sodium reabsorption

Glomerular filtration The glomerular filtrate is any ultra filtrate of plasma and thus is iso-osmolar with plasma water. The amount of sodium excreted varies

directly with the glomerular filtration rate (GFR) and drugs may affect urine volume indirectly by altering GFR.

The proximal tubule The proximal tubule reabsorbs 50–80% of the glomerular filtrate and this is independent of the GFR. Some of the sodium is actively reabsorbed (site 1) while most of the chloride is not. Water is passively reabsorbed as a consequence of sodium reabsorption and the lumen contents remain iso-osmotic with the plasma water throughout this segment of the tubule.

The loop of Henle Chloride is actively reabsorbed along the length of both the medullary (site 2) and cortical (site 3) segments of the ascending limb of the loop of Henle. Sodium is the principal accompanying cation. As the membrane of this limb is largely impermeable to water, the intraluminal contents become hypo-osmolar to the interstitial fluid. In the medullar segment, chloride and sodium reabsorption create an osmolar gradient between the renal medulla and cortex which is maintained and multiplied by the counter current arrangement of the loop of Henle and vasa recta. The hyperosmolarity of the renal medulla provides the entire force for the reabsorption of water from the collecting duct and hence for the concentration of the urine. The process of urine concentration requires also a permeable tubular membrane, a process controlled by the concentration of anti-diuretic hormone.

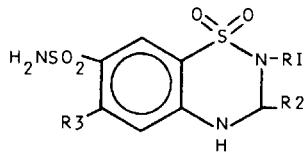
The distal tubule and collecting duct Sodium is actively reabsorbed in the distal tubule (site 4). The ionic balance across the tubular membrane is largely maintained by extrusion of potassium and hydrogen ions out of the tubular cell into the lumen which thus does not require concomitant anion reabsorption. The net result is an exchange of sodium for potassium or hydrogen ions. Aldosterone and other mineralocorticoids enhance this exchange process. Hydrogen ions derived indirectly from CO_2 are exchanged for sodium throughout the proximal and distal tubules, but in the distal tubule only is there a reciprocal relationship between the number of potassium and hydrogen ions exchanged for sodium ions. A decrease in the availability of hydrogen ions will increase the number of potassium ions exchanged for sodium and vice versa.

Anti-diuretic hormone (ADH) increases the permeability of the distal tubule and collecting duct membrane to water. Along this segment of the nephron and especially along the collecting duct which passes back through the hyperosmolar renal medulla, water is reabsorbed independently of sodium, by passive diffusion, the interstitial fluid of the medulla being hyperosmolar to that in the collecting duct lumen.

The thiazides The thiazides (benzothiadiazines) are a group of drugs derived from the sulphonamides. They are weak acids possessing two sulphamyl groups ($SO_2N^{R1}_{R2}$). There are a large number of thiazides in clinical use which differ only in diuretic potency, duration of action and the extent to which they inhibit carbonic anhydrase. Examples of some commonly used thiazides are shown in Table 1.

Table 1
Examples of thiazide diuretics

BASIC STRUCTURE



APPROVED NAME	RI	R2	R3	ADULT 24 H DOSE RANGE (MG)
CHLOROTHIAZIDE	-H	UNSATURATED	-Cl	500 - 2000
HYDROCHLOROTHIAZIDE	-H	-H	-Cl	25 - 100
HYDROFLUMETHIAZIDE	-H	-H	$-CF_3$	25 - 100
BENDROFLUAZIDE	-H	$-CH_2$ 	$-CF_3$	2.5 - 10
POLYTHIAZIDE	$-CH_3$	$-CH_2-S-CH_2CF_3$	-Cl	0.5 - 2
CYCLOPENTHIAZIDE	-H	$-CH_2$ 	-Cl	0.25 - 1

ACTION

Diuretic Thiazides are moderately effective diuretics. They impair sodium reabsorption in the cortical segment of the ascending limb of the loop of Henle (site 3) and it is the effect at site 3 on which their diuretic effect mostly depends. In high doses, they also impair sodium reabsorption in the proximal tubule. The cellular mechanisms involved in this action are not understood.

Carbonic anhydrase inhibition Many thiazides are inhibitors of carbonic anhydrase, but this action accounts for little or none of their diuretic effect. Carbonic anhydrase is present in the renal tubule and in many other cells in the body and facilitates the formation of carbonic acid from CO_2 and water. In the cells of the normal renal tubule, carbonic acid (pK 6·1) dissociates to hydrogen ions and bicarbonate ions and some of the hydrogen ions are exchanged for sodium ions in the tubular lumen. When carbonic anhydrase is inhibited, the rate constant for the formation of carbonic acid is such that only a small proportion of the CO_2

in the tissue is converted to carbonic acid and there is a reduction in the number of hydrogen ions available for exchange with sodium ions. Since hydrogen ion secretion and consequently bicarbonate reabsorption are impaired, there is an increase in bicarbonate excretion and the urine becomes alkaline. There is a reduction in hydrogen ions available to the distal tubule and an increase in sodium in the lumen and hence an increase in potassium excretion.

This sequence of events is only seen with acetazolamide whose diuretic action is explained in full by carbonic anhydrase inhibition. With the other thiazides in common usage, the effect on the ascending limb of the loop of Henle overrides any due to inhibition of the enzyme. The diuretic effect of acetazolamide lasts only 2–3 days as the impairment of hydrogen ion excretion by the kidney it induces causes a metabolic acidosis and hence stimulates ventilation. This, in turn, reduces the amount of sodium bicarbonate in the glomerular filtrate. For this reason acetazolamide is not used as a diuretic but is used in the treatment of glaucoma and petit mal epilepsy (Chapter 17). The other thiazides vary in the extent to which they inhibit carbonic anhydrase, and at diuretic doses inhibition of the enzyme is only appreciable with chlorothiazide. In general, the more the carbonic anhydrase inhibition the more alkaline the urine and the greater the loss of potassium.

Effect on fluid and electrolytes Thiazides cause a negative sodium balance. Chloride is excreted in excess of sodium as the latter is reabsorbed without an anion at the distal tubule in exchange for hydrogen or potassium ions. This results in an increase in hydrogen ion excretion and the development of a hypochloraemic alkalosis, the chloruretic effect overriding the effect of carbonic anhydrase inhibition. Potassium depletion results from an increase in sodium available for cation exchange in the distal tubule. Thiazides are unique amongst diuretics in reducing calcium excretion. They increase magnesium excretion and can cause hypomagnesaemia, which may contribute to the adverse effects of cramps, parasthesiae and nausea and vomiting.

Anti-hypertensive Thiazides reduce both the lying and the standing blood pressure of hypertensive patients at diuretic doses. It is believed that this is due partly to a reduction in the circulating plasma volume and partly to a direct vasodilator effect on the resistance vessels (Chapter 23).

DRUG FATE Thiazides are orally active and are distributed in the extracellular space. A diuresis usually starts within one hour and the duration varies between agents, chlorothiazide having the shortest duration of action, 12 hours, and polythiazide and cyclopenthiazide the longest, 72 hours. The degree of protein binding varies within the group. In general the higher the degree of protein binding, the longer the duration of action. Protein binding is highest with polythiazide which is 85% protein bound at therapeutic concentrations.

Thiazides are mostly excreted unchanged in the urine, although biliary excretion may contribute in part to the rapid clearance from the plasma of chlorothiazide. The short acting thiazides such as chlorothiazide and hydroch-

lorothiazide are partly secreted by the renal tubule, and have a renal clearance 3–4 times that of creatinine. Long-acting agents such as polythiazide have a much lower renal clearance on account of a high pK (11·0), a high degree of protein binding and the high lipid solubility of the associated drugs.

ADVERSE EFFECTS

Overdose Causes an excessive decrease in the extra-cellular and circulating plasma volume, a fall in GFR and ultimately acute circulatory failure. Symptoms of dizziness, muscle cramps, weakness and fainting attacks and signs of an increase in skin turgor and postural hypotension are associated with these changes and there is an increase in the packed cell volume and in plasma urea and creatinine concentrations.

Hypokalaemia A hypokalaemic alkalosis commonly occurs, but the potassium loss is usually only of clinical importance in patients already depleted of potassium or who are excessively sensitive to potassium depletion (*see* potassium replacement, page 293). Hyponatraemia may also occur due to excessive sodium loss, but if severe is often partly due to inappropriate ADH secretion, probably stimulated by hypokalaemia.

Hyperuricaemia Thiazides reduce uric acid excretion, cause an increase in plasma uric acid concentration and may precipitate attacks of gout. They do this by competing with uric acid for sites of active anion secretion in the proximal tubule.

Hyperglycaemia Thiazides impair glucose tolerance in diabetic patients capable of synthesising insulin and in a small number of subjects with normal glucose tolerance. This effect is due to a reduction in insulin release by the beta cells of the islets of Langerhans and is identical to that of the closely related compound diazoxide (Chapter 31).

Miscellaneous effects Rashes occur in a small number of patients. Blood dyscrasias are only rarely attributed to these drugs, thrombocytopenia being the most common. Thiazides, in common with other diuretics, cause an increase in plasma renin and hence aldosterone secretion. On cessation of therapy oedema formation may occur, even in subjects without an impairment of sodium excretion, due to excess mineralocorticoid activity, which reverts to normal values over 1–2 weeks.

Drug interactions

1. Cardiac glycosides. Diuretic induced hypokalaemia enhances the toxic effects of cardiac glycosides on the myocardium.
2. Oral hypoglycaemic agents. Thiazides antagonise the actions of oral hypoglycaemic agents and may increase the dose requirements of these drugs.

CHOICE OF THIAZIDE The dose-response curve of all the thiazides is parallel and although there are large differences in the size of their maximally effective doses, there is no difference in the maximum effect they produce. The more potent agents, such as bendrofluazide, cyclopenthiazide and polythiazide, have a longer duration than the original thiazide chlorothiazide, inhibit carbonic anhydrase to a lesser

degree and cause less potassium depletion at equi-effective diuretic doses. There is no convincing evidence that newer thiazides have any advantages over hydrochlorothiazide.

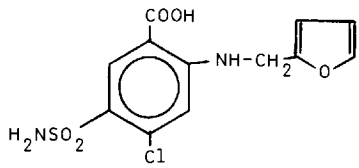
CLINICAL USE Thiazides are administered orally and usually in a single morning dose to avoid nocturia. The dose is established empirically by observations of the body weight, the objective being to lose 0·5–1·0 kg/day in oedematous states. Weight loss in excess of this commonly results in hypovolaemia and major fluid and electrolyte disturbances.

Indications

1. Oedema. Thiazides are drugs of first choice for maintenance diuretic therapy as they are orally active, have few serious adverse effects and are cheap.
2. Hypertension. In mild and moderate hypertension thiazides are agents of first choice and in severe forms are commonly used in combination with other hypotensive agents (Chapter 23).
3. Miscellaneous. In idiopathic hypercalcuria thiazides reduce urine calcium concentration and so the incidence of stone formation and nephrocalcinosis. In diabetes insipidus thiazides, like other diuretics, produce a reduction in urine volume of up to 50%, probably by reducing plasma volume and hence GFR.

Chlorthalidone, metolazone, quinethazone These agents are not thiazides in that they possess only one sulphamyl group (like frusemide and bumetanide). Their clinical pharmacology however is very similar to that of the longer acting thiazides.

Frusemide



Frusemide is a monosulphamyl diuretic. It is often capable of inducing a diuresis in patients who have failed to respond to a maximally effective dose of a thiazide.

ACTION

Diuretic Frusemide is a highly effective diuretic that retains its activity even at low GFRs. The sites of action on which its diuretic effect mostly depend are the medullary (site 2) and cortical (site 3) segments of the ascending limb of the loop of Henle where it inhibits active chloride reabsorption. Diuretics acting at this site are sometimes called 'loop diuretics'. In high doses it impairs sodium reabsorption by the proximal tubule. It is a weak carbonic anhydrase inhibitor but this does not contribute to its diuretic effect.

Effect on fluid and electrolytes Frusemide induces a hypochloraemic alkalosis by the same mechanism as the thiazides (*see* page 286). There is also a net depletion of potassium, although this is less than with an equipotent dose of a thiazide and an increase in calcium, magnesium and phosphate excretion.

Hypotension Frusemide is a weak hypotensive agent producing less of a reduction in blood pressure than an equipotent diuretic dose of a thiazide.

DRUG FATE Frusemide is rapidly but incompletely absorbed from the bowel and has an onset of action within 30 minutes, a maximum effect by 1–1·5 hours and a duration of action in subjects with normal renal function of 3–4 hours. It is 97% bound to plasma albumin at therapeutic doses and can be displaced from binding sites by other acidic drugs including diazoxide, phenylbutazone, aspirin and tolbutamide. The high degree of protein binding probably accounts for its low apparent volume of distribution of 4–7 l. Frusemide is cleared from the plasma rapidly with a $t_{\frac{1}{2}}$ of 1·5–3·5 h in subjects with normal renal function. It is actively secreted into the renal tubule and is excreted mostly as unchanged drug in the urine, the renal clearance being 1·5 times that of creatinine. It is also excreted in the bile and in renal failure, non-renal routes of elimination account for the elimination of most of the drug, the $t_{\frac{1}{2}}$ in oliguric states being 2–3 times normal.

ADVERSE EFFECTS

Overdose Is more common with frusemide than with a thiazide as it is a more effective diuretic. Hypokalaemia, hyperuricaemia and hyperglycaemia may all occur.

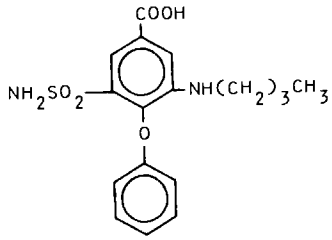
Ototoxicity In very high intravenous doses frusemide may impair both vestibular and cochleal function. This is probably due to changes caused by the diuretic on the endolymph and is usually but not invariably reversible. It rarely occurs after oral administration even when large daily doses (0·5–1·0 g) are given to subjects in renal failure.

Drug interactions Are similar to those of the thiazides. Frusemide may enhance the nephrotoxic effect of cephaloridine and cephalothin in patients with reduced renal function (Chapter 35).

CLINICAL USE Frusemide may be given i.v. or orally and the rate of onset after oral administration is such to render i.v. administration unnecessary in most patients who are conscious and not vomiting. It is usually given in a single dose, although it is more effective given twice daily.

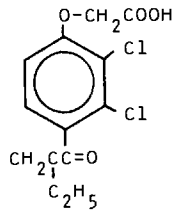
Frusemide is a diuretic of first choice in the treatment of medical emergencies caused by salt and water retention, e.g. pulmonary oedema. For maintenance therapy it has no advantages over thiazides, is more expensive and is less effective than these agents as a hypotensive agent. In acute anuria and oliguria it probably does not prevent acute renal tubular necrosis.

Bumetanide



This agent is identical to frusemide pharmacologically, but is 60 times as potent on a weight basis. It is rapidly active orally, highly protein bound and rapidly excreted by renal and, to a lesser extent, biliary mechanisms. It does not accumulate in renal failure.

Ethacrynic Acid



Ethacrynic acid is not a sulphonamide derivative and has a chemical structure distinct from the thiazides and monosulphamyl agents.

ACTION The maximal diuretic effectiveness of ethacrynic acid is similar to that of frusemide and it has the same site of action. It has a high affinity for sulphydril groups and interaction with enzymes containing such groups in the renal tubule may be the basis of its diuretic effect.

Its hypotensive action is similar to that of frusemide and in high doses it may also induce a diuresis in oliguric states when the GFR is greatly reduced.

DRUG FATE Ethacrynic acid is orally active, has a rapid onset action and a short duration of action. In the plasma it is 90% protein bound and is excreted in the urine as unchanged drug and as a cysteine conjugate. It is also excreted in the bile.

ADVERSE EFFECTS

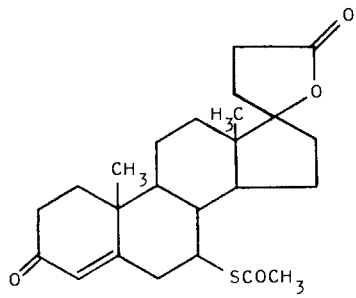
Overdose Hypokalaemia and hyperuricaemia occur as with frusemide. Ethacrynic acid does not impair glucose tolerance to the same degree as thiazides or frusemide. Gastrointestinal symptoms, especially epigastric pain, are common and occasionally gastrointestinal haemorrhage may occur. Ototoxicity is more common with ethacrynic acid than frusemide, sometimes occurring after oral administration in subjects with renal failure and it may be irreversible.

CLINICAL USE Ethacrynic acid is not used as frequently as frusemide in the UK, but in other parts of the world it is used more frequently.

Diuretics Acting only on the Distal Tubule

Diuretics in this group impair the exchange of sodium for hydrogen and potassium ions in the distal tubule. Under physiological circumstances, they are weak diuretics as the distal tubule reabsorbs only a small fraction (0·5–2%) of sodium in the glomerular filtrate. However, in circumstances under which the function of the more proximal parts of the nephron is impaired, e.g. by frusemide or a thiazide, the proportion of the GFR reabsorbed by the distal tubule increases up to 30–40% and the effect of diuretics acting at this site increase proportionately. As they impair potassium secretion, the diuresis they induce may be associated with either potassium retention and hyperkalaemia or no change in the potassium balance.

Spironolactone



ACTION

Diuretic Spironolactone is a steroid and a competitive antagonist of aldosterone. In maximally effective doses it is only a weak diuretic. Secondary hyperaldosteronism is a feature of clinical states in which there is a reduction in renal blood flow, e.g. congestive cardiac failure, ascites due to liver cell failure and accelerated hypertension, and in these situations spironolactone is a useful adjunct to more potent diuretics.

Hypotensive In primary aldosteronism (Conn's syndrome) with or without a demonstrable tumour, spironolactone is an effective hypotensive agent used alone or in combination with other hypotensive drugs. In essential hypertension patients with low plasma renin activity prior to treatment generally respond well to the hypotensive effects of this drug.

DRUG FATE Spironolactone is completely absorbed from the bowel. It is rapidly metabolised, the major metabolite in the plasma being canrenone. Approximately 30% of an oral dose is excreted as metabolites in the urine and 20% in the faeces. The $t_{\frac{1}{2}}$ of canrenone is 16–20 hours so that on repeated dosing a steady state plasma concentration is achieved in 3–4 days.

ADVERSE EFFECTS Hyperkalaemia occurs in a small proportion of subjects with normal renal function and in 20% of those with renal failure. It is even more common when spironolactone is administered in conjuction with potassium replacement therapy to such patients.

Epigastric discomfort is a common symptom and occasionally this drug has

been implicated in the causation of peptic ulceration. Spironolactone may cause gynaecomastia and hirsutism, menstrual irregularities, post-menopausal bleeding and deepening of the voice in women.

CLINICAL USE Spironolactone is administered orally, usually three times a day, starting with a dose of 25 mg and working up according to the clinical response. It is effective in primary hyperaldosteronism, in low renin hypertension and in ascites due to liver cell failure, but in most oedematous states is only used as an adjunct to more potent diuretics.

Triamterine and Amiloride

DIURETIC EFFECT

These agents are relatively strong bases which differ in chemical structure, but have a similar diuretic effect. Their weak diuretic effect is produced by preventing ion exchange in the distal tubule and this effect is independent of aldosterone. Triamterine also increases uric acid secretion. They both have a mild hypotensive effect and enhance the effect of thiazides and other hypotensive agents.

Both drugs are orally active but are only partially absorbed. Triamterine is metabolised principally by para-hydroxylation and sulphate conjugation, but amiloride is excreted unchanged in the urine and may therefore accumulate in renal failure.

ADVERSE EFFECTS

Hyperkalaemia may occur and rarely hyperchloraemic acidosis. Triamterine is a pteridine compound like folic acid (*see* Chapter 32) and inhibits dihydrofolic acid reductase (*see* Chapter 35). It may induce a megaloblastic anaemia in patients predisposed to folate deficiency.

CLINICAL USE

These agents are given orally once or twice a day. Their indications are similar to those for spironolactone. Plasma potassium should be monitored during therapy.

Osmotic Diuretics

Osmotic diuretics are inert substances that are filtered by the glomerulus but not reabsorbed by the renal tubule and therefore exert an osmotic effect in the tubular lumen. Mannitol, a polyhydric alcohol (MW 182) that is not metabolised in the body, is the most widely used osmotic diuretic.

Mannitol Mannitol in the glomerular filtrate is not reabsorbed in the proximal tubule and hence is concentrated during its passage down the tubule as water is reabsorbed. This raises the osmotic pressure of the luminal contents so that water is no longer reabsorbed with sodium. The concentration in the tubular lumen of sodium, potassium and chloride falls with a consequent reduction in their reabsorption. The prime effect of osmotic diuretics is to promote water

excretion, but at higher doses, it also increases the excretion of chloride, sodium and potassium.

CLINICAL USE Mannitol is administered i.v. in 5–20% solution, usually in volumes of 100–200 ml. It is distributed in the extracellular space and causes a rapid increase in extracellular fluid volume through its osmotic effect in abstracting water from cells. The principal adverse effect is the precipitation of acute pulmonary oedema after an overdose or after small doses to predisposed subjects.

Its principal use is in the prophylaxis of acute renal failure in circumstances such as after major trauma or surgery, associated with a period of prolonged hypotension. By maintaining adequate urine flow, osmotic diuretics decrease the liability of developing renal tubular necrosis by a mechanism that is not well understood. It is also occasionally used instead of frusemide in the diagnosis of acute renal failure and in forced alkaline diuresis in the treatment of aspirin poisoning (*see* Chapter 40).

Preparations

Drug	*Adult dose range (mg)*	*Route*	*Dose interval*
Frusemide	40–500	Oral or i.v.	14–24
Bumetanide	0·5–4	Oral or i.v.	14–24
Ethacrinic acid	50–200	Oral or i.v.	12–24
Chlorthalidone	50–200	Oral	24
Spironolactone	25–50	Oral	8–12
Triamterine	25–50	Oral	12–24
Amiloride	5–10	Oral	12–24

Organomercurials The first organomercurial diuretic (Mersalyl) was introduced in 1924. Subsequent to this, these agents were the most effective diuretics available until the introduction of chlorothiazide in 1957.

Organomercurials are potent diuretics but are now obsolete as the adverse effects they cause rashes, fever, albuminuria, nephrotic syndrome, bone marrow depression and cardiac dysrhythmias, are more frequent and more serious than those caused by the thiazides, the monosulphamyl diuretics and ethacrinic acid. With the exception of chlormeredrin, they are inactive orally, being administered i.m. Tolerance develops to their diuretic effect on repeated usage in patients who develop a metabolic alkalosis. Responsiveness can be restored by coadministration of the acidifying agent ammonium chloride.

POTASSIUM REPLACEMENT

All potassium in the glomerular filtrate is reabsorbed by the proximal tubule at sites of sodium reabsorption. In the distal tubule, it is secreted into the tubular

lumen in exchange for sodium ions and there is a reciprocal relationship between the potassium and hydrogen ions secreted at this site. Sodium reabsorption and potassium secretion by the distal tubule are facilitated by aldosterone.

Diuretic therapy and potassium balance All diuretics, other than those impairing ion exchange in the distal tubule, increase potassium excretion and may cause potassium depletion. Potassium loss is expedited by diuretics which cause a hypochloraemic alkalosis or carbonic anhydrase inhibition. The extent of the potassium loss varies very considerably and is difficult to predict in any given patient regardless of the condition for which the diuretic is being prescribed. Potassium loss may be insignificant as has been shown in the majority of patients being treated with thiazides for hypertension. However, in patients on high doses of diuretics or with conditions predisposing to excess potassium excretion, e.g. mineralocorticoid administration, excess aldosterone secretion, or in patients prediposed to the deleterious effects of hypokalaemia, e.g. digoxin therapy, potassium depletion may cause muscle weakness, cardiac dysrhythmias, a negative nitrogen balance and renal tubular damage. Under such circumstances prophylactic potassium therapy is advisable. An alternative approach is the use of a diuretic acting on the distal tubule, e.g. spironolactone or amiloride, although it cannot be assumed that the use of a fixed dose combination of one of these agents with more potent diuretics invariably prevents potassium depletion.

Preparations

ORAL POTASSIUM Potassium is available as the chloride, bicarbonate, citrate and nitrate. Of these, potassium chloride is more effective than the other preparations at replacing the potassium loss as it corrects the hypochloraemic alkalosis that is usually present and which itself perpetuates excess potassium excretion.

Potassium chloride This preparation may cause small bowel ulceration and stricture formation. However this occurs only very rarely with slow release forms which do not produce high local concentrations of KCl in the small bowel. There are a number of slow release potassium preparations containing between 7–10 mmol/tablet. They are large tablets and hence are often difficult to swallow. Poor patient compliance with this form of therapy is common.

Potassium bicarbonate, citrate and nitrate These forms are more palatable than potassium chloride and do not cause small bowel ulceration. However, they are alkalinising agents as the organic anions are metabolised and hence do not correct the hypochloraemic alkalosis. As a consequence, potassium excretion is increased and hypokalaemia is only corrected by high doses of these agents.

INTRAVENOUS POTASSIUM A sudden rise in plasma potassium may cause cardiac asystole. The intravenous route of potassium therapy is dangerous and should only be used in clinical conditions sufficiently serious to justify the risks of this form of therapy, e.g. in digoxin toxicity associated with hypokalaemia and in

diabetic ketoacidosis in which potassium depletion is invariable. To avoid a rapid rise in the plasma concentration potassium chloride should be given slowly, preferably in a large fluid volume and the effects on the myocardium observed on a cardiac monitor. The amount administered depends on the potassium status, but it is usually unwise to give more than 40 mmol/hour.

Monitoring potassium therapy Potassium in the extracellular space constitutes only 2% of the total body potassium and the concentration in it (as determined in the plasma) does not always reflect total body potassium. However, the plasma potassium concentration is the best available measure of the body potassium status, a fall of 0·5 mM indicating approximately a 10% fall in total body potassium. Following the initiation of diuretic therapy, a new potassium equilibrium is usually established within two weeks and during this period the plasma potassium concentration should be monitored. If there is a consistent fall of 0·5 mM or more, potassium replacement is advisable, the size of the dose being adjusted according to the plasma potassium concentrations. There are a large number of proprietary preparations containing a fixed dose of diuretic and potassium, usually as the chloride. Such preparations have the defect that the potassium supplement cannot be adjusted to the needs of the individual patient and that such a presentation may lead the prescribing doctor to the erronious conclusion that monitoring of the plasma potassium is not necessary.

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Chapter 22

Drugs Used in Disorders of Cardiac Rhythm

Disorders of cardiac rhythm may occur as a consequence of a wide variety of pathological changes and the identification of these and their correction is the first objective of therapy. Drugs that are used specifically for their effects on the rhythm disorders themselves are known as antidysrhythmic drugs and these will be discussed in this chapter. The cardiac glycosides, which are amongst the most important anti-dysrhythmic drugs, have been fully considered in Chapter 20.

The anti-dysrhythmic drugs act by causing changes in the myocardial cell membrane and these changes alter the electrical and mechanical properties of the myocardium. To consider the effects of these changes, it is first necessary to consider the physiology of normal rhythm and the mechanisms involved in the genesis of dysrhythmias.

Physiology of normal rhythm The electro-physiological events in the normal heart are summarised in Fig. 1. In most areas of the heart, e.g. the ventricles in Fig. 1, there is a resting transmembrane potential of −80 to −90 mV, and this is maintained throughout diastole until a depolarising event causes a muscle action potential. At the sino-atrial (SA) node (physiological pacemaker), the membrane is more permeable to sodium than elsewhere and during diastole, sodium leaks into the cell in excess of the rate at which potassium leaks out. This causes a fall in transmembrane potential during diastole (diastolic drift; phase 4) and at around −60 mV sufficient sodium carrier in the membrane is occupied to generate an action potential (phase 0) during which there is a rapid influx of sodium and a reversal of the transmembrane potential. Repolarisation occurs initially by means of rapid efflux of potassium from the cell (phase 1), a slow phase, probably due to calcium efflux (phase 2) and phase 3 when sodium is pumped out of the cell by an active carrier mechanism. The membrane potential generated at the pacemaker, passes across the atria, the atrioventricular node (AV node), the His-Purkinje system (conducting pathways) and ventricles and causes first the atria and then the ventricles to contract.

The autonomic nervous system plays an important part in modulating cardiac rhythm and the effects of ACh and vagal stimulation has already been considered in Chapter 20. Noradrenaline released from sympathetic nerve terminals and adrenaline from the adrenal medulla interact with $beta_1$-receptors on the myocardal membrane and increase the rate of diastolic depolarisation

(phase 4) and the rate of generation of the muscle action potential (phase 0). This results in a positive chronotropic and inotropic effect as cardiac contractility varies with the rate of phase 0 depolarisation.

ECTOPIC BEATS AND TACHYDYSRHYTHMIAS

Ectopic beats and tachydysrhythmias may be caused by one of two mechanisms:

1. *Ectopic pacemakers* These may arise as a consequence of a local pathological increase in membrane permeability to sodium. If the rate of diastolic depolarisation is greater at such a site than at the SA node, an ectopic pacemaker is created. Furthermore, a block in conduction can cause an ectopic pacemaker if it prevents impulse traffic from the SA node reaching an area with pacemaker activity, e.g. AV node (Fig. 1).

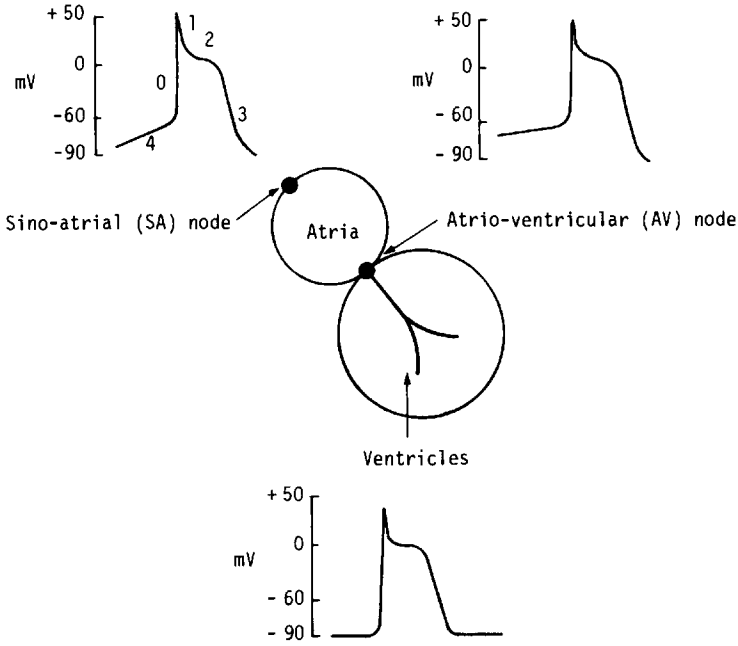


FIG. 1 Schematic representation of electrophysiological events in the normal heart. The phases (0–4) of depolarisation and repolarisation are shown at the SA node. There is some diastolic depolarisation at the AV node but less than at the SA node and there is no diastolic depolarisation of myocardial muscle.

2 *Re-entrant rhythms* These result from a unidirectional block in a conducting pathway (Fig. 2) and may cause ectopic beats or a self-perpetuating tachycardia.

In clinical circumstances, it is often impossible to know which of these mechanisms is causing a dysrhythmia. Drugs may correct the rhythm disorder

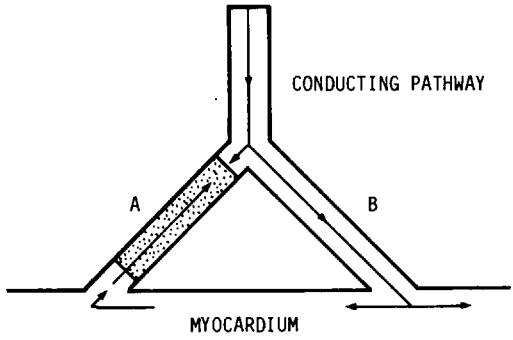
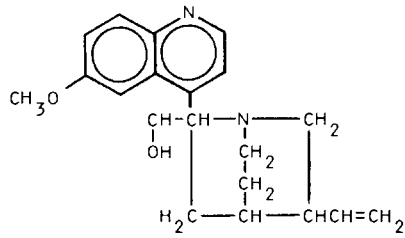


FIG. 2 Re-entrant rhythm: a conducting pathway divides into two limbs, A and B, and there is an undirectional block in A (stippled area). An impulse passes down B to the myocardium and depolarises A in a retrograde direction. If this wave of depolarisation reaches A proximal to the block after it has repolarised, it will depolarise again and an extra systole will result.

by preventing diastolic depolarisation in an ectopic pacemaker as, in general, ectopic pacemakers are more susceptible to drug effects than the physiological pacemaker. In re-entrant rhythms, they may prevent retrograde conduction through a unidirectional conduction block or enhance normal conduction through such an area. The site of an abnormal pacemaker may be identified on the ECG and for the consideration of drug therapy may be divided into ventricular dysrhythmias and supraventricular dysrhythmias which include those arising from the AV node. The effectiveness of any drug in a given tachydysrhythmia is established empirically and in general, digoxin and the beta-blockers are more effective against supraventricular dysrhythmias whereas lignocaine and phenytoin are more effective against ventricular dysrhythmias. Procaine amide and quinidine are effective against both.

Cardioversion Cardioversion is a rapidly effective method of treating all types of tachydysrhythmias, except those due to digoxin toxicity, and as it is relatively trouble free, is often the treatment of first choice. Cardioversion should always be considered before making a decision on drug therapy.

Quinidine



Quinidine is derived from Cinchona bark and is the d-isomer of quinine with which it shares some antimalarial and antipyretic actions.

ANTIDYSRHYTHMIC EFFECT Quinidine is effective at suppressing both supraventricular and ventricular ectopic beats and at slowing supraventricular and ventricular tachycardias.

Electrophysiological effects Quinidine reduces the availability of the sodium carrier in the myocardial membrane and hence slows the rate of diastolic efflux in phase 1. This effect is similar to that of local anaesthetics on peripheral nerves (*see* Chapter 12). The decreased rate of depolarisation results in a reduction in the extent of depolarisation, a decreased rate of conduction, a prolongation of the refractory period and a reduction in myocardial contractility. Quinidine also increases the threshold of excitability. Its antidysrhythmic effect may be due to a slowing of diastolic drift in an ectopic pacemaker or to blockade of retrograde conduction in a re-entrant dysrhythmia.

DRUG FATE Quinidine is orally active and is well absorbed from the bowel with an onset of action within 2 hours. It is 85% bound to albumin at therapeutic plasma concentrations and reaches a concentration in the myocardium approximately ten times that in the plasma. It is cleared from the plasma mostly by hepatic metabolism, very little being excreted unchanged in the urine. It forms an active metabolite, dihydroquinidine, but most of the drug is hydroxylated to the inactive metabolites mono- and dihydroxyquinidine. The $t_{\frac{1}{2}}$ in plasma is 7–8 hours in normal subjects, the range being 3–18 hours, and it does not increase in heart failure or in subjects in renal failure.

ADVERSE EFFECTS Gastrointestinal symptoms are common, especially diarrhoea, but they seldom necessitate stopping therapy.

The negative inotropic effect may precipitate left ventricular failure or hypotension. Impaired conduction may cause heart block, ectopic beats or re-entrant tachydysrhythmias as discussed above (page 298).

Paradoxical tachycardia Quinidine has some antimuscarinic action and may initially increase AV conduction. In atrial flutter with some degree of AV block, the increase in AV conduction caused by quinidine may result in a sudden increase in ventricular rate and precipitate left ventricular failure or myocardial ischaemia.

Some patients develop adverse effects commonly associated with an allergic reaction, urticaria, bronchospasm and anaphylaxis, thrombocytopenia and haemolytic anaemia.

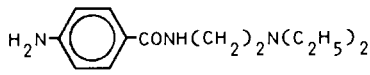
Cinchonism Quinidine can induce cinchonism in high doses (*see* Chapter 36). A small number of subjects are very susceptible to the effects of quinidine and develop symptoms of cinchonism within the therapeutic dose range.

CLINICAL USE

Administration A small initial dose is given to see if the patient is sensitive to the drug. The dose is then established empirically by monitoring the pulse rate and ECG, starting with a small dose and increasing the dose every 24–48

hours. Dosage interval should be 2–3 hours in view of the short duration of action unless a slow release preparation is used.

Indications Quinidine is effective against a wide range of dysrhythmias, but in view of its many serious adverse effects, it is seldom a drug of first choice. It is used most commonly in conjunction with digoxin in the conversion of the unstable atrial flutter to the more stable atrial fibrillation. Digoxin should always be given before quinidine in patients with atrial flutter as this prevents the development of a paradoxical tachycardia.

Procainamide 

ANTIDYSRHYTHMIC EFFECT The pharmacological effects of procainamide are similar to those of procaine, but it is more suitable as an antidysrhythmic drug as it has a longer duration of action. Procainamide is very similar in its antidysrhythmic effect to quinidine and produces similar effects on the myocardial membrane.

DRUG FATE Procainamide is orally active, its onset of action being within 2 hours. It may also be given i.m. or i.v. In the plasma only 25% of the drug is protein bound at therapeutic concentrations but it is extensively bound by the tissues where it achieves a concentration higher than that in the plasma. It is cleared from the plasma partly by metabolism and partly by renal excretion of the unchanged drug. Procainamide is acetylated in the liver to the active metabolite N-acetylprocainamide. The rate of acetylation is determined by a single gene that displays polymorphism (as with isoniazid, etc.) and 3 hours after a single dose, the plasma concentration of N-acetylprocainamide is 2–3 times that of the parent compound for fast acetylators and 0·5–1 times for slow acetylators. The antidysrhythmic activity of N-acetyl procainamide is similar to that of the parent compound so that the acetylator status of the patient is not of great therapeutic importance. The drug is also hydrolysed slowly by blood and tissue esterases. Of an oral dose 40–60% is excreted unchanged in the urine and the drug accumulates in renal failure. The half-life of procainamide in the plasma is 3–4 hours (range 2–5 hours) and that for N-acetylprocainamide is approximately twice as long.

ADVERSE EFFECTS

Hypotension Procainamide has some vasodilator activity and hypotension is commonly the dose limiting effect. Other cardiovascular effects are similar to those of quinidine, including paradoxical tachycardia, as procainamide also has some weak antimuscarinic activity.

Nausea and vomiting are quite common side effects and procainamide may

occasionally precipitate bronchospasm in asthmatics. The major limitation to its long term use is that an appreciable number of patients develop a systemic lupus erythematosus-like syndrome, this occurring more frequently in slow than in fast acetylators.

CLINICAL USE

Administration The principles of administration are similar to those of quinidine except that, as sensitivity reactions are less common, an initial test dose is not necessary. If given intravenously, e.g. in the treatment of ventricular tachycardia, the ECG should be monitored.

Indications Procainamide is an effective alternative to lignocaine or phenytoin in the treatment of ventricular dysrhythmias and it is often effective when these agents have failed. Taken orally, it is also used prophylactically to prevent ventricular dysrhythmias. It is seldom used in supraventricular dysrhythmias, digoxin and beta blocking drugs being used in preference.

Beta-blocking drugs Beta-blocking drugs have been fully discussed in Chapter 11 and only aspects relevant to their use as antidysrhythmic agents will be covered in this chapter. There are no established differences between the various beta-blocking drugs in their antidysrhythmic effects and they will be discussed as a group.

ANTIDYSRHYTHMIC EFFECT Beta-blocking drugs antagonise the positive chronotropic and inotropic effects of noradrenaline, adrenaline and dopamine. They slow the heart rate at rest and after exercise, and are often effective at slowing tachydysrhythmias of supraventricular origin, especially when the latter are precipitated by catecholamines, e.g. in phaeochromocytoma, thyrotoxicosis and anxiety states.

ELECTROPHYSIOLOGICAL EFFECTS These are similar to quinidine. The effectiveness of beta-blockers against supraventricular tachydysrhythmias is due to a reduction in AV conduction. Some beta-blockers, e.g. propranolol, also have a local anaesthetic effect similar to that of quinidine but this probably contributes very little or not at all to their antidysrhythmic effects as it only occurs at concentrations many times those necessary to block beta-receptors or those achieved in the plasma at therapeutic doses.

CLINICAL USE Beta-blocking drugs are antidysrhythmic agents of first choice in supraventricular tachycardia not complicated by left ventricular failure and when catecholamines are the cause of a dysrhythmia. Although they produce fewer adverse effects than quinidine and procainamide, like these agents they have a negative inotropic effect and impair cardiac conductivity. Furthermore, they are commonly less effective than procainamide against ventricular dysrhythmias. They are often effective in the treatment of dysrhythmias due to digoxin toxicity and may be used as alternative therapy to phenytoin.

Lignocaine Like procainamide, lignocaine is a local anaesthetic with antidysrhythmic effects (for other aspects of pharmacology *see* Chapter 12).

ANTIDYSRHYTHMIC EFFECT Lignocaine is effective at suppressing ventricular ectopic foci and ventricular tachydysrhythmias, but is much less effective against supraventricular dysrhythmias. It impairs diastolic depolarisation, but unlike quinidine, does not impair phase 0 depolarisation, myocardial conduction, or increase the refractory period. Lignocaine has some mild antimuscarinic effect and at therapeutic doses, it usually increases AV conduction, although in high doses it may impair it. The antidysrhythmic action of lignocaine may thus be due to direct suppression of ectopic pacemakers or the prevention of re-entrant rhythms by facilitating normal conduction through an area of impaired conduction.

DRUG FATE Lignocaine is well absorbed from the bowel but is almost entirely cleared from the hepatic portal system by hepatic metabolism, only a small fraction of an oral dose reaching the systemic circulation. It is not highly protein bound and as it is a weak base, is slightly concentrated in intracellular water. Its major metabolite, monoethylglycylxylidide, has some convulsant activity and may contribute to the drug's central side effects and it also forms a number of inactive metabolites including glycylxylidide and 4-hydroxylidide.

Lignocaine has a $t_{\frac{1}{2}}$ in normal subjects of 1–2 hours when administered i.v. In hypovolaemic states, the apparent volume of distribution decreases and hence the plasma concentration after a given dose increases. Furthermore, as the drug is cleared in one pass through the liver, the rate of metabolism varies directly with hepatic blood flow and if this falls, as in left ventricular failure or hypovolaemia, the $t_{\frac{1}{2}}$ increases. In patients with severe hepatocellular disease, the $t_{\frac{1}{2}}$ also increases and may achieve values 5–10 times the normal value.

ADVERSE EFFECTS

Convulsions are the most frequent adverse effect when lignocaine is given as a bolus intravenously. This effect is similar to that produced by procaine (*see* Chapter 12). Drowsiness and confusion may occur without convulsions. The major metabolite of lignocaine probably contributes to these central adverse effects (*see* above).

Hypotension is less common than with procainamide and conduction defects only rarely occur.

CLINICAL USE

Administration Lignocaine is usually administered i.v. as a bolus or by continuous intravenous infusion. It is also effective i.m.

Indications Lignocaine is widely used as the drug of first choice in the treatment and prophylaxis of ventricular ectopic beats, ventricular tachycardia and fibrillation, as it does not have the negative inotropic effect or the depressant effect on cardiac conduction of procainamide. It is commonly used in the

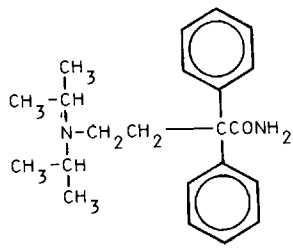
treatment and prophylaxis of ventricular dysrhythmias after myocardial infarction and during cardiac surgery. Its chief limitations are that it is inactive orally and that it has a short duration of action.

Mexilitene This drug is a local anaesthetic like lignocaine and procainamide, but is an ether and not an amide. Its antidysrhythmic properties in man are closer to those of procainamide than lignocaine but as it is only slowly metabolised by the liver, it is orally active having a $t_{\frac{1}{2}}$ of 10–12 hours in subjects with normal cardiac function. In patients after a myocardial infarct it is as effective as procainamide at preventing ventricular dysrhythmias when given orally. Nausea and vomiting are the commonest adverse effects, others being similar to those of lignocaine. The place of this drug in therapeutics has not been established.

Phenytoin Like lignocaine, phenytoin is more effective against ventricular than supraventricular dysrhythmias unless the latter are due to digoxin toxicity. Phenytoin stabilises myocardial membranes in the same way as it does neuronal membranes (*see* Chapter 17) in that it stimulates the sodium pump, hence expediting the extrusion of sodium from the cell and increasing the transmembrane potential. It is particularly effective in digoxin toxicity when it may have a positive inotropic effect.

Though an orally active drug, its anti-dysrhythmic effect being evident at plasma concentrations similar to those optimal for its anti-epileptic effects, it is usually less effective than other agents, e.g. disopyramide or procainamide, in suppressing and preventing most ventricular dysrhythmias. It is, however, a drug of first choice in digoxin toxicity when it may be given by i.v. bolus and infusion. Hypotension occasionally occurs when it is administered i.v.

Disopyramide



This agent differs in structure from quinidine and the local anaesthetics. It has antidysrhythmic effects similar to those of quinidine and procainamide although at equipotent doses it produces less myocardial depression and hypotension. It has appreciable anti-muscarinic activity.

Disopyramide is orally active and is excreted mostly as unchanged drug in the urine. Its plasma $t_{\frac{1}{2}}$, 5–7 hours, is longer than that of quinidine or procainamide.

Adverse effects to disopyramide are the consequence of its quinidine-like and anti-muscarinic activity, left ventricular failure, heart block and re-entrant tachydysrhythmias, hypotension, dry mouth, blurred vision and urinary retention. It has the advantage over quinidine that it does not cause gastrointestinal

symptoms so frequently or allergic reactions, and over procainamide, in that it does not cause a systemic lupus erythematosus-like syndrome. However, though it appears a promising drug in the treatment of both supraventricular and ventricular dysrhythmias, its place in therapy has yet to be firmly established by clinical trials comparing it with older antidysrhythmic drugs.

Verapamil This drug is a derivative of papaverine. It has vasodilator and antidysrhythmic properties and is useful in the management of angina, especially in patients with obstructive airways disease in whom beta-blocking drugs are contraindicated. It also has antidysrhythmic properties as it slows sinus, nodal and ventricular tachydysrhythmias and can convert atrial fibrillation to sinus rhythm. Its mode of action is quite different from the local anaesthetics and beta-blockers, in that it is a calcium antagonist and impairs electromechanical coupling.

After oral administration verapamil is mostly metabolised during its first passage through the liver so that oral doses (40 mg) are appreciably greater than those given i.v. (5 mg). It has a negative inotropic effect and may precipitate left ventricular failure.

The place of verapamil in the management of tachydysrhythmias is not established.

Monitoring antidysrhythmic therapy The objective of antidysrhythmic therapy is to maintain a therapeutic drug plasma concentration. There is considerable interindividual variation in the rates at which many of those drugs are cleared from the plasma and in the plasma concentrations at which they are effective. The dose requirement and dose interval should be established for each

Preparations

Drug	*i.v. dose*	*oral maintenance dose in g/24h*	*dose frequency in hours*
Quinidine		0·2–3·0	2–4
Procainamide	50 mg/min (max 1G)	1·0–6·0	4–6
Lignocaine	50–100 mg (bolus)	–	–
	1–2 mg/min (maintenance)	–	–
Phenytoin	250 mg (bolus)	0·3–0·9	8 hourly
Disopyramide	50–150 mg (bolus)	0·3–0·8	6–8
	4 mg/kg in 1 hour then 0·4 mg/kg/h		
Verapamil	5 mg	0·120–0·240	6–8

patient on the basis of the drug effect on the pulse and ECG. In certain circumstances, determination of the drug-plasma concentration will be helpful, e.g. in deciding whether a dysrhythmia is due to too little or too much drug, as this will facilitate control of the dysrhythmia and the avoidance of side and overdose effects.

SINUS BRADYCARDIA AND HEART BLOCK

Impaired conduction across the AV node and in the conducting pathways may cause sinus bradycardia or any degree of heart block. As with tachydysrhythmias, there are many causes of impaired cardiac conduction and the first objective of therapy is to identify and treat such causes.

Conduction defects may be treated by cardiac pacing or by drugs that increase AV conduction and in general cardiac pacing is the more effective of the two forms of treatment.

Isoprenaline Isoprenaline is a beta adrenoreceptor agonist which increases the conductivity in the AV node and conducting pathways (*see* Chapter 11). It increases heart rate in sinus bradycardia and in heart block. In complete heart block it may prevent periodic episodes of asystole (Stokes–Adams attacks).

Isoprenaline is relatively inactive if swallowed as it is rapidly metabolised in the gut wall and liver, but taken sublingually has an effect on the heart rate for up to 60 minutes. It is also available as a slow release preparation which has a duration of action of 4–6 hours. Dosage is established for each patient on the basis of the effect on the heart rate. In high doses isoprenaline may precipitate ventricular tachycardia or fibrillation.

Antimuscarinic agents Antimuscarinic agents increase AV conduction by antagonising the effects of ACh on the AV node (*see* Chapter 10).

Atropine is effective at increasing the heart rate in sinus bradycardia when the latter is due to increased vagal tone, e.g. after a myocardial infarct. The main danger in this situation is that even small doses (0·6–1·0 mg i.v.) may cause a sinus or ventricular tachycardia or ventricular fibrillation. Atropine and other antimuscarinic agents are no more effective than isoprenaline in chronic therapy of stable forms of heart block and in general causes more side effects.

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Chapter 23

Hypotensive Agents

At all ages life expectancy varies inversely with arterial blood pressure. Blood pressure (BP) increases throughout life and it is generally accepted that in adults, a blood pressure in the lying position that is persistently above 160/90 usually requires hypotensive therapy. Screening tests in the UK and elsewhere have shown that 15–30% of the adult population have BPs above this value. Such individuals are at risk of sustaining one or more of the morbid consequences of hypertension, i.e. left ventricular hypertrophy and congestive cardiac failure, cerebral haemorrhage, chronic renal failure and myocardial infarction. Prospective controlled clinical trials have demonstrated convincingly that the institution of effective hypotensive therapy increase the life expectancy of hypertensive patients and decreases the frequency and severity of morbid consequences other than that of myocardial infarction. As there are now a number of hypotensive agents that are generally well-tolerated, the onus is on doctors to diagnose hypertension early and to institute effective therapy.

Pathophysiology of Hypertension

The arterial blood pressure is determined by the cardiac output (CO) and the peripheral resistance (PR). The PR itself varies with the calibre of the resistance vessels and the viscosity of the blood. These determinants themselves are controlled by other mechanisms which include:

1. The autonomic nervous system Baroreceptors that detect changes in BP are located predominantly in the aortic arch and carotid body. A fall in BP causes an increase in impulse traffic in the afferent fibres between the baroreceptors and the vasomotor centre (VMC) in the medulla. This causes an increase in sympathetic and a decrease in parasympathetic tone to the heart and blood vessels. An increase in sympathetic tone stimulates CO and increases both peripheral resistance and venous return. This causes a rise in BP and, via the vagus, a bradycardia.

2. Circulating hormones Renin-angiotensin-aldosterone system. The proteolytic enzyme renin is secreted by the juxtaglomerular apparatus of the kidney in response to an increase in sympathetic tone, a fall in renal perfusion pressure or hyponatraemia. Its substrate in the plasma is angiotensinogen which it converts to the relatively inactive decapeptide angiotensin I. In the lungs, and to a lesser extent other tissues, angiotensin I is converted to the more active octapeptide angiotensin II by a 'converting enzyme'. Angiotensin II is a potent vasoconstrictor acting both directly on resistance vessels and stimulating an increase in

sympathetic activity by an action at all parts of the sympathetic nervous system. Angiotensin II also stimulates aldosterone secretion which increases sodium retention and hence the extracellular fluid volume and the circulating blood volume. An increase in circulating blood volume increases venous return and hence CO.

3. Intrinsic mechanisms Both myocardial function and vascular smooth muscle tone are partly controlled by intrinsic mechanisms independent of the neuro–endocrine system. For instance, an increase in ventricular volume increases the force of contraction of the myocardium. Similarly, a rise in the intra-luminal volume of arterioles stimulates the smooth muscle in their walls to contract and hence raises the peripheral resistance. Such mechanisms are of importance in the maintenance of BP.

In only a small minority of hypertensive patients (circa 5%) is there an identifiable cause for the raised blood pressure, e.g. acute glomerulonephritis with salt retention, toxaemia of pregnancy, a catecholamine-secreting tumour (phaechromocytoma), an aldosterone secreting tumour (Conn's syndrome), Cushing's syndrome, unilateral renal ischaemia or coarctation of the aorta. In the rest, the raised BP is the only detectable abnormality other than those secondary to sustained hypertension. About one third have an abnormality of plasma renin activity or plasma noradrenaline concentration but it is not established whether these abnormalities are of importance in determining the cause or causes of raised blood pressure.

Drug therapy

The hypotensive agents used in current clinical practice will be considered in this text under the headings diuretics, beta adrenoceptor blocking drugs (beta-blockers), drugs that impair sympathetic nerve function acting either centrally or peripherally and peripheral vasodilators.

DIURETICS

Diuretics (*see* Chapter 21) have an essential role in the treatment of hypertension both as hypotensive agents and in the prevention of salt and water retention caused by most other hypotensive agents.

Thiazides are the most effective hypotensive diuretics causing 5–30% fall in mean arterial BP. The hypotensive effect of these drugs occurs at doses that cause a naturesis and initially, hypotension is associated with a fall in circulating blood volume and cardiac output. During chronic administration however, the blood volume returns towards normal values. Despite this, there is continuing hypotension with a reduction in peripheral resistance. Thiazides cause relaxation of resistance vessels which contributes to the fall in peripheral resistance and blood pressure, but this is seldom sufficient to cause an increase in sympathetic tone and hence heart rate.

Hypotensive doses usually cause a mild hypokalaemic alkalosis, but potassium replacement is required in less than one third of patients with uncompli-

cated hypertension. Hyperuricaemia and hyperglycaemia are other adverse effects (*see* Chapter 21) but are seldom sufficiently serious to stop therapy. The long term consequences of these biochemical changes on the morbidity and mortality of hypertensive patients on chronic thiazide therapy have not been evaluated.

Most potent diuretics such as frusemide, bumetanide and ethacrynic acid are less effective hypotensive agents than thiazides at equi-effective diuretic doses.

Use in hypertension Thiazides are drugs of first choice in hypertension. The maximally effective diuretic dose is similar to the maximally effective hypotensive dose and any increase over this has little effect on BP but increases the incidence of side effects. There are quite wide variations in response to thiazides, but the factors determining responsiveness have not been established although it is generally held that these drugs are most likely to be effective in hypertension associated with sodium retention and an increase in plasma volume. Such patients often have a low plasma renin activity. During the first few weeks of therapy plasma urea and electrolytes and uric acid should be monitored and potassium therapy initiated if hypokalaemia occurs.

The aldosterone antagonist spironolactone is an effective hypotensive agent when hypertension is associated with a raised aldosterone concentration. It is more effective in patients with a low than in those with a high plasma renin activity, although it is probably no more effective than a thiazide in this situation. Amiloride and triamterine are as effective as spironolactone and all three drugs enhance the effectiveness of other hypotensive agents.

BETA-ADRENOCEPTOR ANTAGONISTS (BETA-BLOCKERS)

All beta-blockers lower the BP in hypertensive subjects and in the UK propranolol and oxprenolol are amongst the most widely used hypotensive agents. They cause a fall in systolic and diastolic BP in both the lying and standing positions. After a single acute dose the fall in BP is associated with a fall in cardiac output (due to the negative inotropic and chronotropic effects), no change or a slight rise in peripheral resistance and no consistent change in plasma volume. The full hypotensive effect of any dose takes some days to develop and is associated with a slow fall in the peripheral resistance.

The mechanisms whereby beta-blockers lower BP are not established, but there are at least three sites of action that alone or, more likely, in combination are responsible for the hypotensive effect:

1. The negative inotropic and chronotropic effect of blockade of cardiac beta receptors.

2. Beta receptor agonists (e.g. isoprenaline) stimulate the release of plasma renin causing a rise in plasma renin activity (PRA) and beta-blockers therefore cause a fall in PRA. This occurs in both normotensive and hypertensive subjects. In general, hypertensive patients with high PRA activity respond to the hypotensive effect of these drugs better than subjects with intermediate or

low PRA. The importance of this effect remains in doubt, however, as the effect on PRA correlates poorly with the hypotensive effect and beta-blockers lower the BP in patients with low and intermediate PRA and do not cause a substantial fall in plasma volume at hypotensive doses. It is probably the principle mechanism operative in lowering the BP when used in low doses (e.g. 160 mg/24 hours of propranolol) in patients with high renin values.

3. Propranolol and other beta-blockers lower the BP in experimental animals when injected into the brain and CSF. It is possible therefore that part of the hypotensive effect of the beta-blockers, that readily gain access to the brain, e.g. propranolol and pindolol, is mediated through blockade of central beta receptors acting to decrease impulse traffic in sympathetic efferent neurones. The contribution of this central effect to the hypotensive actions of beta-blockers that do not readily cross the blood brain barrier, e.g. practolol and sotolol, is uncertain.

CLINICAL USE Beta-blockers are drugs of first choice in all stages of hypertension and in mild forms are often effective alone. They are seldom effective alone in hypertensive emergencies. In subjects with normal cardiac function without airways obstruction, adverse effects are few as they seldom affect sexual function or cause postural hypotension. They are contraindicated in subjects with airways obstruction and in those with impaired left ventricular function not on digoxin (for adverse effects *see* Chapter 11). In phaeochromocytoma they should be administered with an alpha-blocking agent as, used alone, they may precipitate acute hypertensive episodes, presumably due to unopposed alpha-receptor mediated adrenergic vasoconstriction.

DRUGS THAT IMPAIR THE FUNCTION OF THE SYMPATHETIC NERVOUS SYSTEM

1. Centrally Acting Drugs

Drugs of this group affect both central and peripheral components of the sympathetic nervous system but it is thought that the central affects are the more important of the two. They rarely cause postural hypotension but central side-effects, e.g. drowsiness, depression of mood, excessive dreaming, etc., are common. By contrast, postural hypotension is an invariable and often dose-limiting effect of peripherally acting anti-sympathetic drugs which do not cause central effects.

Alpha-methyldopa Alpha-methyldopa is the alpha-methylated analogue of the endogenous metabolite L-dopa, the precursor of dopamine and noradrenaline.

ACTION Methyldopa is an effective hypotensive agent in most cases of hypertension and given parenterally may cause a rapid fall in BP in hypertensive emergencies. It causes a fall in supine and erect BPs, orthostatic hypotension being infrequent. There is usually no change in CO, but a fall in peripheral resistance, blood flow to the brain and kidneys being little affected at usual therapeutic doses.

MODE OF ACTION Methyldopa reduces sympathetic nervous tone and, as it causes no reduction in response to stimulation of pre- or post-ganglionic fibres, its principal site of action is assumed to be central. The absence of pronounced postural hypotensive effect also supports this view as does its sedative effect. Methyldopa replaces L-dopa in noradrenergic and dopaminergic neurones and is decarboxylated to alpha-methyldopamine and hydroxylated to alpha-methyl noradrenaline (Fig. 1). As alpha-methylnoradrenaline is not metabolised by

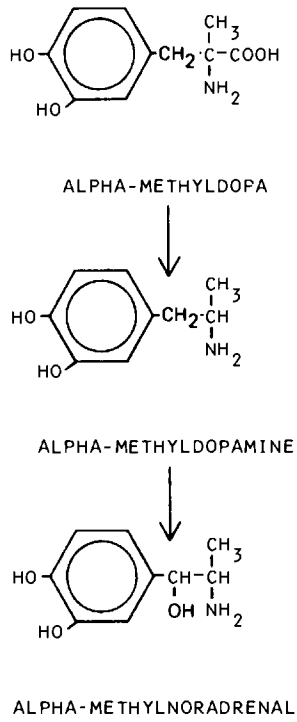


FIG. 1 Mode of action of alpha methyldopa.

intraneuronal monoamine oxidases, it accumulates in sympathetic nerve terminals displacing NA. It also depletes central neurones of dopamine and 5-HT. Alpha methyl noradrenaline is a partial agonist for alpha adrenoceptors. It is a less potent vasoconstrictor than noradrenaline and this peripheral effect may contribute to the fall in peripheral resistance it produces in hypertensive patients. The means whereby it reduces preganglionic sympathetic tone is not fully established but current evidence suggests that it does so by interacting with presynaptic alpha receptors in the medulla (*see* clonidine, p. 314).

DRUG FATE Methyldopa is active orally, but is only partially absorbed from the bowel, approximately 50% (range 15–75%) of an oral dose remaining in the

faeces. Most of the drug is excreted unchanged in the urine. Only a very small percentage of the total dose is excreted as alpha-methyldopamine and none as alpha-methylnoradrenaline. The half-life of the unchanged drug after i.v. administration is 2 hours.

ADVERSE EFFECTS

Resistance A proportion of patients do not respond to high doses (2–4 g/24 hours) of methyldopa, although they may absorb the same proportion of a dose and metabolise the drug in the same way as responders. Resistance is sometimes, but not always, due to fluid retention, which occurs in the majority of cases treated with this drug alone and can be corrected by a diuretic.

Central effects are common and include drowsiness and weakness especially with high doses and a small proportion develop a depressive illness, although this is not as frequent as with reserpine. Nasal stuffiness is common and failure of ejaculation, impotence and postural hypotension occur, but are less frequent than with the guanidinium hypotensive agents.

Others include a positive Coombs test which occurs in 10–30% of patients on chronic therapy with methyldopa, but a haemolytic anaemia develops in only 1 in 2–300 treated patients. Rare adverse effects include jaundice with features of hepatocellular damage and cholestasis which is usually reversible on stopping the drug, rashes, parkinsonism, fever, diarrhoea and blood dyscrasias.

CLINICAL USE Methyldopa is one of the most widely used hypotensive agents. The usual starting dose is 500 mg/day and this may be given as a single daily dose or in divided doses. The dose is increased 1–2 weekly until the desired effect is achieved, the usual upper limit being 2 g/day depending on the occurrence of adverse effects. A diuretic often enhances the response and prevents fluid retention. In hypertensive emergencies, methyldopa 0·5–1·0 g i.v. is effective in 4–8 hours, but quite a high proportion of patients do not respond.

Reserpine Reserpine is an effective hypotensive agent in most mild and moderate cases of hypertension and parenterally is of value in hypertensive emergencies. Both systolic and diastolic pressure are reduced and usually the supine BP falls as much as the erect value. Hypotension is associated with a fall in peripheral resistance, there being little change in CO.

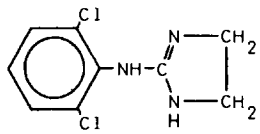
The hypotensive effect of reserpine is related to its ability to deplete central and peripheral neurones of noradrenaline (*see* Chapter 14) and so decrease sympathetic tone by a central and to a lesser extent a peripheral mechanism.

CLINICAL USE Reserpine causes a number of side effects, drowsiness, nasal stuffiness, bradycardia, an increase in gastric acid production and in high doses extrapyramidal syndromes (*see* Chapter 16).

Depression Reserpine causes depression in an appreciable proportion of hyper-

tensive patients and hence increases the liability of such patients to commit suicide. This serious adverse effect is the reason why it is used very infrequently in the UK although it is still very widely used in the USA. It remains a useful agent in the treatment of hypertensive emergencies when 0·25–4·0 mg i.m. causes a drop in BP within 2–4 hours which may last for 12 hours.

Clonidine



Clonidine is an imadazoline derivative and an effective hypotensive agent in all degrees of hypertension. Its mode of action and clinical pharmacology are similar to those of methyldopa. It lowers both lying and standing BP and this is associated with bradycardia and a fall in cardiac output but little change in peripheral resistance.

Clonidine is structurally similar to the alpha agonists tolazoline and phentolamine and is a partial alpha agonist. It probably lowers BP by activation of presynaptic alpha receptors in the vasomotor centre which results in a fall in sympathetic preganglionic tone. It may also have a peripheral effect as, at low impulse frequencies, it impairs noradrenaline release by post ganglionic sympathetic neurones.

DRUG FATE Clonidine is active orally and parenterally and achieves a concentration in the brain, liver and kidney many times that in the plasma. It is mostly excreted unchanged in the urine and partly as a hydroxylated metabolite. The apparent volume of distribution is 1·8–3·2 l/kg and the $t_{\frac{1}{2}}$ for the slow beta phase of its elimination curve is 7–9 hours and may increase in renal failure.

ADVERSE EFFECTS Dryness of the mouth, nasal stuffiness, constipation, drowsiness and depression are common side-effects, as is fluid retention which may be prevented by a diuretic. Postural hypotension occurs rarely as clonidine does not block high frequency sympathetic impulses such as occur when sympathetic tone is high, e.g. in the erect posture.

Withdrawal hypertension There is often an acute rise in the BP on withdrawal of clonidine associated with a rise in urinary catecholamines and this may be sufficiently severe to cause an intracranial haemorrhage. It responds to therapy with alpha and beta receptor blocking agents. As hypertensive patients often stop their drugs spontaneously this is a potentially serious side-effect.

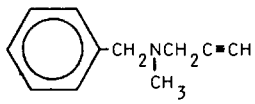
Drug interactions The hypotensive effect of clonidine is enhanced by other hypotensive agents and is antagonised by tricyclic antidepressants and phenothiazines.

CLINICAL USE Clonidine has no major advantages over such drugs as methyldopa, beta-blockers and the guanidinium hypotensive agents and the high

incidence of side-effects and the potentially dangerous withdrawal hypertension are responsible for its infrequent use. Its use in the prophylaxis of migraine is dealt with in Chapter 41.

Monoamine oxidase inhibitors (MAOIs) Postural hypotension is a common side effect of monoamine oxidase inhibitors and one agent, pargyline, is marketed solely for its hypotensive effect.

Pargyline

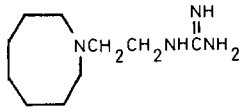


Pargyline is effective in all degrees of hypertension, lowering the erect more than the supine BP. There are no consistent haemodynamic changes as both a fall in cardiac output and exercise induced tachycardia and a fall in peripheral resistance have been reported. Furthermore, the means whereby MAOIs cause hypotension is uncertain as several mechanisms have been postulated, the accumulation of false transmitters, e.g. octopamine and dopamine at sympathetic nerve terminals, the impairment of noradrenaline release from these terminals and ganglion blockade due to accumulation of NA at autonomic ganglia.

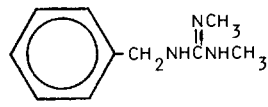
CLINICAL USE Parglyine is used infrequently in the treatment of hypertension, largely on account of the wide range of side-effects and interactions with food constituents and drugs that may occur with this drug, as with other MAOIs (*see* Chapter 15). Common side-effects are dry mouth, impotence or failure of ejaculation, fluid retention, an increase in appetite and non-fluid weight gain, gastrointestinal symptoms, insomnia, hypomania and psychotic episodes characterised by hallucinations and paranoid symptoms. It is most useful in the treatment of depressed hypertensive patients.

2. Peripherally Acting Drugs

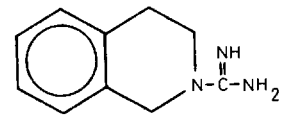
The guanidinium hypotensive agents There are three commonly used hypotensive agents that contain a guanidinium group, guanethidine, bethanidine and debrisoquine, of which guanethidine is the oldest and most widely used. These drugs act in a similar way but there are important differences in their pharmacokinetic properties.



GUANETHIDINE



BETHANIDINE



DEBRISOQUINE

ACTION These agents lower BP in all grades of hypertension. Given i.v. they cause a short lived increase in BP associated with release of noradrenaline from

sympathetic nerve terminals and are thus not appropriate for treatment in hypertensive emergencies. This is followed by hypotension. After oral administration, only hypotension is evident. Both systolic and diastolic BP are lowered, the standing BP being affected to a greater extent than the lying BP, this postural hypotensive effect being enhanced by exercise. Hypotension is associated with a fall in peripheral resistance and occasionally with a fall in CO as well. There is commonly a fall in glomerular filtration rate, especially in the upright position.

MODE OF ACTION Guanidinium hypotensive agents are actively transported into sympathetic nerve terminals by uptake 1 (*see* Chapter 11) and compete with noradrenaline for carrier sites. They are concentrated in the storage granuoles in sympathetic nerve terminals where they achieve a concentration many hundreds of times greater than that in the plasma. They produce hypotension by causing post-ganglionic sympathetic blockade at both high and low impulse frequencies, as they prevent noradrenaline release from sympathetic nerve terminals. They are all strong bases with pKs greater than 11. Consequently, they are highly ionised at physiological pH and do not reach the CNS in effective concentrations.

Guanethidine, but not the other two agents, depletes noradrenaline stores in sympathetic nerve terminals. This is due to the fact that bethanidine and debrisoquine, but not guanethidine, inhibit MAO in the concentrations they achieve in sympathetic nerve terminals and hence, although there is some depletion in storage granuoles, noradrenaline accumulates in the cytoplasm. There is no close relationship in time between the onset of hypotention and noradrenaline depletion with guanethidine, indicating that this action is not responsible for the hypotensive effect.

DRUG FATE The absorption of all three drugs from the gastrointestinal tract is variable 30–90% of a dose being absorbed. Both guanethidine and debrisoquine are extensively metabolised during their first passage through the liver to inactive metabolites. Approximately 10% of the population are not able to metabolise debrisoquine and hence are much more susceptible to its hypotensive effects than are those who can metabolise the drug. Similar data on guanethidine are not available. By contrast, bethanidine is excreted exclusively as unchanged drug in the urine. The $t_{\frac{1}{2}}$ of bethanidine and debrisoquine (4–6 h), is considerably shorter than that of guanethidine.

ADVERSE EFFECTS Dry mouth, nasal stuffiness, impotence and failure of ejaculation and diarrhoea are all quite common with these agents. Fluid retention is sufficiently common to justify coadministration of thiazide diuretic in most instances.

Postural hypotension Hypotension on standing is associated with dizziness, weakness and occasionally with fainting. It occurs most commonly first thing in the morning and after exercise, when vasodilatation in skeletal muscles enhances the hypotensive effect of the drug. Postural hypotension is often the

dose-limiting effect of these drugs, but it may occur at doses that do not adequately control the BP throughout 24 hours.

Muscle weakness Occurs occasionally, especially with guanethidine. It is associated with no impairment of reflexes but may be due to the weak neuromuscular blocking activity of these drugs.

In phaeochromocytoma these drugs are contraindicated as they may cause acute hypertensive episodes since they increase responsiveness to circulating catecholamines.

DRUG INTERACTIONS *Tricyclic antidepressants* and *phenothiazines* antagonise the hypotensive effect of the guanidinium hypotensive agents as they inhibit uptake 1, the active transport mechanism whereby these drugs reach their site of action in sympathetic nerve terminals.

Adrenergic agents Both direct acting adrenergic alpha-agonists such as phenylephrine and agents causing release of endogenous amines from sympathetic nerve terminals, e.g. amphetamine and ephedrine, can antagonise the hypotensive effects of guanidinium hypotensive agents. Occasionally, acute hypertensive episodes have been caused by noradrenaline-releasing compounds in food (e.g. tyramine) or by noradrenaline-releasing drugs given to patients on bethanidine or debrisoquine. This may have been due to the monoamineoxidase inhibitory activity of these drugs.

CLINICAL USE The guanidinium hypotensive agents are seldom used in mild or moderate degrees of hypertension, but are commonly used in more severe forms, usually in conjunction with a diuretic. The dose is increased until the desired effect is achieved or until postural hypotension occurs. Bethanidine has a shorter duration of action than the other two drugs and is usually administered three times a day, whereas with debrisoquine and guanethidine the dose interval may be 12–24 hours. The effect of these drugs should be monitored carefully in subjects with impaired renal function as it is probable that bethanidine at least accumulates under these circumstances.

Ganglion blocking agents (*see* Chapter 10) Ganglion blocking agents, e.g. hexamethonium, were the first effective hypotensive agents. They act by competitive antagonism of ACh at the post-synaptic cholinergic receptor sites of autonomic ganglia. They thus block post-ganglionic sympathetic activity and the fall in BP they produce is associated with a fall in CO, due to a reduction in venous tone and venous return, and a fall in peripheral resistance. Their hypotensive effect is maximal when subjects are erect.

Adverse effects to these drugs are invariable and are principally due to blockade of post-ganglionic parasympathetic neurones. They include tachycardia, mydriasis and blurring of vision, dry mouth, constipation and occasionally paralytic ileus, hesitancy of micturition and urinary retention, impotence and failure of ejaculation.

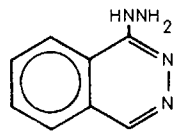
Hexamethonium, pempidine, mecamylamine and pentonilium were com-

monly used in the 1950s, but with the introduction of effective alternative agents, the postural hypotension and other side effects have rendered these drugs obsolete in the maintenance therapy of hypertension.

Hypertensive emergencies Trimethaphan is occasionally used to lower the BP rapidly as this ganglion blocking agent also has a direct vasodilator effect on resistance vessels. Its duration of action is of a few minutes only when administered i.v. and it is best given by a constant infusion pump, small changes in flow rate causing major changes in BP. The head of the bed is elevated to facilitate the postural hypotensive effect and close supervision is necessary to avoid severe hypotension. Constipation and urinary retention are the most troublesome side effects, and rarely paralytic ileus.

Vasodilators

Hydrallazine



Hydrallazine is an effective hypotensive agent for both maintenance therapy and in the management of hypertensive emergencies. It lowers both lying and standing BP and quite commonly causes postural hypotension. It causes vasodilatation of resistance vessels by a direct action on vascular smooth muscle. Hypotension is associated with a fall in peripheral resistance and tachycardia due to an increase in sympathetic tone.

DRUG FATE Hydrallazine is absorbed from the bowel and is rapidly removed from the plasma principally by hepatic metabolism, only a small proportion being excreted unchanged in the urine. It is 55% protein bound in the plasma and undergoes acetylation by the liver enzyme N-acetyltransferase. Like isoniazid (*see* Chapter 35), the rate of hepatic acetylation is determined by a single genetic factor that displays polymorphism, the population being divided into slow and fast acetylators. After chronic administration of a given dose the steady-state plasma concentration of hydrallazine is 2–3 times higher in the slow than in the fast acetylators. It also undergoes hydroxylation and conjugation before being excreted. The plasma half-life is 2–4 hours and does not increase in renal failure. The apparent volume of distribution is 0·5 l/kg.

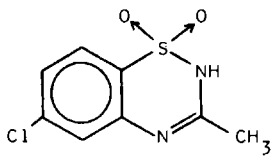
ADVERSE EFFECTS Headaches, flushing, nasal stuffiness and gastrointestinal symptoms are all quite common.

Tachycardia is mediated by increased beta adrenergic activity and may cause palpitations and cardiac tachydysrhythmias. In subjects with coronary artery disease, hydrallazine given alone may precipitate an attack of myocardial ischaemia or infarction.

Systemic lupus erythematosus (SLE) An SLE-like syndrome may occur in patients on long term hydrallazine therapy and is more common in slow than in fast acetylators. It rarely occurs if the daily dose is 200 mg or less.

CLINICAL USE Hydrallazine is used in mild and moderate cases of hypertension. As beta-blockers prevent the tachycardia and associated symptoms, hydrallazine is seldom used except in combination with a beta-blocker.

Diazoxide



Diazoxide is a thiazide derivative with no diuretic or carbonic anhydrase inhibitory effect. It is an effective hypotensive agent, especially when given i.v. Like hydrallazine, it causes vasodilation of resistance vessels, a fall in peripheral resistance by a direct action on vascular smooth muscle, a reflex tachycardia and an increase in CO. Administered in large oral doses (300–1000 mg/day) to hypertensive patients with renal failure, hypotension is usually associated with an improvement in renal function.

DRUG FATE Diazoxide is absorbed from the bowel but is less active orally than after i.v. injection. In the plasma, 90% and more of the drug is bound to plasma albumin. In both children and adults over 50% of an i.v. dose is excreted unchanged in the urine, but there is little information on its metabolism. The renal clearance rate is similar to that of creatinine. The drug is highly bound to tissues and has a volume of distribution 1·50 l/kg. The half-life in the plasma in patients with normal renal function is 9–24 hours and is increased in patients with renal failure.

ADVERSE EFFECTS Nausea and vomiting occur in approximately 50% of patients and tachycardia and lacrimation are also common. Severe hypotension, which is occasionally fatal, may occur if high doses (5 mg/kg or greater) are given as a rapid bolus i.v. (10–30 seconds), especially to patients already on beta-blockers or sympathetic nerve blocking drugs. It is usually advisable to give multiple small doses (e.g. 2·5 mg/kg) rather than an initial large dose. Angina may be precipitated in patients with myocardial ischaemia because of the reflex increase in sympathetic tone and this can be prevented by prior administration of a beta-blocker. Despite its close chemical similarity to the thiazides, diazoxide may cause salt and water retention independent of endogenous mineralocorticoid activity. It impairs insulin secretion and after i.v. administration a transient hyperglycaemia is usual, which may be prevented by prior administration of tolbutamide. After chronic administration of large oral doses, parkinsonism develops in an appreciable number of patients and some develop an acute pancreatitis.

CLINICAL USE

Hypertensive emergencies Diazoxide is a useful drug in the management of hypertensive emergencies as it lowers the BP rapidly (2–3 minutes) and has a long duration of action. The degree of hypotension it causes is related to the rate at which it is administered as well as the size of the dose, presumably as rapid plasma protein binding prevents much of the drug from reaching its site of action. It is usually given rapidly 2–4 mg/kg i.v. over 10 seconds. It is less effective than alpha-blockers in hypertensive crisis due to phaeochromocytoma and it should not be used as a drug of choice in patients with angina, except in those already receiving a beta-blocker or a sympathetic nerve blocking agent.

Maintenance therapy Use of diazoxide in maintenance therapy is not generally accepted, but in high oral doses (0·5–1·0 g/day) it is an effective hypotensive agent, especially in patients with renal failure in whom it does not cause a fall in glomerularfiltration rate. Hyperglycaemia and extrapyramidal symptoms are quite common under these circumstances.

Insulin secreting tumours Diazoxide impairs insulin release from the beta cells of the islets of Langerhans in the pancreas in the same way as alpha adrenoceptor agonists. This effect is used to advantage in the prevention of hypoglycaemic episodes in patients with insulin-secreting tumours that are not amenable to surgery.

Other vasodilators

Prazocin This drug has a direct vasodilator effect and some alpha-blocking effect. It lowers both lying and standing BP without increasing venous return, heart rate or cardiac output. The reason why it does not cause a reflex tachycardia like other alpha-blocking drugs (*see* Chapter 11) is that it does not block presynaptic alpha-receptors. Prazocin is orally active, has a short $t_{\frac{1}{2}}$ (4 h) and is cleared from the plasma mostly by metabolism only 10% of an oral dose being excreted unchanged in the urine.

The only serious adverse effect yet reported is severe hypotension lasting 30–90 minutes after the first dose of 2 mg or more which occurs in approximately 1% of patients. It is therefore wise to start patients on a smaller initial dose, increasing the dose according to response.

Sodium nitroprusside This drug is a vasodilator like the nitrites which relaxes both resistance and capacitance vessels (*see* Chapter 24). It is very short acting and is given by i.v. infusion pump in dose 0·5–10 μg/kg/min usually for only short periods (24–48 h) during hypertensive crises while oral therapy with other hypotensive drugs takes effect. It is usually effective when other drugs have failed and is particularly so when hypertension is complicated by acute pulmonary oedema, as it reduces venous return. Too rapid or too prolonged an infusion may cause the drug's major metabolites cyanide and thiocyanate to accumulate. Cyanide inhibits tissue cytochrome oxidase and hence there is a shift from aerobic to anaerobic oxidation with the development of a metabolic

acidosis. This may be prevented by concomitant hydroxycobalamine administration, as this binds cyanide to form cyanocobalamin.

Drug Combinations in the Treatment of Hypertension

The failure to identify a single pathophysiological mechanism in the great majority of hypertensive patients has meant that the choice of hypotensive agent and the establishment of an effective dose is entirely empirical. No single drug is either effective in all cases or free of adverse effects. Many agents are in use and in the majority of patients, two or more drugs are used at any one time. The justification for using more than one drug is that hypotensive agents usually have additive effects on the BP but slightly different side-effects so that by using small doses of a number of drugs the severity of some side-effects is reduced.

A thiazide diuretic or a beta-blocker may be effective alone in many cases of mild hypertension but if either of these are ineffective in high doses, a second hypotensive agent is usually added. Many drug combinations have proved effective in controlling BP, but no one combination has been shown to be superior to all others and most physicians become familiar with a small number of drug combinations. As fluid retention is an adverse effect of many hypotensive agents, most drug combinations include a thiazide diuretic. Failure to comply with the physicians instructions is probably the commonest cause of the failure of hypotensive therapy and the simpler the regime the more likely it is to prove acceptable to patients.

Preparations

Drug	*Dose (mg)*	*Dose interval (h)*	*Route*
Methyldopa	250–1000	6–24	Oral
	500–1000 in 2 mins	6	i.v.
Guanethidine	25–250	24	Oral
Debrisoquine	20–240	8–12	Oral
Bethanidine	10–75	8–12	Oral
Hydrallazine	25–400	8–12	Oral
	10–50 in 2 mins		i.m. or i.v.
Diazoxide	2–4 mg/kg in 10 secs		i.v.
Reserpine	0·25–4	24	Oral
	0·25–4		i.m. or i.v.
Clonidine	0·150–2·5	8–24	Oral
Pargyline	10–150	24	Oral
Trimetaphan	1–15 mg/min		i.v.

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Chapter 24

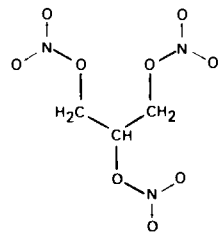
Drugs in the Treatment and Prophylaxis of Arterial Disease

Arterial disease is the single most common cause of death in the west, contributing to a quarter of all deaths in the UK. Coronary artery disease, cerebrovascular disease and peripheral arterial disease are its commonest clinical manifestations, while the major risk factors associated with its development, especially in coronary artery disease, have been identified as smoking, high blood pressure, excessive weight or intake of polyunsaturated fatty acids, lack of exercise etc.

Hypotensive agents lower the risk of the development of cerebrovascular disease in hypertensive subjects (*see* Chapter 23). Hypolipidaemic agents reduce the rate at which arterial disease develops in patients with hyperlipoproteinaemia Anticoagulants, beta-blockers and the anti-platelet agent sulphinpyrazone reduce the morbidity and mortality in a small proportion of patients who have had a myocardial infarct. Otherwise drugs are used most widely in the symptomatic treatment of angina pectoris. In this chapter the drugs used to treat angina and hyperlipoproteinaemia will be considered.

DRUGS IN THE TREATMENT OF ANGINA

Glyceryltrinitrate (GTN)



Organic nitrites and nitrates have been used in the symptomatic treatment of angina since their introduction by Brunton in 1867 and they are still the cornerstone of therapy. While there are a number of nitrites and nitrates available, GTN is by far the most commonly used and as there is no evidence that alternate preparations have advantages over it, the clinical pharmacology of this drug only will be discussed.

PATHOPHYSIOLOGY OF ANGINA The left ventricle is entirely dependent of blood flow via the coronary arteries for its oxygen supply as it is incapable of storing oxygen or of anaerobic metabolism. In angina, chest pain which is usually

related to exertion, is due to myocardial ischaemia, there being ST wave depression on the ECG over the ischaemic area and an increase in the lactic acid concentration of venous blood draining the left ventricle. The pathophysiological change therefore is that the oxygen supply to the left ventricle is inadequate for normal function. The deficit is usually due to atheromatous narrowing of one of more branches of the coronary arteries. These are then incapable of dilating in response to hypoxia, which is the most potent of the local factors regulating myocardial blood flow.

ACTION GTN relieves angina within 1–2 minutes of administration and if taken before exertion, increases exercise tolerance by preventing angina due to lesser degrees of exertion.

GTN is a direct acting vasodilator, affecting both resistance and capacitance vessels and hence contrasts with the vasodilators such as hydrallazine and diazoxide used in hypertension (Chapter 23) which affect principally resistance vessels. The mechanism whereby GTN causes relaxation of vascular smooth muscle is unknown.

The haemodynamic changes associated with the relief of angina by GTN are as follows:

1. Vasodilation of capacitance vessels causes a fall in venous return and in consequence a fall in cardiac output, stroke volume and left ventricular volume. By La Place's law a fall in left ventricular volume is associated with a fall in tension in the myocardial wall and this causes a fall in myocardial oxygen demand.

2. Vasodilation of resistance vessels causes a fall in peripheral resistance and BP, the latter affecting the standing more than the lying BP and a reflex tachycardia. These changes cause a fall in left ventricular work load and a corresponding reduction in oxygen demand.

The net effect of these changes is to increase the amount of oxygen available to the myocardium by lowering myocardial oxygen demand while maintaining an adequate supply.

GTN causes coronary artery vasodilation in normal subjects, but not in most patients with myocardial ischaemia who have atherosclerotic coronary arteries and in some such patients it may cause a fall in coronary blood flow. The fact that vasodilation is not the principal mechanism by which GTN relieves angina is illustrated by the fact that dipyridamol, a more effective coronary dilator than GTN, does not relieve angina or decrease myocardial oxygen demand.

DRUG FATE GTN is rapidly absorbed from the buccal mucosa and the effect on the circulation is evident within 1–2 minutes after sublingual administration. It is rapidly absorbed from the bowel if swallowed, but as nearly all the drug is metabolised during one passage through the liver, effective blood levels are not achieved when conventional doses are swallowed.

GTN is very rapidly metabolised to glyceryldinitrate and glycerylmononitrate

by the hepatic enzyme glutathione organic nitrate reductase. The di- and mononitrate metabolites have much less vasodilator activity than GTN and are excreted in the urine. Even after buccal administration GTN is cleared from the plasma within 5 minutes, the metabolites being excreted more slowly.

ADVERSE EFFECTS

Headache A throbbing headache usually occurs with the onset of the therapeutic effect of GTN due to vasodilation of intracranial vessels. It is worse when therapy is initiated and soon wears off with repeated doses.

Postural hypotension This is an inevitable consequence of the circulatory effects of GTN and may cause dizziness and fainting, especially in younger patients.

Methaemaglobinaemia GTN is a relatively strong oxidising agent and may oxidise oxyhaemaglobin to methaemaglobin. Patients with glucose-6-phosphate deficiency and neonates are particularly susceptible to this effect as the reducing capacity of the RBCs is low and haemolysis may occur if the methaemaglobin in sufficiently severe.

Tolerance Tolerance develops to the circulatory effects of GTN reducing the therapeutic effect of a given dose and the headache that may accompany it. This develops over a number of days if the drug is used in regular doses and there is cross tolerance to the effects of other nitrites and nitrates.

CLINICAL USE GTN tablets are the cornerstone of symptomatic therapy of angina. They (0·3 mg tabs) are taken sublingually and sucked, not swallowed, when angina develops and are usually effective at relieving pain within 1–2 minutes, the effect lasting 20–30 minutes. Taken before exercise they may prevent angina, reduce its intensity and increase exercise tolerance. Its short duration of action and the fact that tolerance develops quite rapidly after regular usage makes GTN ineffective when taken prophylactically at regular intervals throughout the day. There is no limit to the number of tablets taken per day, some patients requiring more than 30 per day. There is no evidence that these agents increase life expectancy of patients with angina.

Other Nitrites and Nitrates

Amylnitrite is a volatile solution taken by breaking a glass vial containing the liquid and inhaling the vapour. Like GTN, it is rapidly active and of short duration of action, but is now seldom used as it is less convenient than GTN.

Long acting nitrates Pentaerythrityl tetranitrate, erythrityl tetranitrate and isosorbide dinitrate are examples of nitrates with a longer duration of action than GTN. Single dose studies have shown that they are active when swallowed and they are marketed as prophylactic antianginal agents, effective when taken regularly (4–6 h) through the day. However, there is no convincing clinical trial evidence to attest to these claims.

Sodium nitroprusside $Na_2Fe(CN)_5NO–2H_2O$ This nitro containing compound

is not currently used for the relief of angina but is used occasionally as a hypotensive agent. It is a potent vasodilator with similar effects to GTN and other nitrates and nitrites (*see* Chapter 23).

Preparations

Drug	*Dose*	*Dose interval*
Glyceryltrinitrate	0·3 mg (sublingually)	When required

Beta-Blocking Agents

The clinical pharmacology of beta-blocking drugs is dealt with in Chapter 11 and only those aspects relevant to their use in angina will be dealt with in this chapter.

ANTI-ANGINAL ACTION Beta-blocking drugs taken prophylactically in doses sufficient to maintain a drug plasma concentration that causes beta-adrenergic receptor blockade reduce the frequency of anginal attacks in the majority of patients with myocardial ischaemia. In a small proportion of those not benefiting, beta-blockers may exacerbate angina. Severe angina presenting at rest and not relieved by GTN may be relieved within hours by beta-blockers. A number of clinical trials have shown that beta-blockers taken prophylactically after a myocardial infarct reduce mortality and the incidence of sudden death in a small proportion of patients.

MECHANISM OF ACTION The beneficial effect of these drugs in angina is due to beta receptor blockade. The haemodynamic effects associated with relief of angina are a fall in BP, a fall in cardiac output and a decrease in the rate of contraction of the myocardium and hence a fall in left ventricular work and in oxygen demand. Beta-blockers usually cause a fall in coronary artery blood flow, but the net effect is to cause an increase in the oxygen available to the myocardium by causing a greater reduction in oxygen used by the myocardium than in oxygen supplied to it.

The negative inotropic effect of beta-blockers may cause an increase in left ventricular end diastolic pressure and left ventricular dilatation with a consequent increase in left ventricular wall tension. This effect and the prolongation of the systolic ejection period, increase myocardial oxygen demand and may predominate in those patients whose angina is exacerbated by beta-blockers.

CLINICAL USE Beta-blockers, of which propranolol is the best established in the treatment of angina, are usually only prescribed when symptoms are not adequately controlled by GTN. In such patients there is a decrease in the frequency of attacks of chest pain and in the number of GTN consumed in 50–80% of patients.

Left ventricular failure is the commonest side-effect of beta-blockers in patients with myocardial ischaemia, occurring in approximately 10% of cases. This can be avoided by excluding patients with symptoms and signs of left

ventricular failure or by digitalising them prior to administering a beta-blocker. There is no evidence that these drugs precipitate myocardial infarction. Sudden withdrawal of beta-blockers from patients who respond well to their anti-anginal effect may precipitate an acute ischaemic episode within two weeks, which may on occasions be fatal. If these drugs have to be withdrawn in such patients, they should be withdrawn slowly. In patients with obstructive airways disease, a relatively selective beta-blocker (atenolol or metoprolol) should be used if GTN is ineffective alone and airways resistance carefully monitored during therapy.

Alternatives to beta-blockers

In patients unsuited to beta-blockers, there are three newer drugs that may be of use.

Verapamil (*see* Chapter 22). This drug decreases myocardial contractility and myocardial oxygen requirement and is an effective antianginal agent taken orally in doses up to 120 mg 8 hourly. It does not effect airways resistance but may precipitate left ventricular failure and hypotension.

Nifedipine Like verapamil, this drug is a calcium antagonist impairing its influx across the myocardial membrane during an action potential. It causes vasodilatation of compliant coronary vessels, increasing coronary blood-flow and decreasing myocardial oxygen usage. It may also increase cardiac output and heart rate, although in some patients it has a negative inotropic effect and may precipitate heart failure.

Adverse effects include flushing, gastrointestinal symptoms, headache and tremor. A small proportion of patients experience a precordial chest pain indistinguishable from angina, 30–60 mins after taking nifedipine.

Prenylamine The obvious advantages of prenylamine over other prophylactic antianginal agents are that it has no negative inotropic or vasoconstrictor effects. It dilates compliant coronary and systemic arterioles and decreases myocardial oxygen requirements. There have been a number of serious adverse affects reported including liver damage, raised intracranial pressure and peripheral neuropathy.

DRUGS IN THE PROPHYLAXIS OF ARTERIAL DISEASE

Vasodilators are ineffective at relieving symptoms due to peripheral arterial and cerebrovascular disease. Hypotensive agents reduce the incidence of strokes in hypertensive subjects and anticoagulants aspirin and sulphinpyrazone may be of some value in preventing strokes in patients with transient cerebral ischaemic episodes. But there are no drugs that have an established place in the treatment of other forms of cerebrovascular or peripheral arterial disease.

The only drugs that have been used at all extensively in trials in the prophylaxis of arterial disease have been investigated with respect to the primary and secondary prevention of coronary artery disease. Those investigated include the oral

anticoagulants, the beta-blockers, oestrogens, aspirin, sulphinpyrazone and the hypolipidaemic agents. The role of anticoagulants in the secondary prevention of myocardial infarction is discussed in Chapter 35, that of beta-blockers is outlined above (page 326), that of oestrogens in Chapter 28 and that of aspirin and sulphinpyrazone in Chapter 19. In this chapter, only the hypolipidaemic agents will be discussed.

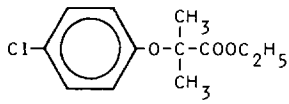
HYPOLIPIDAEMIC AGENTS

The place of hypolipidaemic agents in therapeutics is not clearly established. Preliminary evidence suggests that they are of value in reducing the morbidity and mortality in hyperlipidaemic states but that they have little or no value in the primary or secondary prevention of arterial disease in subjects with normal plasma lipoprotein concentrations.

Hyperlipidaemia is not one disorder, but a group of disorders that may be classified by the concentrations of the various types of lipid in the plasma, or, as lipids in the plasma remain in solution only by binding to plasma protein, by the electrophoretic mobility or density of the lipoproteins. The five major categories of hyperlipoproteinaemia (*see* Table 1) may occur as primary disorders or as metabolic consequences of other diseases, e.g. myxoedema, diabetes mellitus, nephrotic syndrome or ethanol dependence. The choice of an appropriate hypolipidaemic agent depends on the category of the hyperlipidaemia and the ability of the agent to lower particular lipoproteins. Hypolipidaemic agents may be classified according to whether they decrease lipoprotein synthesis or increase its catabolism and excretion.

Agents that Decrease Lipoprotein Synthesis

Clofibrate



ACTION

Hypolipidaemic Clofibrate is a fatty acid ester that lowers very low density lipoproteins (VLDL) and intermediate low density lipoproteins (ILDL), both of which are comprised mainly of triglycerides, in patients with hyperlipidaemias. It also lowers low density lipoprotein (LDL), which is mostly cholesterol, but to a lesser extent than VLDL and ILDL.

The mechanism whereby clofibrate lowers plasma lipoproteins is not clearly established. It decreases synthesis of VLDL and enhances its catabolism so mobilising tissue triglyceride stores. It also enhances the biliary excretion of cholesterol, while preventing enhancement of its synthesis.

Others

1. Free fatty acids. Clofibrate lowers the plasma concentration of free fatty acids by impairing their release from adipose tissue.
2. Fibrinogen. The plasma concentration of fibrinogen falls and this is probably a consequence of clofibrate's effect on free fatty acids.

Table 1
Indications for hypolipidaemic drugs

Fredrickson types	*Principle lipid*	*Lipoprotein density*	*Hypolipidaemic agent*
I	triglycerides (90%)	chylomicrons	nil
IIA	cholesterol (50%)	LDL	cholestyramine D-thyroxine nicotinic acid
IIB	cholesterol triglycerides	LDL VLDL	as for IIA clofibrate
III	triglycerides (40%) cholesterol (30%)	ILDL	clofibrate nicotinic acid
IV	triglycerides (60%)	VLDL	clofibrate nicotinic acid
V	triglycerides	chylomicrons VLDL	clofibrate nicotinic acid

3. Fibrinolysis. Clofibrate increases plasma fibrinolytic activity, reduces platelet turnover and decreases platelet stickiness, all of which decreases blood coagulability.

DRUG FATE Clofibrate is absorbed from the bowel and in the plasma is rapidly hydrolysed by plasma and tissue esterases to chlorophenoxyisobutyric acid. Chlorophenoxyisobutyrate is over 95% bound to plasma albumin and is confined to the plasma compartment, sharing similar binding sites as free fatty acids. It is metabolised in the liver and excreted in the urine as metabolites and has a plasma half-life of 10–12 hours. It is probably that chlorophenoxyisobutyrate accounts for the hypolipidaemic and other effects of clofibrate.

ADVERSE EFFECTS Gastrointestinal symptoms and non-fluid weight gain occur occasionally. There is an increased incidence of gall stones, deep vein thrombosis and pulmonary embolism in subjects on chronic therapy. Rarely there is a rise in serum aspartate transaminase. In patients with liver disease, clofibrate may cause an increase in plasma cholesterol concentration.

Drug interactions Clofibrate enhances the anticoagulant effect of oral anticoagulants.

CLINICAL USE

Hyperlipidaemias Clofibrate is the hypolipidaemic agent of choice in types III, IV and V and may be useful also in types IIa and IIb. There is no convincing clinical trial evidence that it is of value in the primary or the secondary prevention of coronary artery disease.

Nicotinic acid Nicotinic acid (*see* Chapter 34) in high doses (0·9–9 g/day)

impairs VLDL synthesis and hence LDL synthesis and lowers plasma free fatty acid concentration by impairing adipose tissue lipolysis. It is useful in similar situations to clofibrate, but the side-effects of flushing, hyperuricaemia, reduced glucose tolerance and hepatotoxicity are generally more troublesome.

Drugs that Increase Lipoprotein Catabolism

Cholestyramine Cholestyramine resin is a high molecular weight compound with a quaternary ammonium structure that binds bile acids in the gut lumen and prevents their reabsorption. As bile salts are synthesised from cholesterol there is an increase in cholesterol as well as bile salt excretion which is only partially compensated by an increase in cholesterol synthesis. There is a fall in LDL but little change in VLDLs.

Cholestyramine is not absorbed at all from the bowel and is usually tolerated in high doses (8–32 g/24 h). Constipation and colic are common side-effects and in some patients it may cause steatorrhoea, as it depletes the bile salts available for fat absorption. Furthermore, it may impair the absorption of anionic drugs such as warfarin, digoxin, thiazides, tetracycline, thyroid preparations and phenylbutazone.

'Cholestyramine' is indicated when LDLs are raised, e.g. type II a and b lipoproteinaemias. It may cause a rise in VLDLs.

D-thyroxine The dextro-isomer of thyroxine is much less potent than the L-isomer in most of its effects, but the difference is less in respect of their ability to increase LDL catabolism and hence to lower plasma cholesterol concentration. As with cholestyramine, D-thyroxine has little effect on VLDLs and is only indicated in type II hyperlipidaemias when LDLs are raised. At effective hypolipidaemic doses (2–8 mg/day) D-thyroxine usually causes some cardiovascular signs of hyperthyroidism which may be dangerous to patients with myocardial ischaemia.

Preparations

Drug	*Dose/24 hour*
Clofibrate	1–2 g
Nicotinic acid	3–9 g
Cholestyramine	8–32 g
D-thyroxine	16–32 mg

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Chapter 25

Pituitary Hormones

ANTERIOR PITUITARY HORMONES

The anterior pituitary gland is known to secrete 7 hormones, adrenocorticotrophic hormone (ACTH), growth hormone, follicle stimulating hormone (FSH), lutenising hormone (LH), prolactin, thyroid stimulating hormone (TSH) and melanophore stimulating hormone (MSH). Of these, the first 5 have some therapeutic value and only these will be dealt with in any detail in this chapter.

Corticotrophin (ACTH) Corticotrophin is a straight chain polypeptide with 39 amino acids, the first 24 being essential for its corticotrophic role and being common to the human, bovine and porcine hormone. Its release from the anterior pituitary is stimulated by a releasing factor, corticotrophin releasing factor (CRF) elaborated in the hypothalamus. CRF release is stimulated by amphetamine and adrenergic alpha-blockers and is inhibited by phenothiazines. ACTH of porcine origin is used clinically. Tetracosactrin is a synthetic analogue of ACTH consisting of the first 24 amino acids only, with pharmacological effects identical to those of ACTH.

ACTION ACTH stimulates the secretion of cortisol and androgens from the zona fasciculata and the zona reticularis of the adrenal cortex, but has little effect on aldosterone secretion from the zona glomerulosa. The zona reticularis and fasciculata hypertrophy under the influence of ACTH and atrophy in its absence, as in hypopituitarism or after prolonged corticosteroid administration. ACTH stimulates cyclic 3–5 AMP production and this may be the first step in its stimulant effect on cortisol synthesis from cholesterol.

The therapeutic effects of ACTH are all secondary to the increase in cortisol secretion and are outlined in Chapter 27.

DRUG FATE Like all polypeptides ACTH is digested in the gastrointestinal tract and is inactive orally. It is a highly potent compound, the physiological plasma concentration being 1–10 pmol/l. It is rapidly metabolised, partly in the blood and partly in the tissues, including the liver, and its plasma half-life is 15–30 minutes.

ADVERSE EFFECTS

Systemic Chronic administration of high doses of ACTH causes adverse effects identical to those of the glucocorticoids and in addition the mineralocorticoid effects of sodium retention with oedema, hypertension and hypokalaemia may occur. These are usually corrected by reducing the dose,

or if this is undesirable, by salt restriction and potassium replacement therapy. Chronic ACTH therapy causes impairment of the hypothalamic-pituitary-adrenal axis, but as this is associated with adrenocortical hypertrophy, recovery of the axis occurs more quickly than after chronic glucocorticoid therapy and is usually normal after 1–2 months. In high doses ACTH depresses growth hormone secretion.

Acne and hirsutism are quite common and are due to increased androgen secretion. Pigmentation is also common and is attributed to the melanophore stimulating activity of ACTH, as the amino acid sequence of ACTH from amino acids 4 to 11 is identical to that of melanophore stimulating hormone.

Pain at the site of injection is occasionally troublesome being more common with tetracosactrin (*see* below) than ACTH.

Sensitivity reactions rarely occur and are less common with tetracosactrin than with porcine ACTH.

ADMINISTRATION ACTH and tetracosactrin are usually administered i.m., the effect of a single dose being evident in 30 minutes. The short half-life of these preparations necessitates their being administered as depot preparations for all therapeutic purposes. Cortisol secretion is stimulated for 12–24 hours by a 40 I.U. dose of the repository form of ACTH, ACTH gel and 24–48 hours by a 0·5 mg dose of depot tetracosactrin. Therapy with ACTH and tetracosactrin is monitored by determination of the urinary 17-hydroxy corticosteroids.

CLINICAL USES

Diagnostic Tetracosactrin is used in the assessment of adrenocortical function. The rise in plasma cortisol 30 minutes after an i.v. injection of 250μg is normally 2–3 times the control value. Alternatively, 100 iu ACTH gel may be administered i.m. and the rise in the plasma cortisol 6 hours later determined.

Therapeutic ACTH or tetracosactrin may be used in all situations in which glucocorticoids are used (*see* Chapter 27), except when there is primary adrenal failure, fluid retention, hypertension or hypokalaemia. There are no established therapeutic advantages of ACTH over the glucocorticoids. Serious adverse effects and gastrointestinal side-effects are less common with ACTH than after glucocorticoids. Also the hypothalamic-pituitary-adrenal axis recovers more rapidly. However, less severe side-effects are usually more common including mineralocorticoid and androgenic side-effects that do not occur with glucocorticoids. In view of this and the greater ease of administration of the latter drugs in most clinical circumstances, ACTH is rarely preferred.

Other Anterior Pituitary Hormones

Growth hormone Growth hormone is a polypeptide containing 200 amino acids. Its release from the anterior pituitary is controlled by the interaction of a growth hormone releasing factor (GHRF) and a release inhibiting factor, somatostatin. Amphetamine and the dopamine agonist bromocriptine enhance

the release of GHRF and chlorpromazine inhibits its release. Only human growth hormone is of value therapeutically as growth hormone of beef or sheep origin is ineffective in man. As the hormone from 2–300 human pituitary glands is required for a course of therapy for a year, the hormone is very scarce and is only available at a few special centres in the United Kingdom.

Growth hormone stimulates growth in prepubertal subjects and can enable pituitary dwarfs to attain adult stature. The hormone has an anabolic effect on protein and connective tissue; it slows glycolysis and lipogenesis and enhances lipolysis and ketone body formation, hence opposing many of the actions of insulin. Growth hormone has a plasma half-life of 15–20 minutes, but its effects far outlast the presence of the hormone. This is probably due to an active metabolite, a sulphate conjugate of the hormone, somatomedin, which has similar actions to growth hormone but a half-life of 48 hours.

Inadequate endogenous growth hormone production, resulting in dwarfism and hypoglycaemia, is the only established indication for growth hormone therapy.

Gonadotrophins

Follicle stimulating hormone (FSH) stimulates the development of a follicle and oestrogen release from it in the first part of the menstrual cycle. An increase in plasma oestrogen causes a fall in FSH secretion and vice versa. Release from the anterior pituitary gland is controlled by lutenising hormone releasing hormone (LHRH) elaborated in the hypothalamus.

Lutenising hormone (LH) is secreted towards the end of the first half of the menstrual cycle and causes ovulation and progesterone secretion by the corpus luteum. It also stimulates the Leydig cells in the male, increasing testosterone secretion. LH release is inhibited by high concentrations of progesterone and oestrogen and, like FSH, is controlled by LHRH.

Human chorion gonadotrophin is a glycoprotein derived from the urine of pregnant women which has actions similar to those of LH. It is easily obtained and has a longer duration of action than LH. Gonadotrophins derived from post-menopausal women's urine (pergonal) have appreciable FSH and LH effects.

CLINICAL USE FSH, LH and gonadotrophins are used in the treatment of infertility due to gonadotrophin deficiency. They are inactive orally as they are rapidly broken down in the gastrointestinal tract. In the treatment of infertility due to ovarian failure, FSH and LH are administered i.m. daily for 5–7 days, starting with a low dose (75 iu/day) and increasing the dose by increments until a rising urinary oestrogen concentration indicates a maturing follicle. Chorionic gonadotrophin is administered in a single dose after FSH and LH to precipitate ovulation.

This procedure is effective in the majority of cases of infertility due to gonadotrophin deficiency, but multiple pregnancies are quite common. Furthermore, over-stimulation of the ovaries with FSH causes ovarian enlargement and cyst formation, pleural effusions, ascites, changes in blood volume and in

blood clotting mechanisms. As a consequence therapy is started with a small dose and the dose adjusted according to the oestrogen concentration in the urine. The dangers of over stimulation and of multiple pregnancies can be minimised by careful monitoring of urine oestrogens.

THYROTROPHIC HORMONE [TSH] This hormone is also a glycoprotein and is used in the investigation of hypothyroidism, but has no therapeutic use.

PROLACTIN A polypeptide, it is similar structurally to growth hormone. It is released from the anterior pituitary during pregnancy reaching a peak shortly before term and is one of a number of factors stimulating lactation. Suckling, hypoglycaemia and a number of other stimuli cause its release from the anterior pituitary which is controlled by a negative feedback mechanism mediated by a prolactin release inhibiting factor (possibly dopamine) secreted by the hypothalamus.

Prolactin secretion is stimulated by dopamine antagonists, phenothiazines and butyrophenones and by reserpine and methyl dopa. It is inhibited by dopamine agonists, e.g. bromocriptine and L-dopa (*see* Chapter 11). Bromocriptine is the most effective means of suppressing lactation.

POSTERIOR PITUITARY HORMONES

Oxytocin (*see* Chapter 29)

Vasopressin (antidiuretic hormone, ADH) Vasopressin is an octapeptide, with a terminal L-arginine molecule. An analogue, deamino-8-D-arginine vasopressin (dDAVP). is now used clinically, rather than vasopressin of beef origin or lysine vasopressin. The absence of the terminal amino group renders the molecule resistant to plasma peptidases hence prolonging the $t_{\frac{1}{2}}$ and the replacement of L-arginine by D-arginine has reduced its pressor effect.

ACTIONS

Antidiuretic In physiological concentrations the only action of vasopressin is to increase the permeability of the distal tubule and collecting duct to water (*see* Chapter 21). At these sites, urine is hypotonic to interstitial fluid and water, independent of electrolytes, diffuses back into the interstitial fluid. ADH facilitates this process and in maximally effective doses, in water-loaded subjects causes a negative free water clearance and the formation of urine that is hypertonic to plasma.

Vasoconstriction Despite its official name, vasopressin only causes vasoconstriction at concentrations many times those necessary to achieve a maximal degree of antidiuresis. Vasoconstriction affects all vascular smooth muscle, that of arteries being more affected than that of veins. Coronary constriction occurs and there may be an increase in blood pressure. Vasoconstriction of the hepatic, splenic and mesenteric arteries reduces hepatic blood flow and reduces hepatoportal venous pressure. In patients with bleeding oesophageal varices

20 iu i.v. over 10 minutes cause a cessation of bleeding in a majority of cases. Infusion directly into the bleeding artery has also been used successfully to stop acute gastric haemorrhages from a variety of other causes.

DRUG FATE Vasopressin is digested by trypsin and is not active orally. It is rapidly metabolised chiefly in the liver and kidney and has a plasma half-life of less than 20 minutes.

ADVERSE EFFECTS In low doses sufficient for its antidiuretic effect, no serious adverse effects occur. In high doses (5–20 iu as a bolus), vasopressin causes constriction of gastrointestinal smooth muscle with nausea, vomiting, colic and diarrhoea and reduction in bleeding from oesophageal varices rarely occurs unless these effects are evident. Hepato-cellular function may also deteriorate as a consequence of the fall in hepatic blood flow. In patients with coronary artery disease, high doses of vasopressin may cause angina or precipitate a myocardial infarct.

CLINICAL USES

Diabetes insipidus Polyuria and polydipsia due to impaired secretion of ADH responds well to dDAVP which is given i.m. as a depot preparation. Vasopressin tannate suspended in peanut oil is seldom used now. For less serious forms of ADH deficiency powdered lysine vasopressin may be taken by halation 10–20 iu 2–3 times a day. Thiazides and other diuretics are also of value in the management of diabetes insipidus (*see* Chapter 21).

Bleeding oesophageal varices 10–20 iu of posterior pituitary extract i.v. as a bolus over 10 minutes is usually sufficient to stop bleeding at least temporarily and a repeat dose may be necessary when the effect wears off after 30–45 minutes. Vasopressin should not be used in these doses in patients with myocardial ischaemia.

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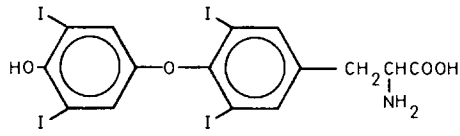
Chapter 26

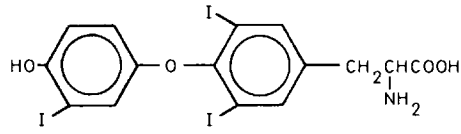
Thyroid Hormones and Anti-thyroid Drugs

THYROID HORMONES

There are two thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3) and for both the L-isomer is approximately 10–40 times as potent as the D-isomer. Thyroid hormones are synthesised by the thyroid gland (*see* below), incorporated into thyroglobulin and stored as colloid in the gland. They are released by the anterior pituitary hormone, thyroid stimulating hormone (TSH). Under physiological conditions, plasma T4 and T3 concentrations are maintained by a negative feed back control mechanism. The hormones bind to receptors in the hypothalamus which inhibits the release of the thyroid stimulating hormone releasing factor (TRF) and causes a fall in plasma TSH.



Thyroxine (T4)



Tri-iodothyronine (T3)

ACTIONS The actions of T3 and T4 are identical, T3 being 4 times as potent as T4. T4 is a major source of T3, the conversion of T4 to T3 occurring in the tissues. There is some evidence to suggest that T4 has no direct action itself its effects being mediated through its conversion to T3, but this is still disputed.

Thyroid hormones are only of value in replacement therapy, having no therapeutic use in large doses. The development and function of all cells is affected by them and their principle actions are evident from the clinical states of hypo- and hyperthyroidism.

Hypothyroidism affecting the foetus or neonate causes cretinism of which the salient features are growth retardation and mental deficiency and recovery from this condition only occurs if replacement therapy is initiated early. In the adult, hypothyroidism causes a decrease in mental and physical activity, a fall in body temperature, an increased sensitivity to cold and a bradycardia. Skin and hair become coarse, deafness develops and oedema, rich in hyaluronic acid and protein (myxoedema), is laid down in the subcutaneous tissues, especially around the face, giving the characteristic appearance of myxoedema. There is retardation of cerebral activity and a delay in relaxation of the limb reflexes. Apart from a fall in the plasma concentration of thyroid hormones, there is a fall in the basal metabolic rate and a rise in plasma cholesterol and triglyceride concentrations.

In hyperthyroidism, apart from changes in the thyroid gland itself, there are general symptoms of heat intolerance, sweating, a tremor, weight loss, an increased appetite, physical and mental over-activity, breathlessness, fatigue and emotional lability. Cardiovascular symptoms consist of tachycardia and tachydysrhythmias and eventually high output heart failure. Eye signs are lid retraction, proptosis and an external ophthalmaplegia. Proptosis and external opthalmaplegia are not due to high concentrations of T4 and T3 but are secondary to immune mechanisms that appear to play a major part in the pathogenesis of the disease. Thyroid hormones cause a fall in plasma cholesterol, an enhancement of glycogen synthesis and glucose uptake, and an increase in release of free fatty acids. There is a negative nitrogen balance and there may be evidence of a myopathy or osteoporosis. There is also increased sensitivity to the actions of catecholamines in hyperthyroidism and many of the symptoms of this condition are mediated by this mechanism and ameliorated by adrenergic beta-blocking drugs.

The widespread effects of thyroid hormones suggest a site of action common to all cells. Although it is not certain if all the actions of the hormones can be explained on the basis of a single site of action, it is probable that they act primarily on a nuclear receptor which controls the energy producing mechanisms of mitochondria, affecting microsomal protein synthesis only indirectly.

DRUG FATE Thyroxine and T3 are absorbed from the bowel and are orally active. At physiological plasma concentrations 99·9% of T4 and 99·5% of T3 is protein bound, the α_2-glycoprotein, thyroid binding globulin (TBG) binding all T3 and 75% of T4, the rest being bound to albumin and pre-albumin. The plasma concentrations of the free hormones are nearly equal. Thyroxine accounts for over 90% of the protein-bound iodine (PBI) and its total concentration in the plasma is 50 times that of T3. Thyroxine has an apparent volume of distribution of 10 l and the less highly protein bound T3, 40 l.

Thyroid hormones are cleared from the plasma chiefly by the liver where they are conjugated with glucuronic acid and sulphate and deiodinated. They are excreted in the bile and undergo extensive enterohepatic circulation, 20–50% of

an oral dose being excreted in the faeces as metabolites. Very little unchanged hormone is excreted in the urine.

PHARMACOKINETICS The plasma half-life of T4 in the euthyroid state is 6 days and that of T3 being 2·5 days, the difference between the two being determined by the degree of protein binding. Approximately 20% of T4 is converted by the tissues to T3. The effects of the hormones outlast their presence in the plasma, wearing off with a half-life approximately twice that of the hormones themselves. It will take up to 30 days for the full effects of a regular dose of T4 to develop (i.e. five times the half-life of the hormone) and approximately 12 days for those of T3. This can be foreshortened considerably by the administration of a loading dose, e.g. 0·5 mg T4 or 100 μg T3. A loading dose should only be administered in severe cases of myxoedema in view of the potential danger of precipitating myocardial ischaemia in patients with coronary artery disease. The plasma half-life of T4 is affected by existing thyroid function and increases to 9 days in the hypothyroid patient and falls to 3 days in the hyperthyroid patient.

ADVERSE EFFECTS

Overdose This causes the signs of hyperthyroidism.

Myocardial effects The positive inotropic and chronotropic effects of thyroid hormones, mediated at least in part by catecholamines, increase myocardial oxygen consumption and, in patients with coronary artery disease, may precipitate attacks of angina or a myocardial infarct. Tachydysrhythmias may also be precipitated in patients with heart disease.

Drug interactions Thyroid hormones increase the clearance from the plasma of some drugs, e.g. antipyrine, by expediting hepatic drug metabolism.

CLINICAL USE Hypothyroidism is the only clinical indication for L-thyroxine and liothyronine. Dextrothyroxine has been used as a hypolipidaemic agent as it lowers plasma cholesterol and triglycerides at doses that have little effect on the cardiovascular system, but its place in therapeutics is not established (Chapter 24).

In hypothyroidism, therapy is initiated with a low dose (50 μg/24 h T4, 10μg/24 h T3) and increased at 2–5 week intervals after the full effect of each dose is achieved (see above). A daily maintenance dose of 100–300μg T4, 45–90μg T3 is adequate in the majority of patients and the usual dose interval is 24 hours but some patients tolerate a longer dose interval of up to one week.

Preparations

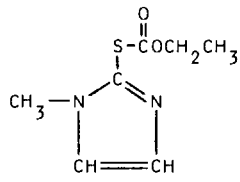
	Initial dose	*24 h adult maintenance dose*	*Dose interval*
L-thyroxine (T4)	0·05 mg	0·1–0·3 mg	24 h–1 week
Liothyronine (T3)	0·01 mg	0·03–0·09 mg	24 h

Monitoring therapy Clinical symptoms, weight and pulse rate are effective in the majority of patients as a means of monitoring therapy. If the response is less than anticipated the T4 and free thyroxine index are useful in establishing patient compliance and an effective dose.

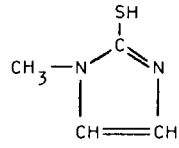
ANTI-THYROID DRUGS

Hyperthyroidism results from an over-production of thyroid hormones by a diffusely enlarged gland in Graves' disease, or by a solitary autonomous toxic adenoma. Treatment of this condition is by use of antithyroid drugs or ablation or partial ablation of the thyroid gland by surgery or by the beta-emitter ^{131}I. The choice between these three in the individual patient is a therapeutic decision and will only briefly be discussed here.

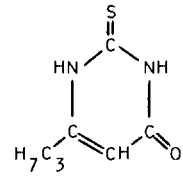
Thiocarbamides The thiocarbamides are derivatives of thiourea and are now the only widely used antithyroid drugs. Carbimazole is the most commonly used thiocarbamide in the UK and propythiouracil in the USA. Methimazole is a hydrolysis product of carbimazole and is responsible for its antithyroid activity *in vivo*. It is also available as a drug in its own right.



Carbimazole



Methimazole



Propylthiouracil

THERAPEUTIC EFFECTS

Thyroid hormone synthesis The initial step in the synthesis of thyroid hormones is the active uptake of iodide by the thyroid where it achieves a concentration upwards of thirty times that in the plasma. The uptake mechanism is not specific to iodide and may be competitively antagonised by other anions. The anions *thiocyanate* and *perchlorate* are effective antithyroid agents which act by inhibiting iodide uptake by the thyroid. They are only used when adverse reactions occur to the thiocarbamides, as there is a relatively high incidence of bone marrow depression associated with their use. Iodide is oxidised in the thyroid to iodine by a metabolic pathway involving thyroid peroxidase, and this is the rate-limiting step in hormonal synthesis. Iodine is rapidly incorporated into the tyrosine residues of thyroglobulin forming mono- and di-iodotyrosine and these are coupled to form tri-iodothyronine and thyroxine. T3 and T4 are stored in the glandular colloid as components of the glycoprotein thyroglobulin and are released into the plasma by the action of thyroid stimulating hormone.

Thiocarbamides ameliorate all the symptoms of hyperthyroidism except the eye signs. The mechanism of action is not certain but they impair the synthesis of T3 and T4, probably by inhibiting thyroid peroxidase. They may also cause some reduction of iodide uptake by the gland, and iodine replacement after stopping these drugs expedites relapse of hyperthyroidism. Hormone synthesis is blocked within hours of administration of these drugs but the effect is not evident clinically for several days owing to the slow clearance of preformed hormone from the plasma and thyroid gland. Propylthiouracil but not carbimazole blocks the conversion of T4 to T3 by the tissues.

DRUG FATE Thiocarbamides are readily absorbed from the bowel. Carbimazole is reduced to the active metabolite methimazole which has an apparent volume of distribution similar to that of total body water, while the more polar propylthiouracil is confined to the extracellular space. Methimazole is partly metabolised and partly excreted unchanged in the urine, but propylthiouracil is mostly excreted unchanged in the urine. The half-life of methimazole is 14 hours and that of propylthiouracil 2·5 hours and both accumulate to some extent in renal failure.

ADVERSE EFFECTS

Overdose A diffuse enlargement of the thyroid gland occurs as the first signs of administering too large a dose due to a high TSH plasma concentration. Later the signs of myxoedema develop. Goitre formation may occur in the fetus if these drugs are given to the pregnant woman.

Adverse effects occur in less than 3% of patients, rashes and gastrointestinal symptoms being the most common. Drug fever, polyarthritis and bone marrow depression are infrequent serious adverse effects that usually occur during the first two months of therapy when high doses are used. If adverse reactions other than overdose effects occur to carbimazole, propylthiouracil may be administered as cross-sensitivity reactions between these agents is unusual.

Relapse Approximately 20% of patients treated for 1–2 years with these drugs relapse within 2 months on stopping therapy and a further 30% over several years.

CLINICAL USE Therapy is initiated with a high dose (3–6 times the maintenance dose) to inhibit thyroid hormone synthesis completely for 4–6 weeks, allowing glandular depletion and a reduction in T4 secretion. The dose is then lowered and maintained at a level sufficient to achieve a euthyroid state. The duration of therapy is usually for 1–2 years, although relapse appears to be no more frequent when it is stopped after only 4–6 months of therapy.

Monitoring Body weight, pulse rate and symptoms are the best means of monitoring therapy, but the T4 and free thyroxine index may be useful when the clinical signs are equivocal.

Preparations

	Adult loading dose/24 h	*Maintenance dose/24 h*	*Dose interval*
Carbimazole	20–45 mg	5–15 mg	8–12
Methimazole	20–40 mg	5–15 mg	12–24
Propylthiouracil	200–600 mg	50–150 mg	6

Iodide Iodide has long been known to depress thyroid activity temporarily. It depresses all aspects of thyroid function in hyperthyroid but not in euthyroid subjects, impairing thyroid hormone release. The effect of iodide is rapid, a euthyroid state being induced within days suggesting an immediate cessation of T3 and T4 release. The thyroid gland shrinks and becomes harder and less vascular. These effects begin to wear off within 2 weeks and if iodide therapy continues, the hyperthyroid state may eventually become worse than that before iodide administration.

CLINICAL USE Iodide is used in hyperthyroid patients undergoing a partial thyroidectomy to decrease the vascularity of the gland. It is usually given as Lugol's iodine 1·0 ml/day in divided doses. It may be given alone for 10 days, or more commonly with a thiocarbamide.

Beta-blockers in hyperthyroidism Hyperthyroidism is associated with an increased sensitivity to the effects of catecholamines and many of the symptoms, e.g. nervousness, tremor, heat intolerance, sweating and tachycardia may be ameliorated by beta-blockers which have no effect on thyroid function. These drugs, therefore, are not curative but may be useful in relieving symptoms during initiation of therapy with either antithyroid drugs of ^{131}I.

Cardiac tachydysrhythmias occurring in hyperthyroid patients respond well to beta-blockers. Propranolol given i.v. in doses of 1–2 mg over 10 minutes and then increasing the dose as required up to 10 mg has proved effective at treating ventricular tachycardias and ventricular fibrillation occurring in severe hyperthyroidism (thyroid storm). Despite the interactions between catecholamines and thyroid hormones, there is no clinical trial evidence that beta-blockers are superior to other antidysrhythmic drugs in this condition.

Choice of Treatments in Hyperthyroidism

The major disadvantages of antithyroid drugs are:–

that 50% of patients relapse on cessation of therapy;
regular pill taking is necessary for 1–2 years;
adverse reactions occur in 1–3% of patients;
there are potential teratogenic effects in the first trimester of pregnancy.

These must be compared with the major drawbacks to the alternative forms of therapy. For partial thyroidectomy they are:–

inconvenience of surgery;
the rare but serious adverse side-effects such as parathyroidectomy and section of the recurrent laryngeal nerve;
removal of too little or too much of the thyroid gland.

^{131}I therapy is by far the most convenient consisting usually of one or two doses of ^{131}I. The disadvantages are:–

unsuitable for those under 40 in view of the potential, but as yet unproven, mutagenic and teratogenic effects of ^{131}I;
hypothyroidism develops insidiously in nearly all patients. All treated

Table 1
Effect of drugs on thyroid function tests (TFTs)

	Mechanism	*Change in TFT*	*Examples*
1.	Increased plasma iodide	↑ in non-T4 PBI*	Iodide – as stimulant of bronchial sections
		No change in T4	Topical antiseptics
			Contrast media in radiology
			Di-iodohydroxyquinoline (amoebicide)
		↓ T3 resin uptake	Gallaminetriethiodide (muscle relaxant)
		↓ ^{125}I uptake	Tetraiodofluorescein (pharmaceutical dye)
2.	Altered thyroid binding globulin		
	(a) ↑	↑ PBI	Oestrogens
			Phenothiazines
		↓ T3 resin uptake	
		— ^{125}I uptake	
	(b) ↓	↓ PBI	Androgens
			Anabolic steroids
		↑ T3 resin uptake	
		— ^{125}I uptake	
3.	↓ Protein binding	↓ PBI	Salicylates
			Phenytoin
		↑ T3 resin uptake	
		— ^{125}I uptake	
4.	Impaired thyroid hormone synthesis	↓ PBI	Sulphonamides
			Sulphonyl ureas
		↑ T3 resin uptake	PAS
			Phenylbutazone
		↓ ^{125}I uptake	

* PBI = protein-bound iodine

patients therefore should have a long-term follow up. Total ablation of the gland by a high dose of ^{131}I and full thyroid replacement after six weeks is an alternative form of therapy.

The Effect of Drugs on Thyroid Function

There are four ways in which drugs, other than those used in the treatment of hyperthyroidism, may affect thyroid function tests and these are summarised in Table 1.

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Chapter 27

Corticosteroids

The physiological effects of the hormones produced by the adrenal cortex are considered under the headings of glucocorticoid and mineralocorticoid effects, glucocorticoid referring to the effect on carbohydrate metabolism and mineralocorticoid to that on sodium and potassium reabsorption and disposition. There are a number of steroids produced by the adrenal cortex and, under physiological circumstances in man, cortisol (hydrocortisone) is the principle glucocorticoid and aldosterone the principle mineralocorticoid.

Corticosteroids are used for their physiological effects in replacement therapy in patients with dysfunction of their adrenal cortex due to either a primary disorder of the adrenal gland itself or secondary to dysfunction of the anterior pituitary gland. They are also used for effects that are not usually discernible at physiological doses but are evident at doses above this range and of these the most important are anti-inflammatory and immunosuppressive effects. In replacement therapy, both glucocorticoid and mineralocorticoid effects are of therapeutic value, but only agents with glucocorticoid activity have anti-inflammatory and immunosuppressive activity. Cortisol has some mineralocorticoid as well as glucocorticoid activity, but synthetic steroids have been produced that have negligible mineralocorticoid activity and it is these that are used most commonly in therapeutics.

The place of corticosteroids is not always comprehensible from knowledge of their physiological effects or from the known pharmacological actions. In most disorders their therapeutic values have been established empirically and only rarely on the basis of clinical trial data.

MINERALOCORTICOIDS

Aldosterone is the most potent naturally occurring mineralocorticoid, although corticosterone, and to a lesser extent cortisol, also have mineralocorticoid activity. Aldosterone is inactive orally and so unsuitable for chronic replacement therapy and the synthetic steroid and potent mineralocorticoid fludrocortisone (*see* Fig. 1) is most commonly used for this purpose.

ACTION Mineralocorticoids enhance sodium reabsorption by the renal tubule, probably acting along the length of the nephron. They promote cation exchange whereby sodium is reabsorbed in exchange for potassium and hydrogen ions and hence they increase potassium and hydrogen ion excretion in the urine, causing hypokalaemia and a metabolic alkalosis. They cause an increase in total body sodium and water and in consequence an increase in extracellular fluid volume, an increase in plasma volume and a rise in blood pressure.

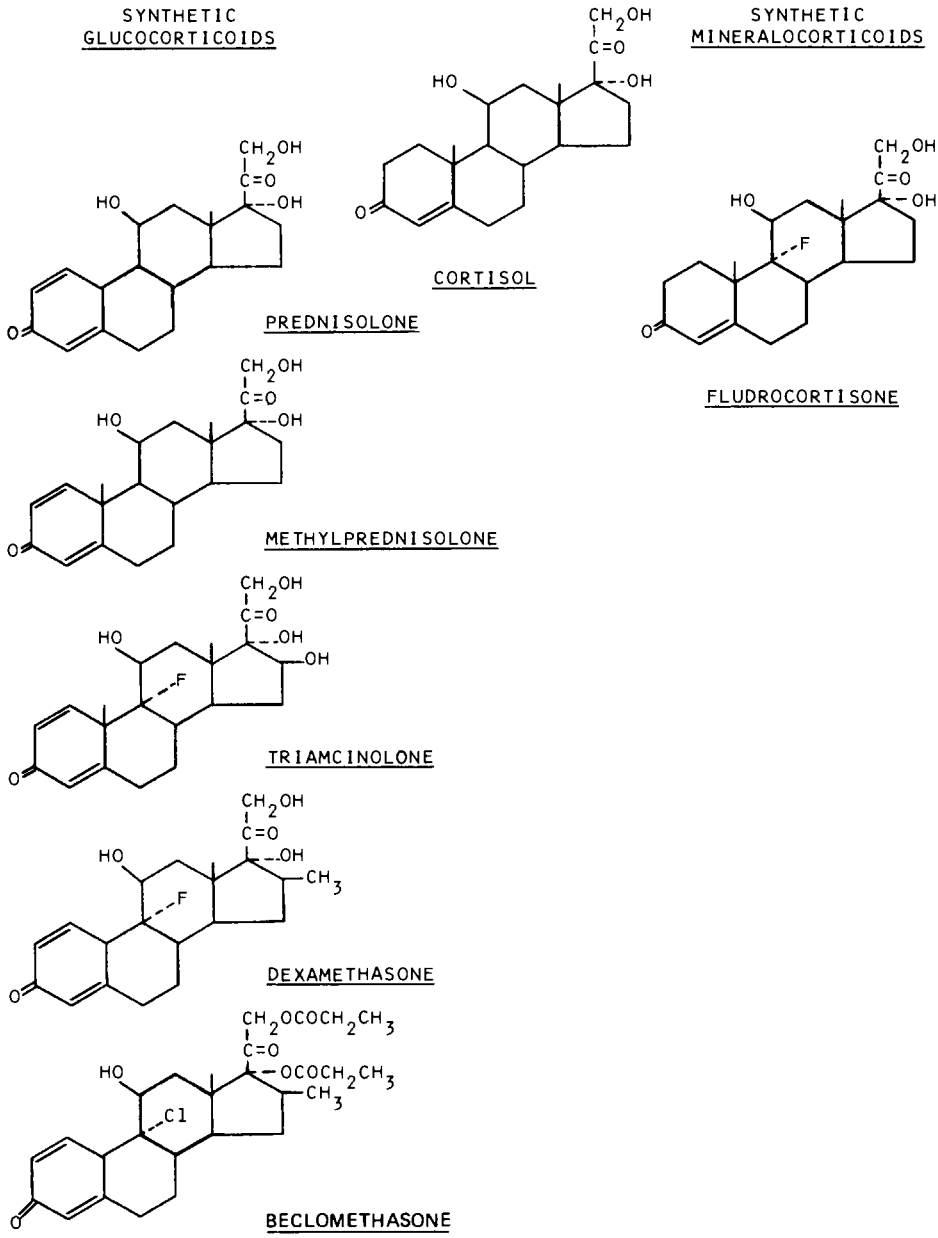

FIG. 1 Glucocorticoid and mineralocorticoid structures.

DRUG FATE Aldosterone is rapidly absorbed from the bowel and only 10% is bound to plasma proteins. It is very rapidly metabolised by the liver, having a metabolic clearance rate over ten times that of cortisol so that negligible amounts reach the systemic circulation after oral administration.

Fludrocortisone is active orally and has a prolonged duration of action, although details of its metabolism are not available. A single daily dose is usually sufficient in replacement therapy.

ADVERSE EFFECTS Overdosage is the principal adverse effect of fludrocortisone. During the first few days of overdosage there is sodium retention and an increase in the extracellular fluid volume but thereafter a new equilibrium is established by mechanisms that are not fully established. Hypokalaemia and a metabolic alkalosis develop and persist during the period of overdosage.

CLINICAL USE

In adrenal failure In an Addisonian crisis aldosterone may be administered i.v. (0·5 ng/h) in conjunction with NaCl although cortisol, as the hemisuccinate 100–200 mg 8 h for 24 hours, is the usual therapy. For maintenance therapy cortisol or cortisone acetate (12·5–25 mg twice or three times daily) is used alone initially with adequate salt replacement. If the blood pressure remains low and postural hypotension persists, or if there is biochemical evidence of a negative sodium balance, fludrocortisone is administered at a low dose (0·1 mg/day) and the dose increased to achieve the desired response.

GLUCOCORTICOIDS

Cortisol has mainly glucocorticoid activity, but some mineralocorticoid activity. There are a number of synthetic steroids that are potent glucocorticoids with negligible mineralocorticoid activity (*see* Table 1, Fig. 1). The glucocorticoid activity of the synthetic steroids is qualitatively similar to that of cortisol, although there are considerable differences in the potency and pharmacokinetics of individual glucocorticoids.

Table 1
Relative potency of corticosteroids

Corticosterois	*Glucocorticoid anti-inflammatory immunosuppressive activity*	*Mineralocorticoid activity*
Cortisol	1	0·01
Prednisolone	3–5	0·008
Methylprednisolone	3–5	0·005
Triamcinolone	3–5	—
Betamethasone	20–30	—
Dexamethasone	20–30	—
Fludrocortisone	10	5

ACTION

Metabolic Glucocorticoids are so named because of the effects they have on carbohydrate metabolism. They cause an increase in blood glucose by increasing hepatic glucose release; they reduce amino acid uptake by peripheral tissues such as muscles and increase hepatic glycogen synthesis. As a consequence of impaired amino acid uptake there is a rise in plasma amino acid concentration and, possibly as a consequence of this, increased glucagon release. Glucocorticoids cause an increase in hepatic enzymes involved in gluconeogenesis (e.g. glucose-6-phosphatase, fructose-6-phosphatase) due partly to the increased plasma concentration of amino acids and partly to a direct enzyme-inducing action of the steroids themselves. The net effect of these actions is to maintain the blood glucose concentration and to reduce protein synthesis.

Lipogenesis is impaired in subcutaneous tissues of the limbs, but is enhanced in that of the trunk, face and dorsal fat pad.

Anti-inflammatory Glucocorticoids depress all stages of inflammation, including healing, regardless of the cause of the inflammatory response. Anti-inflammatory activity is proportional to the concentration of steroid at the site of inflammation but there is no satisfactory unitary theory of how this effect is achieved.

The anti-inflammatory actions of glucocorticoids are intimately related to their metabolic effects and it seems reasonable to suppose that their cellular effects may be secondary to alterations in the metabolism of individual cells, e.g. leucocytes, lymphocytes, monocytes and fibroblasts, whose response to inflammation is greatly altered by glucocorticoids. The cellular and biochemical effects of glucocorticoids that may be related to their anti-inflammatory activity are as follows:

1. Leucocytosis They increase the rate of release of leucocytes from the bone marrow and decrease the rate at which they accumulate at sites of inflammation. The net result is a leucocytosis and an increase in the survival time of these cells, changes that are probably secondary to alterations in the leucocyte cell membrane.

2. Lymphopenia There is a transient lymphopenia after glucocorticoids, probably due to a shift of lymphocytes from the circulation to the bone marrow. Human lymphocytes are relatively resistant to the cytotoxic effects of these agents on lymphocytes although this is pronounced in certain other species, e.g. rodents. Eosinophil and monocyte concentrations also fall by a similar mechanism.

3. Membrane function Glucocorticoids decrease the permeability of cell membranes including the capillary cell membrane and hence decrease the accumulation of oedema at sites of inflammation. High concentrations *in vitro* protect lysosomal membranes from rupturing in response to cell injury. Lysosomes contain acid hydrolases that cause autolysis when released and, by preventing their release, glucocorticoids reduce acid hydrolase-mediated cell injury.

4. Prostaglandin biosynthesis The synthesis of prostaglandins E_2 and $F_{2\alpha}$ by the tissues is inhibited by glucocorticoids. As these agents are present at sites of inflammation and may be responsible for some aspects of inflammation, this may contribute to the anti-inflammatory effects of glucocorticoids.

IMMUNOSUPPRESSIVE It is often difficult to differentiate the anti-inflammatory from the immunosuppressive effects of these drugs. Lymphopenia is the principle mechanism whereby glucocorticoids affect immunity but it is probably suppression of the inflammatory response that is most helpful in steroid suppression of the heterograft rejection process. Thymus-dependent lymphocytes (T-lymphocytes), which are responsible for cell-mediated immunity, take up glucocorticoids and are more readily affected by them than bone marrow-dependent lymphocytes (B-lymphocytes) which are responsible for antibody production. Immunoglobulins and serum complement concentrations are only reduced by very high doses of these agents so that at most therapeutic doses, antibody production is little affected by glucocorticoids.

OTHER THERAPEUTIC ACTIONS

Calcium absorption Glucocorticoids reduce calcium absorption by impairing the active carrier mechanism in the ileum responsible for calcium absorption. Thus, in sarcoidosis in which there is increased sensitivity to vitamin D and enhanced calcium absorption, glucocorticoids reduce calcium reabsorption and lower plasma calcium concentrations.

Circulatory effects In Addisonian patients glucocorticoids, not mineralocorticoids, have a positive inotropic effect and increase blood pressure. This may be a direct effect or be due to a steroid induced increase in responsiveness to endogenous catecholamines.

In endotoxin shock, high doses of glucocorticoids (1 g cortisol/24 h or more) are commonly used in the belief that glucocorticoid secretion is reduced. This is not so in most cases and there is no convincing clinical evidence that glucocorticoids are of value in endotoxic shock or in other hypotensive states, unless impaired adrenocortical function is established.

Cerebral oedema High doses of glucocorticoids reduce cerebral oedema from any cause and clinically are most effective in oedema due to cerebral tumours, neurosurgery and subarachnoid haemorrhage. The mechanism responsible for this action is not established.

DRUG FATE All glucocorticoids are rapidly absorbed from the bowel and reach the systemic circulation in effective concentrations. They have a volume of distribution equivalent to that of total body water. In the plasma, cortisol in physiological concentrations (100–500 nmol/1), is 80% bound to an alpha globulin and cortisol-binding globulin, a smaller proportion being much less tightly bound to albumin. Synthetic glucocorticoids do not displace cortisol from protein-binding sites and are less protein-bound than cortisol.

Cortisone is the C11 keto-analogue of cortisol, as is prednisone of pred-

nisolone. Both of these steroids are rapidly reduced by liver enzymes to the more active compounds cortisol and prednisolone respectively. This process is impaired in severe liver disease. Cortisol is metabolised by the liver to polar metabolites, especially tetrahydrocortisols, and these are mostly conjugated before being excreted in the urine. Less than 1% of an oral dose of cortisol is excreted unchanged in the urine.

Synthetic glucocorticoids are metabolised more slowly than cortisol and their half-lives are longer (*see* Table 2), but the metabolic pathways involved in their degradation are not known. They are metabolised, at least in part, by hepatic microsomal enzymes and their metabolic clearance rate can be increased by up to 50% by phenobarbitone and presumably other enzyme inducing drugs (*see* Chapter 9).

Table 2
Half lives in the plasma

Steroid	*Plasma* $t_{\frac{1}{2}}$ *(hours)*
Cortisone	0·5
Cortisol	1·5
Prednisolone	2·5–3·5
Methylprednisolone	2·5–3·5
Triamcinolone	5
Betamethasone	5 or longer
Dexamethasone	3–6

The biological effects of glucocorticoids are prolonged after their disappearance from the plasma. For example, their suppressive effect on endogenous cortisol secretion declines with half-lives 5–7 times those of the individual glucocorticoids themselves.

ADVERSE EFFECTS The broad spectrum of biological effects of glucocorticoids makes it inevitable that their use for a given therapeutic effect, e.g. anti-inflammatory effect, is accompanied by other adverse effects (Table 3). In general, the severity of these undesirable effects is dose-related.

Hyperglycaemia Glucocorticoids decrease carbohydrate tolerance and may precipitate or exacerbate diabetes mellitus, but only rarely do they cause ketoacidosis or non-ketoacidotic hyperglycaemic coma.

Osteoporosis These agents cause a negative nitrogen balance in non-physiological doses, impairing protein synthesis and protein catabolism. Osteoporosis, which may be associated with pathological fractures, especially crush fractures of the vertebrae, may result. In many of the conditions for which

Table 3
Summary of adverse reactions to glucocorticoids

Metabolic	Hyperglycaemia and precipitation of diabetes mellitus. Impaired proteins synthesis and osteoporosis, myopathy, aseptic necrosis of bone. Altered fat metabolism and moon face, trunkal obesity.
Hypothalamic	Hypothalamic-pituitary-adrenal axis: acute cortisol deficiency on sudden withdrawal Amenorrhoea.
Immune mechanisms	Increased susceptibility to infection.
Anti-inflammatory	Reduced clinical response to infection. Impaired wound healing. Increased suceptibility to peptic ulceration.
CNS	Affective disorders. Acute psychoses. Reduced threshold to convulsions.
Eye	Cataract formation. Glaucoma.
Mineralocorticoid	Hypokalaemic alkalosis. Hypertension. Oedema.
In children	Growth retardation.

glucocorticoids are prescribed, they are not the only factor predisposing to osteoporosis.

Myopathy, principally affecting proximal muscle groups and which occurs most commonly with triamcinolone, cataract formation and aseptic necrosis of bone are uncommon complications of glucocorticoids that may be consequences of their effect on protein synthesis.

Trunkal obesity with a moon face, buffalo hump and thin limbs, results from the effect of steroids on fat metabolism.

Infections Patients on large doses of glucocorticoids are prone to bacterial and fungal infections as they prevent or reduce the inflammatory response, decrease cellular immunity and impair the responsiveness of neutrophils and monocytes to infection. The clinical symptoms and signs that accompany infections are also reduced so that the diagnosis may be delayed. Pulmonary tuberculosis occurs quite commonly in patients on high doses and many such patients have regular chest X-rays to facilitate early diagnosis and some receive prophylactic isoniazid.

Peptic ulceration There is a widely held clinical impression that peptic ulcers and their complications are more common in patients on large doses of glucocorticoids than in patients with similar diseases not treated with these agents. However, there is no convincing clinical trial data on this association and as there is an increase in the incidence of peptic ulcers in some of the disorders treated by these agents in any case, their ability to cause peptic ulceration remains unproven.

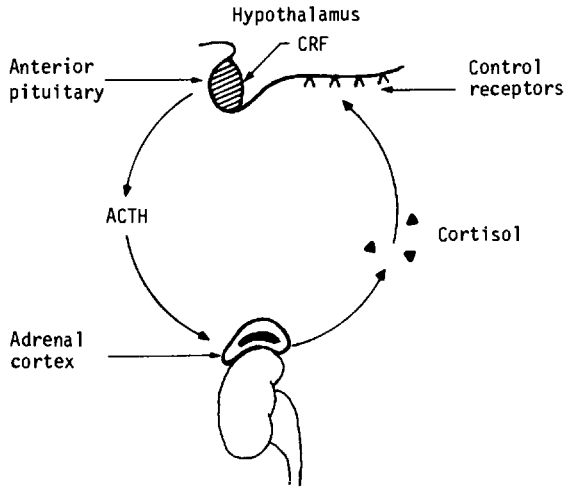

FIG. 2 Negative feedback control mechanism of cortisol release. Cortisol interacts with hypothalamic receptors which inhibits CRF release by the hypothalamus hence ACTH release by the anterior pituitary.
CRF = corticotrophin releasing factor.

Wound healing Post-operative wound healing is sometimes delayed in patients on high doses of glucocorticoids.

Mineralocorticoid effects Cortisol may cause adverse mineralocorticoid effects (*see* page 348). Prednisone in high doses may rarely cause hypokalaemia.

Hypothalamic-pituitary-adrenal axis Cortisol secretion by the zona fasciculata of the adrenal cortex is controlled by a feedback mechanism. Cortisol reacts with receptors in the hypothalamus inhibiting release of corticotrophin-releasing factor by the hypothalamus and hence there is a reduction in ACTH release by the anterior pituitary gland.

Administration of glucocorticoids in supra-physiological doses for two weeks or longer causes atrophy of the zona fasciculata and impaired release of cortisol in response to stressful stimuli. This alteration in hypothalamic-pituitary-adrenal axis may last for up to one year. Rapid withdrawal from

glucocorticoids after chronic therapy may precipitate an acute cortisol deficiency state and death. Such a reaction may not be immediate but be precipitated by a stressful circumstance such as an infection or traumatic event, weeks or months after withdrawal.

Glucocorticoids have a direct effect on hypothalamic-pituitary function as evidence by an impaired release of ACTH in response to stress that persists many months after withdrawal of these agents. Growth hormone release is also reduced during therapy with large doses. Amenorrhoea associated with a reduction in FSH secretion also occurs.

Growth Prolonged high doses of glucorticoids to children causes retardation of growth. This is probably due to depression of bone growth by a direct effect of these agents on epiphiceal cartilage although reduction in growth hormone secretion may also be contributary.

OTHER EFFECTS

On CNS High doses of glucocorticoids commonly induce a sense of well-being in patients that seems disproportionate to their effects on symptoms. In high doses, they may also induce hypomania, depression and psychotic episodes.

Glucocorticoids lower the threshold to convulsions and may cause fits in patients who have not previously had fits, or they may exacerbate existing epilepsy.

Glaucoma Topical glucocorticoids applied to the conjunctiva may increase intra-ocular pressure and cause glaucoma. There are a small number of subjects who are particularly susceptible to this effect, the susceptibility being genetically-determined and arising from an autosomal dominant gene.

CLINICAL USE As can be seen from Table 4, glucocorticoids are used in a wide range of diseases. They are only curative in adrenal failure and hypopituitarism, in other cases only suppressing symptoms. In each condition and in each patient, the effectiveness of glucocorticoids and the dose requirement is established empirically. Because of the large number of possible adverse effects and the life-threatening consequences of rapid withdrawal, glucocorticoids are prescribed only when less dangerous drugs have failed to give symptomatic relief. They are prescribed in the lowest effective dose and for the shortest possible time, and if prescribed for two weeks or more, must be withdrawn slowly, the rate varying between one week for a course of 3–4 weeks, to six months if they have been prescribed daily for years. Patients should be warned of the consequences of sudden withdrawal and be provided with a card or other means of indicating the dosage they are receiving.

CHOICE OF AGENT

Replacement therapy Cortisol and cortisone are the drugs of choice and are often sufficient alone with an adequate salt intake. Fludrocortisone may be

Table 4
Clinical conditions in which systemic corticosteroids may be used

Replacement therapy in primary or secondary adrenal failure.	
Systemic	Anaphylaxis
Respiratory disease	Asthma Fibrosing alveolitis Sarcoidosis
Connective tissue disorders	Rheumatoid arthritis Systemic lupus erythematosus Systemic sclerosis Polymyalgia rheumatica Dermatomyositis
Diseases of arteries	Polyarteritis nodosa Temporal arteritis
Renal disease	Membranous glomerulonephritis
Gastrointestinal disease	Ulcerative colitis Crohn's disease Chronic active hepatitis
Nervous diseases	Cerebral oedema Retrobulbar neuritis Myositis
Skin diseases	Eczema Pemphigus Exfoliative dermatitis Pemphigoid Psoriasis
Eye diseases	Sympathetic ophthalmia Uveitis Conjunctivitis Allergic blepharitis
Blood diseases	Lymphatic and stem cell leukaemia Idiopathic thrombocytopenia Haemolytic anaemia
Diseases of lymphatics	Lymphomas Myelomas
Organ transplants	Renal and other organ transplants

added if mineralocorticoid activity is inadequate (*see* above). In adrenal failure secondary to hypopituitary failure, prednisolone is used in preference to cortisol.

Glucocorticoid therapy There is little to choose between the more potent glucocorticoids with negligible mineralocorticoid activity. Prednisone and prednisolone are the most widely used, triamcinolone rarely being used on account of the myopathy it occasionally causes. The use of one agent in preference to another has mostly been determined by fashion rather than the intrinsic virtues of a particular preparation.

ROUTE OF ADMINISTRATION Oral therapy is only used when glucocorticoid effects are required at many sites in the body or when sufficient effect is not achieved by topical application.

Parenteral therapy Intravenous steroids are commonly used in status asthmaticus when large doses (e.g. 1 g hydrocortisone/24 h) are administered. The water soluble hydrocortisone hemisuccinate is the preparation of choice for this route.

Topical steroids The systemic effects of glucocorticoids can be reduced by topical application to the desired site of action. This is the preferred method in diseases of the skin and eye (*see* Chapter 41). In ulcerative colitis, retention enemas containing glucocorticoid are most effective at relieving symptoms of diarrhoea in mild and moderately severe cases. In asthma, inhalation of the potent glucocorticoid beclomethasone dipropionate is often sufficient to prevent asthmatic attacks without causing suppression of plasma cortisol concentration. Beclomethasone is a more potent anti-inflammatory agent than dexamethasone when applied topically, but when taken orally is very rapidly hydrolysed to the less active beclomethasone monopropionate and the inactive beclomethasone.

DOSE In replacement therapy (12·5–37·5 mg/day) cortisol in divided doses is usually sufficient. The dose required to give symptomatic relief in other conditions varies with the disease itself and is usually small in some (e.g. idiopathic thrombocytopenia and polymyalgia rheumatica) and large in others (e.g. polyartertis nodosa and systemic sclerosis). In many conditions, e.g. status asthmaticus, ulcerative colitis, systemic lupus erythematosus, large doses are used initially (40–80 mg prednisolone) to suppress inflammation. When symptoms improve, however, it is often possible to suppress the disease with a much smaller maintenance dose.

DOSE INTERVAL The therapeutic effect of glucocorticoids often outlasts their effect on the hypothalamic-pituitary-adrenal axis, on immune mechanisms and on neutrophils. It is often possible therefore to increase the dose interval (e.g. from 8 or 12 hourly to 48 hourly) without altering the total 24 hour dose. By doing so, it is possible to minimise lasting suppression of ACTH or growth

hormone, as these recover during the dose interval, and hence avoid the danger of an Addisonian crisis on sudden withdrawal, or of growth retardation. Similarly, an increase in dose interval decreases the incidence of infections in patients on large doses. For prednisone, prednisolone and methylprednisone, and alternate-day therapeutic regime achieves these objectives, but for the longer acting steroids, such as dexamethasone, dose interval may be increased to 72 hours. The dose interval must be evaluated in each patient as many do not respond with dose intervals longer than 24 hours.

WITHDRAWAL Sudden withdrawal of glucocorticoids after supra-physiological doses for two weeks or more may precipitate an Addisonian crisis. This may be avoided by withdrawing the steroids slowly, allowing hypothalamic-pituitary-adrenal axis to recover. The hypothalamus and pituitary recover approximately twice as rapidly as the adrenal cortex, as the ACTH response to stress recovers well before that of plasma cortisol.

In general, the longer the course and the higher the dose, the slower the withdrawal. After a two week course, withdrawal may be completed in one week, after a three month course in six weeks, etc.

As it is often impossible to predict the ability of the adrenal cortex to respond to stress, it is advisable to recommend a supplementary dose in periods of stress during withdrawal and for up to one year afterwards if the duration of therapy has been longer than one month.

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Chapter 28

Gonadal Steroids

Gonadal steroids include oestrogens, progestogens and androgens. As their generic name suggests, these agents, with few exceptions, have a common chemical structure, the oestrane ring (Fig. 1) but despite seemingly close chemical similarities, there are major differences in the biological effects of the three groups of gonadal steroids with only a small degree of overlap. The naturally-occurring agents are hormones with an essential role in reproduction. The gonadal steroids are used in therapeutics for their physiological effects in replacement therapy and also for other effects that cannot readily be described as physiological. The discovery of the contraceptive effect of oestrogens and progestogens and the development of preparations that are active orally has resulted in the very widespread use of these drugs, mostly in healthy women.

Oestrogens

ACTIONS

Female secondary sex characteristics In the prepubertal female, oestrogens cause enlargement of the breasts, external genitalia, uterus and appendages and the development of the gynaecoid subcutaneous fat distribution.

Anabolic effect They cause epiphyseal fusion and if given without growth hormone to patients with hypopituitarism, will cause stunting of growth. The increase in growth is associated with a positive nitrogen, calcium and sodium balance.

Menstruation Oestrogens cause proliferative changes in the endometrium and vaginal endothelium and alterations in the glycoprotein of cervical mucus so that it becomes less viscous. Withdrawal of oestrogens causes a shedding of the endometrium and vaginal bleeding.

Follicle-stimulating hormone (FSH) release Oestrogens inhibit lutinising hormone-releasing hormone (LHRH) release from the hypothalamus (*see* Chapter 25) and hence FSH release by the anterior pituitary, causing atrophy of the ovaries and a fall in endogenous oestrogen production. This is part of the negative feedback mechanism controlling FSH release and hence ovulation in physiological circumstances.

Cytotoxic effect In carcinoma of the breast, oestrogens may increase the rate of tumour growth in premenopausal women and in a relatively small proportion of post-menopausal women they slow the tumour growth.

In carcinoma of the prostate, oestrogens cause regression in the size of the primary tumour and of secondary deposits in 80% of patients. The remission may last two or more years, although eventual regression is inevitable. The

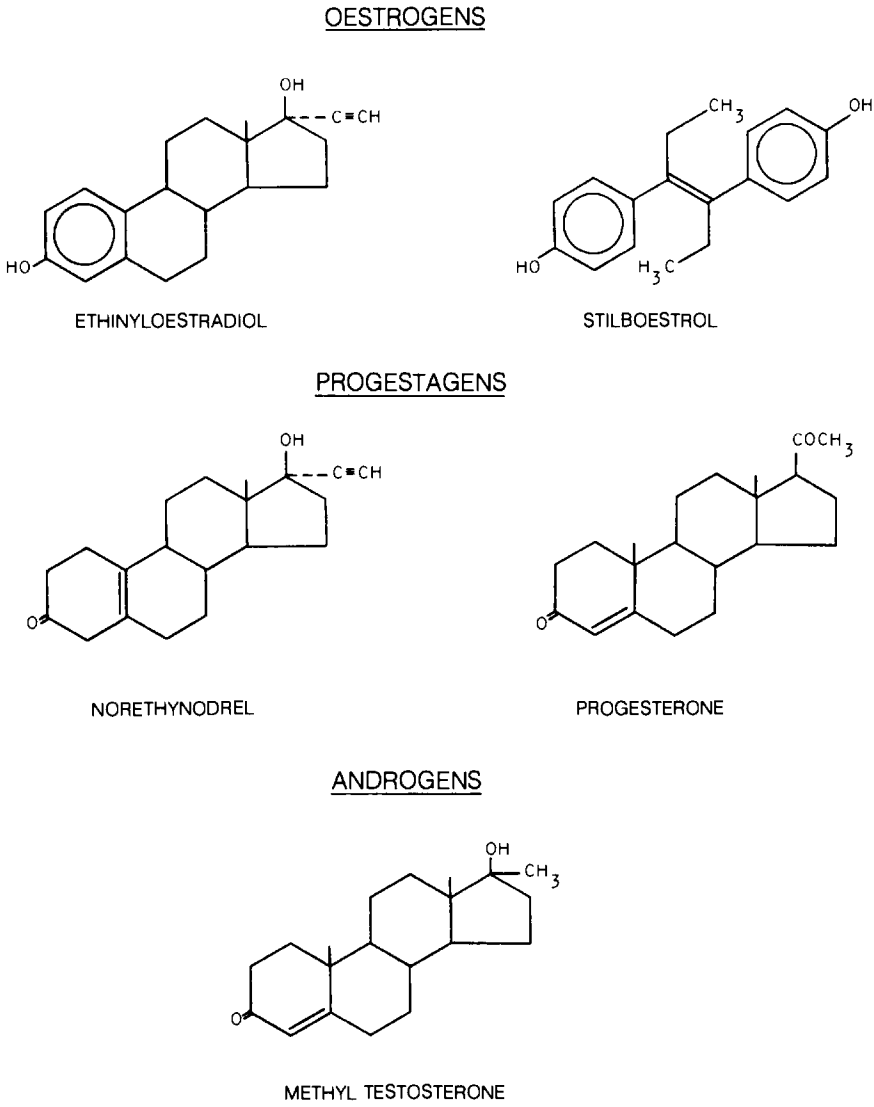

FIG. 1 Structural formulae of some commonly used gonadal steroids.

mechanism of this cytotoxic effect is, at least in part, suppression of androgen secretion by the testis as the growth of prostatic carcinoma is enhanced by androgens.

Effects on blood lipids and arterial disease Oestrogens cause a relative increase

in the proportion of alpha to beta plasma lipoproteins and the low incidence of arterial disease in premenopausal women compared with men of a similar age has been attributed in part to this effect. However, oestrogens taken prophylactically by men who have established coronary artery disease do not prevent myocardial infarction, and in patients with carcinoma of the prostate long-term high dose oestrogen therapy increases the prevalence of fatalities due to arterial disease.

Uricosuric effect Oestrogens increase the renal clearance rate of uric acid which may account for the low incidence of gout in premenopausal women.

DRUG FATE Oestrogens are rapidly absorbed from the bowel but the naturally occurring agents are rapidly metabolised in the liver to less active compounds. They are also in part excreted in the bile but are reabsorbed in the bowel, being excreted in the urine mostly as glucuronic and sulphate conjugates. As a consequence, they are relatively inactive orally, usually being administered as depot preparations i.m. The orally active agents are much more slowly metabolised, having a duration of action at therapeutic doses of over 24 hours. Little is known about their metabolism but, like the naturally occurring oestrogens, they undergo enterohepatic circulation. When given concurrently with other drugs they may slow the plasma clearance rate of drugs metabolised by liver microsomal enzymes, e.g. phenylbutazone and antipyrine. Conversely, enzyme inducing agents, e.g. rifampicin, may increase the rate at which they are inactivated and hence decrease their duration of action. The non-steroidal oestrogen, stilboestrol, is conjugated in the liver, excreted in the bile, and in the intestine is hydrolysed by bacterial flora undergoing enterohepatic circulation.

ADVERSE EFFECTS

Nausea and vomiting Oestrogens are potent emetic agents acting through receptors in the medulla. Men and pregnant women can tolerate much higher doses than non-pregnant women.

Feminisation Gynaecomastia and testicular atrophy occur when oestrogens are administered to men.

Fluid retention Oestrogens commonly cause some fluid retention with a gain of a few pounds in weight and often ankle oedema. In subjects with impaired ability to excrete sodium they may precipitate left ventricular failure.

Blood hypercoagulability Oestrogens increase the coagulability of the blood. They shorten the prothrombin time by increasing the plasma concentrations of factors II, VII, VIII, IX and X, and expedite the synthesis of factors VII and X especially. They also increase platelet adhesiveness and reduce fibrinolytic activity (for clinical consequences *see* below page 365).

Carcinogenesis Stilboestrol given in early pregnancy causes changes in the vaginal mucosa of female neonates (vaginal adenosis) and in a small proportion of affected subjects vaginal carcinoma develops in early adolescents. The coincidence of these changes with steroidal oestrogens has not been established.

Oestrogens enhance the growth of carcinoma of the breast in pre-menopausal women. There is also evidence that in genetically predisposed women, oestrogens alone cause endometrial hyperplasia and carcinoma of the endometrium.

CLINICAL USES

Indications: Replacement therapy At the menarche, oestrogens, usually in conjunction with progestogens, are prescribed for primary or secondary ovarian dysfunction. When the ovarian dysfunction is secondary to hypopituitarism, growth hormone should also be prescribed, otherwise oestrogens will cause premature fusion of the epiphyses and loss of 6–9 inches in potential height of the patient.

At the menopause, ovarian replacement may alleviate vasomotor symptoms such as flushing and heat intolerance and the atrophic changes in vulva and vagina as well as the loss of a sense of well-being that some women experience during this period of waning endogenous oestrogen production. Routine use of oestrogens at this time has been recommended as a means of prolonging youthfulness. There is no evidence that oestrogens prolong life and the dangers of thromboembolism and the other chronic adverse effects must be considered before using these agents for the relief of menopausal symptoms.

As anabolic agents Oestrogens given within six years of oophorectomy prevent osteoporosis, but there is no convincing evidence that they prevent postmenopausal osteoporosis.

Oral contraception—see below.

In carcinoma of the prostate and breast Oestrogens either alone, or preferably in conjunction with orchiectomy, induce a remission in a high proportion of patients with carcinoma of the prostate. Small doses are often sufficient to suppress androgenic hormone synthesis in patients whose testes are intact so that a dose of stilboestrol 1 mg 8 h or 5 mg once per day may be sufficient to cause tumour regression. They are also used in disseminated carcinoma of the breast in postmenopausal women when they induce a remission in a small proportion of patients.

In menstrual disorders Oestrogen/progestogen preparations are commonly used to normalise the menses in menstrual disorders.

The dose and duration of therapy varies with the clinical condition for which it is being prescribed, but as the risk of thromboembolism (*see* below, page 365) is related to the oestrogen dose, the smallest effective dose in any clinical situation should be used. During the ages when menstruation occurs,

Preparations

Oestradiol benzoate	1– 5 mg	i.m.	24–72 h
Ethinyloestradiol	30– 50 mg	oral	24
Mestranol	30–100 mg	oral	24
Diethylstilboestrol	3– 10 mg	oral	8

oestrogens are normally prescribed in a cyclical fashion to maintain a menstrual pattern. The choice of agent is usually determined by the rate of metabolism, and three orally active preparations are most widely used, there being no major differences between them.

Progestogens

As with oestrogens, there are some naturally occurring progestogens and a number of synthetic orally active preparations. There is some variability in the biological effects of the progestogens, some having weak oestrogenic effects, others weak androgenic effects, while some have anti-oestrogenic effects.

ACTIONS

Menses and pregnancy Progestogens cause secretory changes in the endometrium and vagina and changes in the mucopolysaccharides of the cervical mucus so that it becomes more viscid. These changes facilitate implantation of the fertilised ovum and prevent access to the uterus via the cervical canal. A fall in plasma progestogen, in conjunction with a fall in oestrogens, precipitates menstruation. Progestogens also decrease smooth muscle activity in the uterus and fallopian tubes. In high doses with oestrogens they impair luteinising hormone release from the anterior pituitary gland.

Oestrogenic effect Some progestogens have a weak oestrogenic effect and may impair FSH secretion, e.g. norethisterone, ethynodiol.

Androgenic effects Some progestogens have weak androgenic effects and cause mild virilisation e.g. norethynodrel, norethisterone.

Anti-oestrogenic effect Some progestogens, e.g. megestrol and hydroxyprogesterone caproate, are competitive antagonists of oestrogens and, by occupying oestrogen receptors in the hypothalamus, stimulate rather than suppress FSH production.

Cytotoxic effect Progestogens in high doses suppress tumour growth in a proportion of cancers of the endometrium.

DRUG FATE Progestogens are absorbed from the gut, but the naturally-occurring hormones are rapidly metabolised and undergo enterohepatic circulation. They are relatively inactive orally. Progesterone is given as an i.m. depot preparation. Pregnandiol is one of its main metabolites in the urine and measurement of this metabolite may be used to quantify endogenous progesterone secretion. The orally active progestogens are more slowly metabolised, but little is known about their fate.

ADVERSE EFFECTS Progestogens have few adverse effects. Acne and hirsutism may occur and be treated by changing to an agent with no virilising effects. Depressive episodes that commonly occur premenstrually have been attributed to progestogens, as have depressive episodes in women on the oral contraceptives (*see* below). There is some evidence suggesting that they have a teratogenic effect and so their use in the first trimester is best avoided.

CLINICAL USES Progestogens are used in combination with oestrogens or alone

in oral contraceptives, in menstrual disorders and in the treatment of endometriosis. They may be used to suppress tumour growth in carcinoma of the breast and uterus. Choice of agent is determined by the indication for prescribing the drug and the side-effects of the particular agents as outlined under actions (*see* above).

Preparations

	Dose (mg)	*Route*	*Dose frequency*
Progesterone	25–50	i.m.	24 h
Hydroxyprogesterone caproate	125–250	i.m.	24 h
Megestrol	2·5–5·0	oral	24 h
Norethynodrel	5–15	oral	24 h
Norethisterone acetate	1–4	oral	24 h
Ethynodiol diacetate	0·5–3·0	oral	24 h

Oral Contraceptives

The most frequent use of both oestrogens and progestogens is in oral contraceptive agents. In 1969, 18·5 million women in the world were using this form of contraception and the figure now is probably much higher. Both oestrogens and progestogens given alone have some contraceptive effect, but the most effective oral contraceptives are preparations in which both these agents are combined.

CONTRACEPTIVE EFFECT Effective contraceptive doses of oestrogens suppress FSH secretion and inhibit ovulation. While progestogens, especially the 19-nortestosterone derivatives, are also capable of suppressing LH and FSH production, they are effective contraceptives at doses below those necessary to do this. Progestogens, therefore, probably owe their contraceptive effects to the changes they cause in the endometrium and cervical mucosa and their ability to reduce smooth muscle activity of the Fallopian tubes and uterus.

When oestrogens and progestogens are used together in effective doses, the probability of conception occurring is negligible unless the woman forgets to take her tablets as prescribed.

ADMINISTRATION Steroidal contraceptives may be administered in two ways:

1. A combination of an oestrogen (ethinyloestrodiol or mestranol) and a progestogen for 21 days in a 28 day cycle.
2. Progestogen only preparation in which a progesterone is taken alone for 21 days in a 28 day cycle.

ADVERSE EFFECTS A large number of adverse effects have been attributed to oral contraceptive agents. However, these drugs are well tolerated on the whole and the incidence of serious effects is very low by comparison with other commonly consumed drugs. As the vast majority of women taking oral contraceptives are healthy, the acceptable frequency of adverse effects is lower

than for drugs used in the treatment of debilitating or life-threatening disorders. They are best considered in comparison with those of recurrent normal pregnancies as there is an increased incidence of many of the more serious side effects of these agents during pregnancy e.g. thromboembolic phenomena, hypertension, hepatitis and an appreciable maternal mortality. Furthermore, an unwanted pregnancy and an unwanted child cause psychological and social problems for the mother if they do not directly threaten her health.

MILD ADVERSE EFFECTS Nausea, break-through bleeding, breast pain and ankle oedema are quite common and normally attributed to the oestrogen component. They are treated by changing to a preparation with a low oestrogen content.

Acne, hirsutism and headaches are usually attributed to progestogens. They are treated by changing to a low dose progestogen or one with negligible androgenic activity, e.g. ethynodiol.

MODERATE AND SEVERE ADVERSE EFFECTS *Amenorrhoea* and secondary infertility occurs infrequently after stopping oestrogen/progestogen oral contraceptives and is commonest in women with irregular or infrequent periods before taking these preparations. It is almost invariably reversible, amenorrhoea seldom lasting more than three months.

Depression There is a higher incidence of depression and loss of libido in women taking oral contraceptives than in those using an intra-uterine device and it is highest in women with a history of premenstrual tension and depression during pregnancy.

Hypertension There is a small but statistically significant rise in systolic and diastolic blood pressure in women on oral contraceptives. In the great majority of cases it is reversible within three months of stopping therapy although, very occasionally, it may be associated with irreversible renal damage. The mechanisms producing this effect are not established but it occurs most commonly in those with a history of hypertension in previous pregnancies or in their families, in older women and in those who are overweight.

Obstructive jaundice A small proportion of women on oral contraceptives develop jaundice which is predominantly cholestatic in nature, although there may be histological and biochemical evidence of mild hepatocellular damage. Jaundice usually develops within three months of starting treatment, occurs most commonly in women with a past history of jaundice in pregnancy and is reversible, resolution occurring 1–8 weeks after stopping the drugs.

Thromboembolism There is an increased incidence of deep-vein thrombosis (DVT) and pulmonary embolus, cerebrovascular accidents and myocardial infarction in women on oral contraceptives compared with matched controls. These complications cause a small but statistically significant increase in mortality rates when the oestrogen content is 100 μg/24 h or greater. The

incidence of thromboembolic phenomena is related to the oestrogen content, the risk with 100 μg of ethinyloestradiol/24 h being twice that with 50 μg; to age, the mortality rates in the 34–44 age group being three times that in the 20–34 age group; and to blood group, the incidence of groups A, B and AB being three times that of group O. The effects of oestrogen-containing oral contraceptive agents last as long as the preparation is taken, but are reversible on stopping the drug. Progestogen-only contraceptives do not affect blood clotting or increase the incidence of thromboembolic phenomenon. However, they are less effective than combined preparations and are poorly tolerated because of the high incidence of menstrual disorders associated with them.

MISCELLANEOUS EFFECTS There is a higher incidence of gallstones and gall-bladder disease, cervical erosions and hepatocellular adenomas in subjects on oral contraceptives than in age-matched controls. These agents also cause a decrease in glucose tolerance occasionally precipitating glycosuria and they may precipitate acute attacks of both intermittent porphyria and prophyria cutanea tarda. They cause an increase in α_2-globulins, in thyroxin-binding globulin, protein-bound iodine and protein-bound cortisol.

Carcinogenesis There is no evidence in man or experimental animals that oral contraceptives increase the incidence of benign or malignant tumours.

Preparations

There are a large number of oral contraceptive preparations. The following are examples of these:

Combined Preparations

Oestrogen	*Progestogen*	*Dose/24 h*	*Tablets in 28 day cycle*
Ethinyloestradiol 50 mg	Norethisterone acetate	1, 2·5 or 4 mg	21
Ethinyloestradiol 50 mg	Ethynodiol diacetate	0·5, 1·0 mg	21
Ethinyloestradiol 50 mg	Megesterol acetate	4 mg	21
Mestranol 50 mg	Norethisterone	1 mg	21

Progestogen Only Preparations

Ethynodiol diacetate	0·5 mg	28
Norethisterone	0·35 mg	28

Androgens

Androgens are agents with similar actions to the male sex hormone testosterone. As with the other gonadal steroids, there is the naturally-occurring hormone testosterone and a large number of synthetic agents with androgenic activity. The androgens are much less used in therapeutics than are the oestrogens and progestogens.

ACTION

Development of the male secondary sex characteristics. In the prepubertal male, androgens cause an enlargement of the external genitalia, development of the adult male hair distribution and enlargement of the larynx with deepening of the voice. They also stimulate the growth of sebaceous glands of the skin.

Anabolic effects Androgens are potent anabolic agents. They are responsible, with growth hormone, for the growth spurt at puberty, and like oestrogens, without growth hormone, cause premature closure of the epiphyses and stunting of growth. They also cause growth of muscles and a positive nitrogen and electrolyte balance. Androgens stimulate erthropoetin production and increase the blood count of both the red and white cell series.

DRUG FATE Testosterone is rapidly metabolised and is inactive orally, as are a number of synthetic androgens. These agents are given as lipid depot preparations i.m. from which diffusion into the plasma is slow and the duration of action of days to weeks depending on the preparation. There are a small number of androgens that are more slowly metabolised and that are, as a consequence, orally active. Little is known of their metabolism.

ADVERSE EFFECTS

Virilism In women, androgens cause enlargement of the clitoris, deepening of the voice, hirsutism and acne.

Fluid retention Mild fluid retention may occur with a gain of a few pounds in weight and occasionally ankle oedema.

Hepatitis Many androgens are 17-alkylated steroids, e.g. methyl testosterone. These agents rarely cause jaundice, the predominant histological change being intrahepatic cholestasis, although there may be some hepatocellular changes. The jaundice is dose-related, usually starting some months after the commencement of treatment. It is commonest with oral preparations and is nearly always reversible.

Testicular atrophy In large doses androgens suppress FSH secretion and cause testicular atrophy.

CLINICAL USES

Replacement therapy At puberty, androgens may be used alone in primary testicular dysfunction and with growth hormone in testicular dysfunction secondary to pituitary failure. In elderly men, androgens are quite commonly administered as a treatment to prolong youthfulness. They may increase muscle power in elderly men, but they do not increase sexual potency or prevent the changes associated with ageing and will increase the growth rate of a pre-existing cancer of the prostate.

Anabolic effect Androgens may increase bone density, cause a positive nitrogen balance and perhaps prevent pathological fractures in osteoporosis. Their therapeutic effectiveness in these conditions however is not great and in many patients, especially women, does not justify their virilising side effects.

They are commonly taken by athletes to build up muscle bulk and athletic performance. The effects on health of this practice have not been evaluated.

Bone marrow aplasia In aplastic anaemia and conditions in which there is impaired bone marrow function, androgens may increase production of red and white cells and platelets. The mechanism of this action is not clear and these agents are usually only of value to milder cases.

Preparations

All androgens have some virilising and some anabolic effects, but there are differences in the ratio of these two effects within the group. Examples of androgens are shown below.

Drug	*Dose/24 h*	*Route*	*Dose frequency*	*17-Alkylation*	*Virilising*	*Anabolic*
Testosterone propionate	10–100 mg	i.m. in (in oil)	1–6 mths	–	++	++
Methyl testosterone	5–25 mg 10–50 mg	s.l.* oral	24 h	yes	++	++
Methandrostenolone	5–10 mg	oral	24 h	yes	+	++
Norethandrolone	10–30 mg 25 mg	oral i.m.	24 h	yes	+	++
Oxymethalone	5–15 mg	oral	24 h	yes	+	++
19-Nortestosterone phenylpropionate	25–50 mg	i.m. (in oil)	1 week	–	+	++

* s.l.: sublingual

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Chapter 29

Drugs in Pregnancy

The use of drugs in pregnancy is unique in that consideration has to be taken not only of the drug effects on the mother, but also of those on the fetus and gravid uterus.

Drug effects on the mother Apart from drug effects on uterine smooth muscle which are dealt with below (page 374), drug effects on the pregnant woman are similar to those on the non-pregnant woman. Exceptions to this rule are diuretics and hypoglycaemic agents. The pregnant woman, with an extracellular fluid volume and plasma volume approximately 50% above normal, is very sensitive to diuretics so that mild diuretics such as thiazides are those of first choice in pregnancy rather than more potent agents. The reverse is true with hypoglycaemic agents as pregnancy increases the dose requirement of both insulin and oral hypoglycaemic agents. This is of importance therapeutically as the incidence of complications of diabetes mellitus to mother and fetus are reduced by adequate control of the blood sugar.

Drug effects on the fetus Until fairly recently it was assumed that the fetus was impervious to effects of drugs administered to the mother as an impermeable placental diffusion barrier separated the maternal from the fetal circulation. It is now known that this is not the case and that drugs may have profound effects on the fetus at all stages of pregnancy.

Maternal-fetal drug transfer The placental barrier separating maternal placental sinus blood from that in the fetal placental capillaries, consists of the trophoblast, a layer of mesochymal cells and the fetal capillary endothelium. Like the gastrointestinal tract and the blood-brain barrier, the placental barrier has the properties of a lipid membrane and drug diffusion across it is by passive diffusion. The factors affecting passive diffusion of drugs across lipid membranes (*see* Chapter 2) are operative in the case of the placental barrier as elsewhere. The placental barrier differs from the blood-brain barrier in that the plasma protein concentration is equal on both sides of the barrier, so that although protein binding of drugs in the maternal blood lowers the concentration gradient and so slows diffusion across the barrier, it does not prevent equilibration between drug in maternal and drug in fetal blood. There is usually a maternal-fetal concentration gradient of drug metabolites as the fetal liver metabolises drugs much less rapidly than the maternal liver.

The placental barrier is generally more permeable to drugs than is the blood-brain barrier. Only highly charged, large molecules such as heparin or drugs that are very highly protein bound such as thyroxine, do not diffuse at all readily

across it. On the evidence of drug concentrations obtained at birth from the maternal venous and fetal venous cord blood, most drugs, even highly polar agents such as quaternary compounds, can diffuse across, although the rate at which they do so varies considerably. However, the drug concentration in fetal placental venous blood does not represent that in the tissues and equilibration between drug in the maternal blood stream with that in the tissues is a relatively slow process, being limited by the fact that only a proportion (40%) of the blood leaving the fetal heart is carried directly to the tissue, the remainder returning to the placenta capillary bed via the placental artery (Fig. 1).

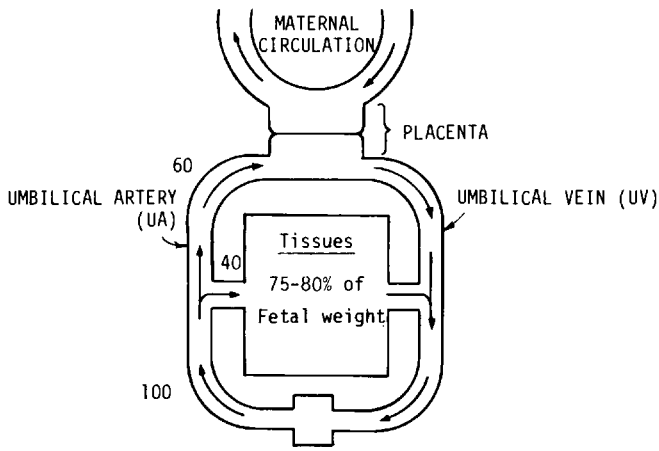

FIG. 1 Schematic representation of the maternal-fetal circulation. Drugs cross the placental barrier into the umbilical vein (UV) to the heart and lungs. Sixty percent of the fetal cardiac output returns to the placenta via the umbilical artery (UA) the remaining 40% being delivered to the tissue which represents 75–80% of the fetal body weight. Thus the concentration gradient for drugs that reach the fetus is UV > UA$\gg$ tissues and if the maternal plasma concentration remains constant there is considerable delay before the concentration in fetal tissues equilibrates with that in maternal blood.

Note that only 40% of the blood in the umbilical vein flows directly to the fetal tissues.

It has been calculated that for highly lipid soluble drugs, such as the short acting anaesthetic agent thiopentone, equilibration between drug in maternal blood and that in fetal tissues is only achieved after one hour if the concentration is maintained constant in the maternal blood. For most drugs, therefore, that do not diffuse across lipid membranes as readily, the process of equilibration must take several hours.

Drug Effects in the First Trimester

Teratogenic effects

Teratogenic effects of drugs are malformations of the fetus due to drug exposure *in utero*. There are major difficulties in determining the teratogenic effect of drugs in man as drugs are only one of a number of potentially teratogenic environmental factors (e.g. maternal viral infections and X-rays) to which the fetus may be exposed. The incidence of all fetal malformations is around 2% of all pregnancies and in many instances, when there is a serious fetal abnormality, the pregnancy terminates by spontaneous abortion or miscarriage. Furthermore, it is often difficult for a mother to remember all the drugs she may have had at the early, critical stage of pregnancy. There is no reliable animal model to allow prediction of teratogenic effects in man and in general humans are more resistant to such effects than are laboratory animals.

Factors determining teratogenic effects of drugs

Time of exposure Organogenesis in the human fetus starts at around the 20th day of gestation and terminates around the 60th day. It is during this period that drugs and other agents may induce teratogenic effects. For the woman with normal periods who becomes pregnant, the time when she is susceptible to the teratogenic effects of drugs begins about one week after she has missed her first period. As a high proportion of women are not able to accurately predict the time of their periods, there is a considerable risk of such women taking drugs at a time when they do not know they are pregnant.

The nature of the fetal abnormality alters with the time of exposure, e.g. with the minor tranquilliser thalidomide (which was withdrawn on account of its teratogenic effects in the early 1960s), exposure at 21–22 days was associated with absence of external ears and cranial nerve palsies, whereas limb changes, total absence or vestigeal limbs occurred if the mother took the drug on the 24–29th day of gestation. There are considerable interindividual differences in sensitivity to these effects, e.g. only 25% of children born to women exposed to thalidomide suffered from deformities.

Drugs

Because of the difficulties of determining the teratogenic effects of many drugs, there are only a few which are established as being teratogenic and a large number that are suspected of being so.

Cytotoxic drugs All cytotoxic drugs may induce fetal abnormalities and induce an abortion. The anti-metabolites, e.g. methotrexate, 6-mercaptopurine, azothioprine, seem particularly effective in this respect.

Progestogens and androgens One of the first drug-induced teratogenic effects to receive medical attention was the virilisation of the fetus, with enlargement of the clitoris and fusion of the labia, that occurred when progestogens (19-

nortestosterones) with some androgenic activity, were administered during pregnancy for threatened abortion. Androgens may also induce such changes. As yet, there is no evidence that contraceptive agents cause fetal abnormalities, but stilboestrol taken during the first trimester causes vaginal adenosis in the fetus and in a number of cases the offsprings of treated mothers have developed vaginal carcinomas at puberty.

There exist a large number of agents about which there is only circumstantial evidence concerning their teratogenicity in man. There is a 2–3-fold increase in the incidence of fetal abnormalities in children of epileptic mothers on anti-convulsant drugs and this increased incidence has been attributed to phenytoin. A small increased incidence of fetal abnormalities has been attributed to maternal treatment with warfarin, imipramine and chlorpromazine and oral hypoglycaemic agents, salicylates, barbiturates, iron preparations, antacids and some vitamins. In each incidence the evidence implicating the drug is tenuous and not sufficient to label any of these agents as definite teratogens in man.

Prescribing during the first trimester Because of the uncertainty concerning the teratogenicity of many established drugs and all new drugs, it is best for the mother to avoid all drugs during the first trimester from the time she misses her first period or experiences symptoms of pregnancy. When the mother is ill, the necessity of prescribing is determined by the severity of the illness, the effects of drugs on the fetus being considered along with other adverse drug effects. When drug therapy is judged necessary it is best to use a well-established agent rather than a newer drug, unless the latter has unique effects.

Drugs During the Second and Third Trimester

The effects of drugs on the fetus during the second and third trimester are often similar to those on maternal tissues, but the consequences are different. For example, anticoagulants may cause intrauterine haemorrhage with intrauterine death and spontaneous abortion; anti-thyroid drugs, such as carbimazole, may cause goitre formation which may be large enough to affect labour or obstruct the airway at birth; reserpine and propranolol may cause fetal bradycardia and perhaps impair fetal circulatory responses during delivery and the first few hours of life; reserpine also causes nasal stuffiness and drowsiness in the neonate. Streptomycin may impair vestibular function and this may not be detected in the child until years later; tetracyclines may stain the primary dentition and cause hypoplasia of the enamel.

Drugs to which the mother is addicted may also have profound effects on the fetus or neonate. Infants born to alcoholic mothers commonly have a low intelligence and disorders of extraocular movements. Infants born to mothers addicted to heroin often develop withdrawal symptoms within 18 hours of delivery. Characteristically, the infant has an irritable cry and develops diarrhoea which may be sufficient to cause fluid depletion. As heroin is present in

breast milk in appreciable amounts, such infants should not be breastfed. Heroin withdrawal symptoms respond to chlorpromazine given for 1–2 weeks.

Drugs at Term

During parturition, the fetus first breaths for itself and becomes independent of the maternal blood supply. It is therefore only at this period that possible drug effects on respiration and circulation have to be considered, especially as many of the drugs administered to the mother during labour may affect fetal respiration, e.g. narcotic analgesics, sedatives, local and general anaesthetics and muscle relaxants. However, it is a commonplace observation that a lively infant is delivered of a comatose mother, e.g. at caesarian section. The explanation for this is based on the pharmacokinetic considerations dealt with on page 371, in that equilibration between maternal blood and fetal tissues is slow for even highly lipid soluble drugs such as the short-acting barbiturates and for most drugs takes several hours. For instance, the peak depressant effect of narcotic analgesics on neonatal respirations occurs if delivery occurs 4–6 hours after the mother first received the drug. For ionised drugs such as the quaternary agents curare and suxamethonium that are administered to the mother for short periods only, diffusion across the placental barrier is so slow as to give insignificant tissue concentrations in the fetus.

The effect of drugs that reach the fetal circulation at term may have a prolonged effect on the neonate because of the poorly developed drug metabolising and excreting mechanisms (*see* Chapter 42). Furthermore, some drugs inhibit hepatic conjugation processes, including bilirubin conjugation. As a consequence, bilirubin accumulates in the plasma and central nervous system and if the concentration in the basal ganglia is sufficiently high kernicterus develops. Examples of drugs inhibiting bilirubin conjugation are sulphonamides, menadione (vit K) and bishydroxycoumarin. Acidic drugs may displace bilirubin from plasma binding sites and again facilitate its diffusion into the central nervous system (*see* Chapter 9).

Drug Effects on the Uterus

Oxytocin Oxytocin is a polypeptide hormone derived from the posterior pituitary gland. Oxytotics are drugs that increase motor activity of uterine smooth muscle.

ACTION

The uterus Oxytocin causes an increase in the frequency and force of uterine contractions by a direct action. This effect is more pronounced on the gravid than non-gravid uterus and the uterus is most responsive at term. It is used in the medical induction of labour when it is capable of initiating forceful uterine contractions and cervical dilatation. Once labour has started it is seldom necessary to continue oxytocin administration.

The breast Oxytocin causes constriction of myoepithelium of breast tissue and may initiate lactation. This is of no therapeutic value.

DRUG FATE Oxytocin is digested by chymotrypsin and is inactive when swallowed. It is usually given i.v. but is also readily absorbed from the buccal mucosa. It is rapidly degraded by enzymes in the liver, kidney, uterus and placenta and has a half-life of only 10 minutes after i.v. bolus injection. Insignificant amounts are excreted unchanged in the urine.

ADVERSE EFFECTS These are related to giving too much oxytocin which may cause excessive contractions and eventually a sustained increase in uterine tone (hypertonus), fetal hypoxia and death of the fetus. Given during labour it may delay labour by causing forceful contractions around the emerging fetus.

In large doses, oxytocin causes vasodilation and hypotension, but this is seldom of clinical importance. It also has an anti-diuretic effect in large doses.

ADMINISTRATION i.v. oxytocin is given by continuous infusion starting with a low dose (5 μg/min) and increasing the dose at regular intervals (15–30 min) according to the progress of labour. It is desirable to monitor the fetal response to the oxytocin-induced contractions and to reduce the dose if distress, occasioned by fetal hypoxia, is evident.

Prostaglandins Prostaglandins E_1, E_2 and $F_{2\alpha}$ all cause uterine contractions similar to those induced by oxytocin. They are more effective at term than earlier in pregnancy, but are more effective than oxytocin at inducing abortion in pregnancies of 9–28 weeks duration. As with oxytocin, hypertonus only occurs at high doses. They have the advantage over oxytocin in that they have no anti-diuretic effect.

Prostaglandins are usually given by i.v. infusion as they have a very short duration of action and their effects are monitored as for oxytocin. Vomiting and diarrhoea are the most common side effects but these usually only occur after high doses.

Ergometrine Ergometrine is one of a number of ergot alkaloids and is the most selective oxytotic agent.

Effect on the uterus Ergometrine causes an increase in the force and frequency of uterine contractions in small doses and in higher doses a prolonged hypertonus. As with the other oxytotics, the gravid uterus at term is much more responsive than earlier in pregnancy or the non-pregnant uterus. Ergometrine readily induces uterine hypertonus and fetal hypoxia and is not used therefore to induce labour. Given after delivery of the placenta, it is most effective at minimising post-partum haemorrhage.

Other effects Ergometrine has little vasoconstrictor effect in therapeutic doses. Very occasionally, after i.v. administration, an acute rise in blood pressure has been observed. It has negligible alpha-adrenergic blocking activity.

DRUG FATE Ergometrine is active orally, but is most commonly given i.m. or i.v. The duration of action is much longer than with oxytocin, lasting 30–40

minutes after therapeutic doses i.m. There are no details concerning its metabolic fate, but it is assumed that, like ergotamine, it is metabolised by the liver.

ADVERSE EFFECTS Ergometrine may cause a retained placenta if given prematurely. In a multiple pregnancy, early administration may cause fetal retention with intrauterine fetal death.

ADMINISTRATION Ergometrine is usually given i.m. (0·2–0·3 mg) immediately after delivery of the placenta to all patients. Repeated doses may be necessary in cases of post-partum haemorrhage. In some instances, ergometrine is given orally three times a day for 7–10 days post-partum to increase the rate of uterine involution.

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Chapter 30

Drugs in the Treatment of Gastrointestinal Disorders

DRUGS IN THE TREATMENT OF PEPTIC ULCERATION

Gastric and duodenal ulcers are common causes of morbidity and mortality and the drugs used in their treatment are amongst the most widely consumed of all drugs. The pathogenesis of peptic ulceration is not well understood but gastric acid is thought to play a central role in that, although there is no characteristic abnormality of gastric acid secretion in either benign gastric or duodenal ulceration, neither condition occurs in subjects with achlorhydria. Moreover, procedures such as vagotomy and drugs that reduce gastric acid secretion and concentration, relieve the principal symptom of peptic ulcer, epigastric pain, and may expedite the rate of ulcer healing.

Hydrogen ions in gastric acid secretions are ultimately derived from carbonic acid in the blood. They are secreted by gastric parietal cells as hydrochloric acid and in normal subjects the pH of gastric contents between meals is 1–1·5. HCl has no digestive role itself but it maintains the gastric pH during digestion within a range (1–4) in which the proteolytic enzyme pepsin is most effective. Gastric acid and pepsin secretion is increased by vagal stimulation and by the polypeptide gastrin, which is released by both chemical and mechanical stimuli to the antral mucosa. Quantitatively, the vagus is the more important of these two factors and vagotomy eliminates basal acid secretion and greatly reduces the response to gastrin. Histamine also stimulates gastric acid secretion, an action that is mediated by H_2-receptors and it is possible that local histamine release is the final common pathway in gastric acid release as H_2-receptor antagonists are capable of reducing gastric acid secretion to the same degree as vagotomy. Drugs used clinically to reduce gastric acidity act by neutralising gastric acid, by reducing the response to vagal stimulation or by blocking H_2-receptors.

Antacids

Antacids are weak bases that act by neutralising gastric acid. They are commonly effective at relieving the symptoms of peptic ulcer and in large doses may expedite the rate of ulcer healing.

Sodium bicarbonate The most alkaline antacid, it acts rapidly as it is very soluble in the stomach contents and reacts with the HCl forming carbon dioxide, salt and water, and the CO_2 is released.

$$NaHCO_3 + HCl \longrightarrow NaCl + H_2O + CO_2$$

Sodium chloride does not neutralise the sodium bicarbonate present in the pancreatic secretions and as a consequence this is reabsorbed in the small bowel.

ADVERSE EFFECTS 1 g of sodium bicarbonate contains 12 mmol of sodium and bicarbonate. The increase in the extracellular fluid volume that even small amounts cause may be sufficient to produce peripheral or pulmonary oedema in patients with an impaired capacity to excrete sodium ions or cardiopulmonary insufficiency.

A metabolic alkalosis occurs with sodium bicarbonate. In patients with a high calcium intake due to concomitant milk or calcium carbonate ingestion, this combination may cause soft tissue calcification, the 'milk-alkali syndrome', in which renal failure, due to nephrocalcinosis, is the most serious consequence and may be irreversible.

CLINICAL USE The systemic effects of sodium bicarbonate are likely to cause more adverse effects than occur with other antacids. Notwithstanding this, it is contained in many proprietary antacids.

Calcium carbonate is insoluble and reacts with HCl in the stomach to form calcium chloride. Calcium chloride is soluble and some is absorbed from the small bowel and colon, although the proportion of a total dose of calcium absorbed is small. In the duodenum, calcium carbonate is reformed as a result of the reaction between sodium bicarbonate and calcium chloride so that there is only a slight increase in hydroxyl ions reabsorbed which produces a slight increase in urine pH values. The duration of action of calcium carbonate is longer than that of sodium bicarbonate owing to its relative insolubility in the stomach.

ADVERSE EFFECTS *Constipation* is an invariable effect, the mechanism for which being poorly understood. This effect may be antagonised by magnesium salts and the use of a fixed-dose combination of these two antacids is common practice.

Soft tissue calcification is only a problem if high doses are used, e.g. 2–4 g per hour for prolonged periods or when sodium bicarbonate is administered concomitantly.

Acid rebound occurs in the stomach after calcium carbonate administration and is associated with an increase in serum gastrin which does not occur with other poorly absorbed antacids. Its clinical importance has not been fully evaluated.

Magnesium salts Magnesium hydroxide and magnesium trisilicate are similar to calcium carbonate in being insoluble and in forming a soluble chloride, magnesium chloride, in the stomach. This in turn neutralises sodium bicarbonate in the duodenum and magnesium carbonate is formed. Magnesium carbonate, unlike calcium carbonate, is soluble but not absorbable and acts as an osmotic bulk laxative. Magnesium trisilicate is no more effective than other

antacids and it seems unlikely that its therapeutic effect is dependent on it forming a tenacious protective layer over an ulcer which is impermeable to hydrogen ions and pepsin.

ADVERSE EFFECTS *The laxative effect* of magnesium salts is antagonised by coadministration of aluminium or calcium salts. Magnesium salts are commonly used as laxatives (*see* below).

Magnesium accumulation 15–30% of a dose of magnesium salts is absorbed from the bowel and excreted in the urine. Accumulation only occurs in patients with renal failure who receive large doses (2–4 g/h) for long periods. Magnesium ions cause neuromuscular blockade with depression of reflexes and ultimately respiratory paralysis.

Silicate stones may result from long term administration of magnesium trisilicate.

Aluminium hydroxide Aluminium hydroxide is also similar to calcium carbonate in being poorly soluble and forming aluminium chloride in the stomach. It is not such an effective antacid as calcium carbonate or magnesium hydroxide since its chloride is a more acid salt than the chlorides of calcium and magnesium. Aluminium hydroxide has an antipepsin effect independent of its effect on gastric pH but it is doubtful whether this contributes to its therapeutic effect. It neutralises bicarbonate in the duodenum and there is only a slight systemic alkalinising effect. A number of insoluble basic aluminium salts are formed in the small bowel.

ADVERSE EFFECTS *Constipation* Like calcium salts, aluminium hydroxide causes constipation.

Hypophosphataemia Aluminium forms insoluble phosphates in the bowel and reduces phosphate absorption. It is used for this purpose in the treatment of the hyperphosphataemia of renal failure and in the treatment of phosphate stones. Chronic administration of high doses may cause hypophosphataemia with anorexia, weakness and osteomalacia, characterised by a low plasma and urine phosphate concentration, a raised plasma alkaline phosphatase and a high urine calcium.

Drug absorption Aluminium hydroxide reduces absorption of iron salts and of tetracyclines.

Aluminium toxicity Small amounts of aluminium are absorbed and if large doses are administered to patients with renal failure on chronic dialysis, aluminium may accumulate in the tissues and cause an encephalopathy.

Tripotassium dicitratobismuthate This is a recently introduced bismuth salt with antacid and antipepsin activity that forms a layer of bismuth oxide over ulcer tissue. It has been shown to relieve symptoms and to expedite healing of both gastric and duodenal ulcer, but there is no clinical trial evidence comparing it directly with other antacids. Five ml are administered with 15 ml of water as

required. It has negligible toxicity but is much more expensive than ordinary antacids.

Antacid therapy Antacids are best given 1 hour after meals and on retiring to bed when they increase the gastric pH for up to 3 hours. When administered to relieve symptoms, the dose, dose frequency and choice of agent are adjusted according to the symptomatic response. In high doses, antacids may increase the rate an ulcer heals. A typical 'high dose' regime is 20 ml (1 tablespoonful) of a magnesium–aluminium mixture given 1 and 3 hours after meals and on retiring to bed.

Choice of agent depends on the *in vitro* neutralising capacity, the sodium content and the price, the ideal agent being an effective base with negligible sodium content and a lower price. Many proprietary preparations contain a minor tranquilliser, although there is no clinical trial evidence to justify the use of these drugs in the treatment of peptic ulcers.

Antacids also give symptomatic relief in hiatus hernia and peptic oesophagitis. Apart from their antacid action, they also raise the tone of the oesophago-gastric sphincter and this may contribute to the beneficial effect in these conditions.

The dose shown under preparations is only a guide to the size of dose of each agent given alone. If a combination of magnesium salts with either aluminium hydroxide or calcium carbonate is given, the proportions of each may be varied according to the effect on bowel function.

Preparations

	Dose	*Dose interval*
Sodium bicarbonate	1–4 g (12–48 mmol)	2–6 h as necessary
Calcium carbonate Magnesium hydroxide Magnesium trisilicate Aluminium hydroxide	1–4 g	2–6 h as necessary

Antimuscarinic agents

The cholinergic receptors of the intestine are muscarinic in nature and may be inhibited by atropine and related antimuscarinic agents. Antimuscarinic agents do not abolish the effects of vagal stimulation but they reduce gastric acid and pepsin secretion, reduce gastric motility and delay gastric emptying. Doses sufficient to produce these effects do not alter gastric pH as the volume of gastric secretions is also reduced, but they do produce obvious side effects (*see*

Chapter 10) of which dry mouth, tachycardia, blurring of vision and urinary retention are the most common. Used alone, antimuscarinic agents are of little value in peptic ulceration.

CLINICAL USE Antimuscarinic agents are usually added to an antacid regime when the latter has not proved adequate alone, as these agents often enhance the effectiveness of antacids, presumably by delaying gastric emptying. Quaternary compounds such as propantheline or poldine (*see* Chapter 10) are the drugs of choice as they have little or no effects on the eyes. They are administered 3–4 times a day, the dose (e.g. 15 mg propantheline) being increased until symptoms are relieved or side effects become intolerable.

Carbenoxolone sodium

ACTION Carbenoxolone sodium is a triterpenoid derivative of liquorice which has been shown in double-blind controlled clinical trials to expedite the rate of healing and the relief of symptoms of gastric ulcers in ambulant patients. It also increases the rate of healing of duodenal ulcers.

The mechanism of action of carbenoxolone sodium is not established. It has mineralocorticoid activity that is antagonised by spironolactone but this aldosterone antagonist also antagonises its therapeutic effect. Carbenoxolone has some anti-inflammatory activity and in animals this activity is reduced by adrenalectomy.

DRUG FATE Carbenoxolone sodium is orally active and in the plasma a high proportion is bound to albumin. It is only slowly conjugated by the liver and is excreted almost exclusively in the bile, less than 1% appearing in the urine. It undergoes extensive enterohepatic circulation.

ADVERSE EFFECTS *Sodium retention* Mineralocorticoid activity causes sodium retention and may precipitate oedema and left ventricular failure in patients with impaired ability to excrete sodium or cardiopulmonary insufficiency.

Hypokalaemia associated with muscle weakness is also quite common so that plasma electrolytes should be monitored during therapy and potassium replacement therapy initiated if necessary. A thiazide or frusemide are effective at counteracting fluid retention without counteracting the therapeutic effect.

Other derivatives of liquorice Liquorice contains glycyrrhizinic acid, the precursor of carbenoxolone, which has actions similar to those of carbenoxolone. Liquorice from which glycyrrhizinic acid has been removed, (deglycyrrhizinised liquorice) also expedites the rate of healing or gastric ulcers without having the mineralocorticoid side effects of carbenoxolone or liquorice.

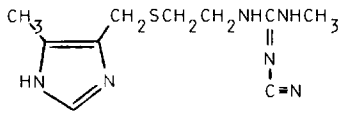
CLINICAL USE OF LIQUORICE DERIVATIVES Carbenoxolone (50–100 mg orally/8 h) is used in ambulant patients with gastric ulcers for as long as symptoms persist or until there is barium meal or endoscopic evidence of ulcer healing. The role of this drug in the prophylaxis of gastric ulcers is not established and in

duodenal ulceration it is not as well established as that of antacids or cimetidine. Mineralocorticoid side-effects are common and in the elderly and in subjects with impaired myocardial or renal function, it is best to use de-glycyrrhizinised liquorice and to monitor drug side effects carefully.

H_2-receptor antagonists

There have been three H_2-receptor antagonists administered to man, burimamide, metiamide and cimetidine. Both burimamide and metiamide may cause bone marrow depression and are therefore not available for clinical use but cimetidine has no such serious adverse effects and is the only H_2-receptor antagonist available for clinical use.

Cimetidine



Cimetidine inhibits gastric acid production stimulated by the vagus, by gastrin and by histamine. It reduces gastric acid in normal subjects and in patients with gastric and duodenal ulcers by the same degree as vagotomy.

FATE Cimetidine is orally active and 70% of an oral dose is excreted as unchanged drug in the urine, the remainder as hepatic metabolites. Its peak effect occurs in 1·5–2·0 hours and the drug's $t_{\frac{1}{2}}$ is approximately 2 hours in subjects with normal renal function. A single 200 mg dose produces achlorhydria for up to 6 hours and a 400 mg dose for 8 hours.

ADVERSE EFFECTS No serious adverse effects have been found for this drug during the first 2 years of its uncontrolled clinical use. Confusion is the most persistent effect and others include dizziness, diarrhoea and muscle pains. Gynaecomastia occurs rarely in males and a rise in serum creatinine and transaminases has also been reported.

CLINICAL USE For the treatment of duodenal ulcers and gastric ulcers cimetidine 200 mg three times during the day and 400 mg at night relieves symptoms and increases the rate of healing in up to 80% of patients but is no better in this regard than high dose antacids (*see* above). In doses of 400 mg at night or 400 mg night and morning, it prevents relapse of peptic ulcers in the majority of patients, most of whom relapse however, within six months of stopping therapy. Thus its place in the long-term management of peptic ulceration is not clearly established. A common pattern of usage is to use full doses for 1–2 months and then to give 400 mg at night for 6–12 months, using antacids in conjunction, but in low doses. Cimetidine is also of value in the management of reflux oesophagitis and in the prevention of stress ulcers. As it is a new compound, it should not be used in pregnant women or in lactating mothers.

Drugs in the treatment of peptic ulceration

Peptic ulceration is a disease of relapses and remissions and the objectives of therapy are to relieve symptoms during a relapse and, where possible, to expedite healing and to prevent relapse during a remission. Measures other than drug therapy are commonly beneficial. Stopping smoking has been shown to increase the rate of ulcer healing in the case of gastric ulcers and decrease the instance and severity of relapses. Food is a most effective antacid and small frequent meals raise gastric pH and help to relieve ulcer symptoms. Bed rest increases the rate of healing of gastric ulcers and the rate of symptomatic relief for duodenal ulcers.

Antacids are the first line drug therapy and if high doses do not give adequate symptomatic relief an antimuscarinic is worth a trial. Cimetidine is most likely to be of value in patients who have failed to respond to the much cheaper regime of antacids and anticholinergic agents. In ambulant patients with gastric ulceration, carbenoxolone sodium or de-glycyrrhizinised acid liquorice in conjunction with antacids should be tried. Therapeutic response is determined on the basis of the symptomatic response, but as the state of an ulcer cannot be determined from the symptoms alone, this should be obtained from barium meal and endoscopic evidence. Surgical treatment is undertaken in patients failing to respond to medical therapy or when complications such as perforation, pyloric stenosis and haemorrhage supervene.

ANTIEMETICS

Nausea and vomiting are symptoms very commonly encountered in clinical medicine and have many causes including disease of the gastrointestinal tract, motion sickness, chemical causes, e.g. emetic drugs, psychic causes, e.g. fear or excitement and unidentified causes.

The neuronal pathways involved in the vomiting reflex are only partially understood. The neuronal locus regulating vomiting, the vomiting centre, is situated in the lateral reticular centre, close to the vasomotor and respiratory centres. It receives afferent fibres from the vestibular apparatus, the chemoreceptor trigger area (a collection of neurones in the medulla close to the area postrema that is stimulated by emetics in the circulation) and from the gastrointestinal tract via the autonomic nervous system.

As the site of action of antiemetics is not clearly established, these drugs are classified clinically according to their ability to suppress motion sickness.

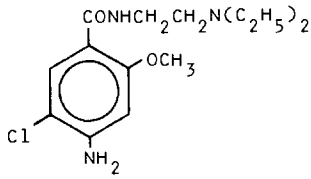
Motion sickness: antihistamines (H_1-antagonists), antimuscarinic agents
These are more effective than the phenothiazines or metoclopramide against motion sickness. The H_1-antagonists that are most effective in this regard are the piperazine, ethanolamine and phenothiazine derivatives. The piperazine derivatives meclizine and cyclizine are the most commonly used (*see* Chapter 39). L-hyoscine is the most effective of the antimuscarinic agents (*see* Chapter 10). Both groups of drugs have antimuscarinic activity and are thought to act by

reducing impulse traffic between the vestibular apparatus and the vomiting centre, possibly by blocking central cholinergic receptors. They are relatively ineffective against vomiting from other causes.

ADVERSE EFFECTS Drowsiness, dry mouth and blurring of vision may be more troublesome than the sickness itself. Agents are taken half to one hour before a journey, the duration of action of cyclizine and L-hyoscine (4–6 hours) being considerably shorter than that of meclizine (12–24 hours).

Other causes of vomiting: phenothiazines These agents, of which the highly lipid soluble compounds, e.g. perphenezine and trifluoperazine are the most potent, are effective against chemical stimulants of vomiting, e.g. apomorphine and morphine, cardiac glycosides and oestrogens, which act via the chemoreceptor trigger zone and against vomiting due to psychic causes. They are relatively ineffective against motion sickness, unless they also have antimuscarinic and antihistamine activity, against cupric sulphate, which is a direct stimulant of the vomiting centre, and when vomiting is the consequence of gastrointestinal disease, e.g. gastroenteritis or peritonitis. Extrapyramidal disorders are the most common adverse effects (*see* Chapter 14).

Metoclopramide



Metoclopramide is a derivative of procainamide with antiemetic activity. It probably acts by blockade of central dopamine receptors. It prevents vomiting caused by the dopamine agonist apomorphine, which acts on the chemoreceptor trigger zone, and by cupric sulphate, which act on the vomiting centre. It also has a direct action on the gastrointestinal tract increasing bowel transit time and oesophageal tone. Clinically, it is as effective as phenothiazines against drug induced and post-operative vomiting but is probably less effective than antihistamines and antimuscarinic agents in motion sickness.

Metoclopramide is cleared from the plasma principally by metabolism but little is known of its fate in the body. Drowsiness is the commonest adverse effect and extrapyramidal disorders, similar to those attributed to phenothiazines, occur but are infrequent, although they may occur after only small doses. As metoclopramide expedites gastric emptying it may increase the rate of absorption of drugs given concomitantly.

DRUGS IN THE TREATMENT OF DIARRHOEA

Diarrhoea, like nausea, is a common symptom of disease of the gastrointestinal tract, but may also be due to a large number of other diseases and conditions.

The drugs described in this chapter are not curative in any instance, acting only to relieve the symptoms of diarrhoea and colic.

Bowel motility The motility of the bowel is determined by the autonomic nervous system via the vagus (parasympathetic) and splanchnic (sympathetic) nerves, by a nerve network in the bowel wall itself and by compounds acting directly on bowel smooth muscle. The overall contractions of the bowel are 'propulsive' when they move luminal contents along the bowel, or 'mixing' when the contractions do not affect the position of the luminal contents. Bowel tone, i.e. whether the smooth muscle is contracted or relaxed, can be affected by drugs independent of their effect on propulsive movements.

In diarrhoea, the increase in the frequency of motions is usually associated with an increase in motor activity of bowel smooth muscle. Drugs may reduce this activity by a direct action on the muscles, by an alteration in autonomic tone or by indirect means.

There are three main groups of drugs used in symptomatic relief of diarrhoea:–

1. Antimuscarinic agents Vagal stimulation increases bowel muscle tone and increases both mixing and propulsive movements. Similar effects are achieved by cholinergic agents, e.g. methacholine and anticholinesterases. These actions are antagonised by atropine and related antimuscarinic agents, although even in maximally tolerated doses, atropine does not completely abolish vagal tone.

The use of antimuscarinic agents is limited by side-effects (Chapter 10) as doses that do not produce side-effects are seldom effective. Quaternary compounds, e.g. propantheline bromide and poldine, are commonly used as they cause fewer visual symptoms and no central side-effects.

2. Morphine and related compounds (*see* Chapter 19) Morphine increases the tone of bowel smooth muscle and the amplitude of 'mixing' contractions, but decreases 'propulsive' movements. The increase in muscle tone is partly antagonised by atropine.

Clinical use of morphine is limited by its high liability to abuse. It is often included in homeopathic doses with kaolin (e.g. 0·7 mg morphine in 10 mls of kaolin and morphine mixture BPC). In effective doses its use is restricted to the treatment of diarrhoea in the terminally ill.

Codeine phosphate is as effective as morphine and is orally active. It has few adverse effects, a low abuse liability and is cheap. It is a suitable anti-diarrhoeal agent in most situations, relieving colic at the same time.

Diphenoxylate is a synthetic derivative of pethidine with similar effects on bowel smooth muscle as codeine. Five mg is equivalent to 15 mg codeine phosphate. It has a low liability to abuse. In high doses in children after an accidental overdose, it causes respiratory depression that is rapidly antagonised by naloxone. Diphenoxylate is only available in the UK in tablet form with very small doses of atropine (2·5 mg + 0·025 mg atropine sulphate). Dry mouth,

nausea and dizziness occur more commonly than with equipotent doses of codeine phosphate.

3. Adsorbants Aluminium trisilicate (kaolin), the carbohydrate pectin and activated charcoal have in common the physical property of a large surface area and the ability to adsorb molecules in air or in solution. They are also effective anti-diarrhoea agents. Although their mode of action is not established it is generally assumed that they act by adsorbing chemicals in the bowel lumen that cause diarrhoea and by altering bowel flora.

Kaolin is the most widely used adsorbant and all such agents produce negligible side-effects as they are not absorbed. Kaolin is made up as a suspension, usually containing small amounts of morphine, the normal adult dose being 10 ml as required.

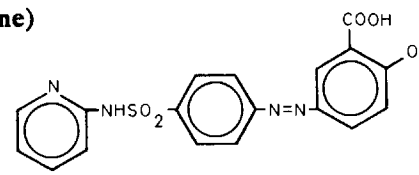
Choice of anti-diarrhoeal agent

Clinical comparisons of agents effective against common but frequently short lived symptoms such as nausea, vomiting and diarrhoea, that may have many causes, are very difficult. As a consequence, there is a dearth of clinical trial evidence on which to base a preference for one group of drugs as against another. In diarrhoea the negligible toxicity of the adsorbant agents makes them drugs of first choice, although their bulk is often inconvenient, e.g. when travelling. Codeine phosphate (15 mg) is an established and effective agent if adsorbants are ineffective, the dose and dose frequency being determined by the symptoms. Intestinal colic is commonly treated by an antimuscarinic agent.

Diarrhoea in Inflammatory Bowel Disease

Diarrhoea is one of the most troublesome symptoms of the common forms of 'idiopathic' inflammatory bowel disease, ulcerative colitis and Crohn's disease. Topical steroids in the form of retention enemas are used in the treatment of mild cases of ulcerative colitis, as their beneficial effect is seldom associated with systemic side-effects (*see* Chapter 27) when they are administered via this route. In severe relapses of ulcerative colitis and in Crohn's disease oral steroids are usually employed. In ulcerative colitis salicylazosulphapyridine is of value in reducing the rate of relapse.

Salicylazosulphapyridine (Sulphasalazine)



This drug is a combination of the sulphonamide sulphapyridine and aminosalicylic acid and was originally introduced for rheumatoid arthritis in the 1930s when that disease was thought to be due to a bacterial infection.

In ulcerative colitis, sulphasalazine (2–4 g/day) reduces the incidence of relapses but is of questionable (unproven) value in treatment of established diarrhoea. There have been some reports of its value in the treatment of Crohn's disease but its place in the management of this condition is not established. The mechanism of action is not understood but is probably not related to the antibacterial effect of the sulphapyridine and may be due to a direct action of the unchanged drug on the intestinal mucosa or to the anti-inflammatory action of the salicylate component.

Sulphasalazine is absorbed from the small bowel, excreted into the bowel by bilary secretion and hydrolysed by colonic bacteria to 5-amino-salicylic acid and sulphapyridine. The latter drug is absorbed via the colonic mucosa, acetylated by the liver and excreted in the urine, but most of the aminosalicylate is excreted unchanged in the faeces.

Adverse reactions to sulphasalazine are common, occurring in 20–50% of cases. The incidence increases with the dose and with the plasma concentration of sulphapyridine and is higher in slow acetylators than fast acetylators. Nausea, vomiting, headaches and rashes are the most common adverse effects; haemolysis, leucopenia and agranulocytosis are more serious effects.

Other drugs

Immunosuppressive agents A number of these agents have been used in both ulcerative colitis and Crohn's disease of which azathioprine (*see* Chapter 38) is now the most popular. The use of azothioprine in these conditions is similar to that in other conditions of unknown aetiology in which inflammation plays an important part in pathogenesis, e.g. rheumatoid arthritis, systemic lupus erythematosus and chronic active hepatitis. Its effects, which are similar to those of steroids, occur at doses liable to cause bone marrow depression. Azathioprine is therefore used only in severe cases in conjunction with steroids so as to avoid a high dose of either drug.

Metronidazole (*see* Chapter 35) This antibacterial agent, which is active against anaerobic bacteria, amoebae and trichomonas vaginalis, gives symptomatic relief in a proportion of patients with Crohn's disease. Its place in the therapy of this condition is not yet established.

DRUGS IN THE TREATMENT OF CONSTIPATION

Constipation is a decrease in frequency of defaecation. It is a very common symptom and as it is widely but erroneously held that constipation is a cause in itself of poor health, drugs taken in its relief (aperients or laxatives) are very widely consumed. Aperients relieve the symptom of constipation but do not affect its cause and their use in therapeutics is only logical if steps are also taken to identify and correct causative factors.

Bulk laxatives

Agents include fibre of plant origin, bran, agar psyllium, sterculia and ispaghula husks and the semisynthetic hydrophilic cellulose derivative methylcellulose.

They are all hydrophilic compounds which swell on contact with water, holding water in a gel-like form, hence increasing stool bulk. The increase in luminal contents stretches the bowel smooth muscle which in turn stimulates motility both mixing and propulsive. These agents also decrease faecal transit time.

Some of the components of fibre are broken down to short-chain fatty acids, hydrogen, carbon dioxide, methane and water, but as no pharmacologically active metabolites are absorbed, these drugs cause no systemic adverse effects. Very occasionally they may cause bowel obstruction.

The physiological mode of action of fibre commends these drugs as agents of first choice in the treatment of constipation. They usually take 8–18 hours to take effect and may be taken either morning or night and usually with a meal or in water.

Bulk laxatives are of established value in the symptomatic relief of diverticular disease and are probably of value in the irritable colon syndrome. There is some speculation that increasing the fibre component of diet decreases the risk of developing diverticular disease, haemorrhoids, varicose veins, inguinal hernias and colonic carcinoma, but there is as yet not proof that this is the case.

Saline laxatives

Saline laxatives are salts that remain in solution in the bowel lumen and by virtue of their osmotic effect increase the luminal fluid content and volume and, like the bulk laxatives, stimulate smooth muscle activity by stretching the muscle wall.

AGENTS *Sodium phosphate and sulphate, and potassium sodium tartrate:* in each case, the cations but not the anions are readily absorbed. Sodium salts are therefore contraindicated in situations when sodium excretion is impaired.

Magnesium hydroxide and *magnesium sulphate* are also effective saline laxatives. Magnesium is much less readily absorbed than sodium and is only liable to accumulate in subjects with severe degrees of renal failure.

CLINICAL USE Saline laxatives have a more rapid onset of action than bulk laxatives taking 3–6 hours to work and as a consequence are usually taken in the morning. They are unpalatable to some, but are safe compounds except in the circumstances outlined above.

LACTULOSE Lactulose is a mixture of the synthetic disaccharide fructose-1,4-β-galactoside, lactose and galactose, which is broken down by colonic bacteria to lactic acid and CO_2. It lowers the pH of the stools from 7 to 5 and has a cathartic action principally due to an osmotic effect. It is effective in relieving the symptoms of porto-systemic encephalopathy, lowering plasma ammonia levels by trapping ammonium ions (pK ammonia = 8·9) in the bowel as a consequence of its acidifying effect on the faeces. Lactulose is seldom used as a cathartic but may be used in addition to neomycin in the management of porto-systemic encephalopathy.

Irritant laxatives

Agents of this class stimulate colonic smooth muscle by a direct action.

Phenolphthalein This compound stimulates colonic smooth muscle by a mechanism that remains obscure, increasing both mixing and propulsive movements. Very little of an oral dose is absorbed. Less than 15% is excreted in the urine, mostly as conjugated metabolites, but an appreciable amount is excreted in the bile and undergoes enterohepatic circulation. The onset of action, 6–8 hours, is determined by the time taken by the drug to reach its site of action in the colon. At pH values above 8·0 phenolphthalein begins to turn red and alkalinisation of urine and faeces may be helpful in detecting 'laxative abuse' of this drug (*see* below).

ADVERSE EFFECTS Colicky abdominal pain is common as with any irritant laxative. Skin rashes may also occur, of which a fixed drug eruption is quite common, i.e. a rash, usually macula and irritant, that fades on stopping the drug, but recurs in the same sites on taking it again. Phenolphthalein is quite commonly abused, as with other irritant laxatives, and a rare adverse effect is a malabsorption syndrome.

Biscodyl A derivative of phenolphthalein, biscodyl differs from the parent compound only in so far as it does not turn red at alkaline pHs and is available in suppository and oral forms. Adverse effects are few but it has been implicated as a cause of malabsorption.

Anthraquinone laxatives

Laxatives of this group, of which senna and cascara sagrada are the most commonly used, are glycosides which, though inactive themselves, are hydrolysed in the colon, by colonic bacteria, to the active anthraquinone metabolite, emodin. Emodin is very poorly absorbed from the colon, stimulates the colonic smooth muscle directly or via the myenteric plexus and increases both mixing and propulsive movements. The rate of onset with these drugs is 6–8 hours and is determined by the time taken for the drugs to reach the colon and they are therefore taken at night.

ADVERSE EFFECTS Colic is common. These agents are the most commonly abused laxatives (*see* below). Emodin is a neurotoxin and the atonic colon that may result from chronic ingestion of anthraquinone laxatives has been attributed to this effect on the myenteric plexus. Other adverse effects are rare.

Other irritant laxatives, e.g. castor oil, that are more potent than those considered here, have no place in modern therapy.

Lubricant Laxatives

ACTION These agents facilitate defaecation by softening the stool. They do not increase bowel motility.

Liquid paraffin This time-honoured laxative is a mineral oil derivative of

petroleum. It is taken orally, is not absorbed and if it reaches the rectum in sufficient quantities will soften the stool and make defaecation easier. As it has no effect on bowel motility it is not indicated when constipation is associated with bowel hypomotility.

ADVERSE EFFECTS These are common and sometimes serious. Its failure to stimulate bowel motility may cause it to perpetuate constipation. Leakage of the mineral oil may occur and rarely, it may cause a foreign body granuloma in the anal area. In sufficient quantities it may cause impaired absorption of fat soluble vitamins, especially A and K and lipid soluble drugs. Lipid inhalation pneumonia has occurred in elderly patients.

CLINICAL USE The large number of adverse effects of liquid paraffin and its unphysiological mode of action should limit its use to situations in which constipation is associated with hard faeces or when straining at stool is potentially harmful to the patient.

Dioctyl sodium sulphosuccinate This is an anionic surface active agent which, like liquid paraffin, softens faeces but does not increase bowel motility. It is taken orally and takes 12–24 hours to be effective. In contrast to liquid paraffin, it has no serious adverse effects.

Laxative abuse

Dependence Laxative dependence is a common form of drug dependence. Its cause is most probably multifactorial but one of these is the undue haste with which laxatives are prescribed to treat constipation when simpler methods of bowel education, diet etc. may be adequate. For instance, in one study of constipation in elderly patients, 70% of the patients responded to a placebo. The use of laxatives is analogous to the use of hypnotics. The patient gains relief of the symptom constipation, without being cured of the underlying cause, but the effect only lasts as long as the drug is taken. Chronic drug dependence is the consequence.

Chronic laxative overdosage The irritant laxatives are the most commonly abused in this way. They are taken in large doses to produce one or often many motions a day, the patient usually presenting complaining of diarrhoea. The diarrhoea may be associated with biochemically detectable deficiency of sodium, water and potassium and occasionally is associated with muscle weakness and paralysis due to potassium deficiency. The diagnosis is often obscure as the patients seldom admit to laxative ingestion. In severe cases there may be radiological changes of loss of haustrations in the large bowel similar to those in ulcerative colitis. The condition has been fatal on occasions and on others has necessitated total colectomy, the principle morbid changes being loss of intrinsic enervation, atrophy of smooth muscle and melanosis coli. These changes have been attributed to the neurotoxicity of emodin.

Choice of laxative

Laxatives are indicated only when other methods have failed to relieve

constipation. It is best to start with a bulk laxative and resort to irritant agents when these have failed. Laxatives are best given in short courses because of the dangers of dependence and both doctors and patients alike should be made aware of the problems to which such apparently innocent drugs may give rise.

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Chapter 31

Hypoglycaemic Agents

Glucose metabolism The monosaccharide D-glucose is the principle source of energy inside normal cells. Glucose is manufactured in the liver from glycogen and is a highly polar water-soluble molecule. It does not readily diffuse across cell membranes to reach the intracellular sites of its utilisation and in most tissues it is transported across cell membranes by active carrier mechanisms. In skeletal and cardiac muscle and in adipose tissue, insulin is an essential cofactor to this carrier mechanism but in other tissues including the liver, the CNS (which takes 50% of glucose produced by the liver), peripheral nervous tissue, the gut, kidney and RBCs there are carrier mechanisms for glucose that do not require insulin.

In normal subjects insulin production is stimulated by a rise in plasma glucose so that blood glucose concentrations are maintained within fairly narrow limits. In diabetes mellitus, hyperglycaemia and glycosuria develop as a consequence of impaired glucose uptake by insulin dependent tissues. There are two patterns of insulin release in this condition (Fig. 1). In juvenile or growth-onset diabetes, hyperglycaemia is associated with reduced or absent insulin secretion, but in maturity onset diabetes, insulin secretion may be normal and is often increased.

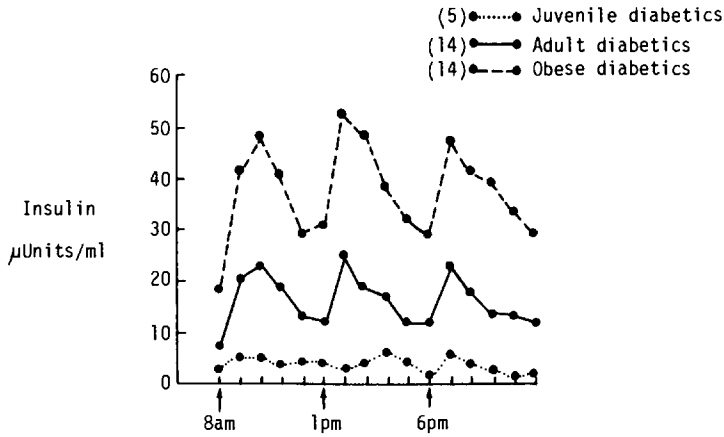


FIG. 1 Patterns of insulin release: comparison of the mean hourly plasma insulin concentration from 8 am to 12 pm in 5 juvenile diabetics, 14 adult diabetics weighing less than 120% of their ideal body weight and 14 adult diabetics weighing more than 120% of their ideal body weight. Meals are indicated by arrows. (From Genuth, 1973.)

These patients are usually obese and the impaired glucose uptake by the tissues is proably associated with tissue resistance to insulin.

The major complications of diabetes are ketoacidotic and hyperosmolar non-ketoacidotic coma, retinopathy and cataract formation, nephropathy, neuropathy and an increase in the incidence of cardiovascular, cerebrovascular and peripheral vascular disease. There is a reduction in fertility in untreated diabetic women and a marked increase in a number of complications of pregnancy including pre-eclamptic toxaemia and hydramnios and an increase in fetal and perinatal mortality.

The objective of therapy in diabetes mellitus is to maintain the blood sugar concentration as close to the physiological range as possible. There is good evidence that by so doing diabetic comas, both ketoacidotic and hyperosmolar, can be prevented and that symptoms associated with hyperglycaemia such as frequency of micturition, thirst, infections of the skin and urine etc., are reduced in frequency and severity. There is also evidence that in juvenile onset diabetes, the onset of retinopathy is delayed and its severity reduced in patients whose blood sugar is well controlled. Fertility in diabetic women increases when the blood sugar is maintained in the normal range, and during pregnancy control of the blood sugar causes a reduction in the incidence of complications and a marked improvement in the number of live infants born to diabetic mothers. The effect of therapy on the cardiovascular complications including nephropathy is not established. However, there is a widespread impression amongst diabetologists that close control of blood glucose is effective at preventing these complications but this has not yet been established in clinical trials.

Diet and hypoglycaemic agents are the therapeutic means whereby the blood sugar is controlled. All diabetics are encouraged to achieve or maintain a weight close to their 'ideal' and to limit severely their intake of purified carbohydrate and animal fat. Approximately one-third of all diabetics can be managed by diet alone, the remainder requiring insulin or an oral hypoglycaemic agent.

Insulin Insulin is a polypeptide with a MW of 6000 consisting of two chains of amino acids, an alpha and a beta chain, joined by two disulphide bridges. It has an isoelectric point of pH 5·3 and hence carries a net negative charge at physiological pHs.

ACTION Insulin facilitates glucose uptake by skeletal and heart muscle, adipose tissues and other insulin-dependent tissues. How it produces this effect is uncertain. Insulin binds to receptors on the cell surface and releases calcium from membrane-binding sites and it is possible that it produces allosteric changes in cell membranes increasing their permeability to glucose. Insulin also promotes the synthesis and inhibits the catabolism of glycogen, triglycerides and protein by stimulating various intracellular enzyme systems and it is possible that these are the consequence of its ability to increase the availability of intracellular calcium.

The biochemical consequences of a reduction in insulin production or of

tissue responsiveness to insulin is that alternative energy stores are utilised. Glycogen stores are depleted; protein catabolism occurs with gluconeogenesis and a negative nitrogen balance is established. There is a net breakdown in fat with lipolysis of triglycerides to free fatty acids and an increase in production of acetoacetic acid, α-ketobutyric acid and acetone. In severe cases, the biochemical and physiological changes may be sufficient to cause a metabolic acidosis, coma, fluid depletion and profound fluid and electrolyte disturbances. The principal effect of insulin in diabetes mellitus is to prevent this sequence of events and so prevent coma.

DRUG FATE Insulin, being a polypeptide, is rapidly broken down in the gastrointestinal tract and is therefore inactive orally. After i.v. administration it is rapidly converted to inactive metabolites by enzyme mediated and non-enzyme-mediated reactions, principally in the liver and kidney. It has a $t_{\frac{1}{2}}$ of 15–40 minutes. The apparent volume of distribution is similar to that of the extracellular space. Negligible amounts are excreted unchanged in the urine.

ADVERSE EFFECTS

Hypoglycaemia Overdosage is the most common and most severe adverse effect. It is associated with tiredness, dizziness, abnormal behaviour, hunger and faintness. Eventually coma may supervene with convulsions and irreversible brain damage or even death if hypoglycaemia is prolonged. There are many factors other than the insulin dosage that affect blood glucose concentrations. These include diet, exercise (which increases glucose uptake by skeletal muscles) and hormones such as adrenaline, cortisol and growth hormone that antagonise the effects of insulin on blood glucose. The physician has only partial control over a number of these factors and in some diabetics, despite meticulous attention to diet and insulin dosage and administration, control is inadequate and hypoglycaemic attacks are frequent. It is advisable to inform all diabetics of the symptoms of hypoglycaemia and to ensure that they always carry a supply of sugar.

Local reactions Erythema and itching at the site of injections are quite common initially and occasionally depigmentation and atrophy of the subcutaneous tissues occur. Rarely there is a typical type I allergic reaction to insulin with urticaria, bronchospasm and hypotension.

Resistance In some patients there is an increasing dose requirement which may result in the daily dose exceeding 200 units/day. In such patients there is nearly always an increase in the titre of insulin-binding antibodies which block the active site of the molecule and prevent it binding to its receptor. Insulin antibodies may have a much higher affinity for beef rather than pork or human insulin and the daily dose requirement can often be reduced very considerably by use of pork insulin only. Insulin antibodies also increase the plasma half-life of insulin by acting as a circulating depot of the hormone and so increase the dose interval of insulin therapy. Mono-basic, non-

immunogenic insulins are highly purified forms and the use of these is less likely to be complicated by insulin resistance due to antibody formation.

TYPES OF INSULIN Beef and pork insulin are available commercially in the UK either alone or in combination. The three forms of insulin set out below are also available in highly purified or mono-basic form. Insulin is given s.c. in maintenance therapy and as it is cleared very rapidly from the plasma its duration of action is determined by the rate of its release from s.c. depot sites. There are three forms in which insulin is available for clinical use:

1. In solution Soluble insulin, in a phosphate buffer pH 3·2, has a rapid onset (30 minutes) and a short duration of action (6–8 hours). Neutral soluble insulin has a pH 7·0 and identical pharmacokinetics.

2. Protein-bound Protamine zinc insulin is a depot preparation in which the predominantly negatively-charged insulin forms a complex with the predominantly positively-charged protein protamine, from which insulin is slowly released into the blood stream. Isophane (NPH) insulin is a form of protamine zinc insulin containing excess free insulin. Protamine zinc insulin has an onset of action of 7–8 hours and a duration of 36 hours. Isophane has an onset of action of 2 hours and a duration of 18–24 hours.

3. In suspension Insulin in suspension is achieved by preparing the insulin in an acetate buffer pH 7·2, the size of the crystals being determined by altering the constituents of the buffer.

Semilente—the crystals are small (amorphous), the onset rapid (1 hour) and the duration of effect intermediate (12–16 hours).

Ultralente—the crystals are large (crystalline), the onset slow (6–8 hours) and the duration long (36 hours).

Lente—is comprised of 3 parts semilente and 7 parts ultralente.

Combinations Soluble insulin may be mixed with isophane insulin before s.c. administration, but not with protamine insulin which has spare binding sites for soluble insulin and will thus prolong its effect. Lente insulins should only be mixed with neutral soluble insulin as any change in the pH of the depot site would cause a change in the size of the insulin crystals.

CLINICAL USE Insulin is mandatory in growth-onset diabetes and in those patients who fail to produce sufficient endogenous insulin. This obtains in the great majority of diabetics who develop the disease before 20. It is rarely needed in the maturity-onset diabetic as such patients seldom develop ketoacidosis. In maturity-onset diabetes it is required if hyperglycaemia is inadequately controlled by diet alone or by diet and oral agents. It should also be used to control the blood sugar of maturity-onset diabetics undergoing surgery or a severe illness and during childbirth.

ADMINISTRATION In diabetic coma and pre-coma and in situations in which rigid control of diabetes is desirable, e.g. during surgery or childbirth, soluble

insulin is administered, usually i.v. In diabetic coma the dose requirement is usually small 3–10 units/hour by continuous infusion if sodium, potassium and water replacement is adequate. In less severe forms of ketoacidosis, the insulin is given S.C., the dose being determined by the glucose concentration in blood and urine, the dose interval varying between 4–8 hours. Once the daily dose requirement is established a daily routine of soluble/isophane insulin or lente insulin given once or twice a day is usually adequate to maintain the blood sugar close to the physiological range throughout the 24 hours.

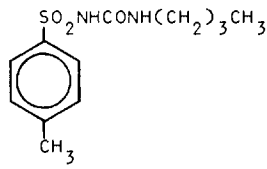
ORAL HYPOGLYCAEMIC AGENTS

Sulphonylureas

The sulphonylureas are a group of compounds that are weak acids and are derived from the sulphonamides. They have a common mode of action and they differ only in their pharmacokinetics and adverse reactions.

ACTION Sulphonylureas lower the blood glucose concentrations in normal subjects and in diabetics capable of insulin secretion. They are ineffective in 70% or more of diabetics aged 20 or less but in only 10% of those of 40 or more. Coincident with hypoglycaemia, sulphonylureas cause a rise in plasma insulin concentration so that their hypoglycaemic effect is due to a stimulatory effect on beta cells of the islet of Langerhans.

Tolbutamide



Tolbutamide is the oldest sulphonylurea and the least potent on a weight basis, but is well established clinically.

DRUG FATE Tolbutamide is well absorbed, its onset of action occurring within 1 hour and reaching a peak by 4–6 hours. It is partially bound to plasma albumin binding sites and may be displaced by other highly-bound acidic drugs, e.g. phenylbutazone, sulphonamides and aspirin. Tolbutamide is cleared from the plasma by hepatic metabolism, very little unchanged drug being excreted in the urine. The drug is oxidised by the hepatic microsomal enzyme system and 80% of an oral dose is excreted as the inactive metabolite carboxytolbutamide. The plasma half-life is around 4 hours and increases only slightly in subjects with severe hepatocellular damage. In view of the short half-life it is usually administered 6 hourly to maintain its action throughout 24 hours.

ADVERSE EFFECTS *An increase in appetite* is a side-effect common to all sulphonylureas which severely limits their usefulness, as an increase in weight

antagonises their hypoglycaemic effect. Their use in the obese maturity-onset diabetic is controversial (*see* below).

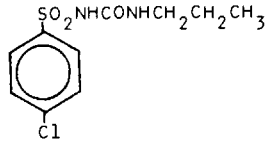
Hypoglycaemia is much less common than with insulin.

Gastrointestinal intolerance, rashes and haematological abnormalities occur in less than 3% of patients.

Drug interactions The action of the sulphonylureas and all hypoglycaemic agents is antagonised by glucocorticoids which increase glucose production from hepatic glycogen and by diazoxide and thiazide diuretics, which inhibit insulin secretion.

Drugs that displace tolbutamide from plasma albumin (*see* above) enhance its effect. Enzyme-inducing drugs, e.g. phenobarbitone, increase the rate of tolbutamide metabolism and therefore reduce the effectiveness of any given dose. Ethanol may do the same in the absence of hepatocellular damage. Conversely, tolbutamide metabolism is inhibited by a number of drugs including some sulphonamides and dicoumarol which increase the plasma half-life and enhance the hypoglycaemic effect.

Chlorpropamide



Chlorpropamide differs from tolbutamide in the following respects: only 50% is metabolished to inactive metabolites, the rest being excreted unchanged in the urine. The mean plasma half-life is 35–40 hours with a range of 28–70 hours. As appreciable amounts of unchanged drug are excreted in the urine the drug accumulates in patients with impaired renal function.

ADVERSE EFFECTS *Hypoglycaemia* is more common than with tolbutamide, especially in the elderly, and may be severe.

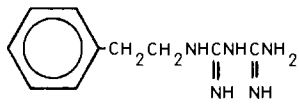
Adverse reactions are similar to those due to tolbutamide but are more frequent. Cholestasis occurs occasionally. Chlorpropamide may induce water retention and hyponatraemia through an antidiuretic hormone-like effect and is effective at reducing urine volume in diabetes insipidus. A number of other sulphonylureas have similar effects.

Ethanol intolerance In 10–30% of patients on chlorpropamide there is a syndrome similar to that caused by disulphiram with flushing, breathlessness, palpitations and sweating occurring within 10 minutes of ethanol ingestion.

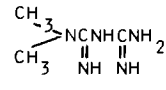
OTHER SULPHONYLUREAS Acetohexamide, tolazemide, glibenclamide, glibornuride and glipizide are alternative sulphonylureas available in the UK. They vary considerably in their potency (*see* preparations) but are similar in their pharmacokinetics, half-lives varying between 5 hours (acetohexamide) to 12 hours (glibenclamide). Pharmacologically they are identical to tolbutamide and

none cause ethanol intolerance. Glymidine is a sulphapyrimidine similar in its actions to the sulphonylureas, but as there is no cross sensitivity between these groups, it may be used in subjects who develop adverse reactions on a sulphonylurea.

Biguanides



PHENFORMIN



METFORMIN

The biguanides are oral hypoglycaemic agents containing two guanido groups sharing a common nitrogen atom. They are thus highly polar basic compounds. (N.B. diguanides contain two guanido groups but they do not share a common nitrogen atom.)

There are two biguanides in clinical use, phenformin and metformin.

ACTIONS Biguanides enhance the tissue responsiveness to insulin and hence only act in the presence of insulin. They reduce the insulin requirement in diabetics on insulin. Hypoglycaemia is not associated with a rise in plasma insulin.

The mechanism of action of biguanides is complex. They impair glucose absorption from the gut lumen, increase insulin uptake by the tissues *in vivo*, inhibit gluconeogenesis and the utilisation of pyruvate. *In vitro*, like insulin, they release calcium from membrane-binding sites. It is thus possible that these agents interact with insulin on the cell membranes of insulin dependent tissues.

DRUG FATE Little information is available on the fate of these compounds in the body. They are absorbed from the bowel with an onset of action within 1 hour and a duration of 4–12 hours depending on the size of the dose. The half-life of the parent compound is short (3–6 hours) and one-third of a dose of phenformin is excreted as hydroxy metabolites, the rest as unchanged drug. The dose should therefore be reduced in subjects with renal failure.

ADVERSE EFFECTS *Anorexia, nausea and vomiting* are common side-effects and in obese maturity-onset diabetics who have not lost weight on diet alone, these may be advantageous in helping them to lose weight. Hypoglycaemia is rare if these drugs are given alone. Both agents reduce B_{12} absorption and may cause a B_{12} deficiency syndrome.

Lactic acidosis occurs more commonly in diabetics on phenformin. In high concentrations *in vitro*, phenformin impairs anaerobic carbohydrate metabolism and in diabetic patients causes an increase in the plasma lactic acid concentration and in the lactate/pyruvate ratio. Lactic acidosis has many causes, e.g. congestive cardiac failure, renal and hepatic failure, chronic ethanol ingestion and it is most likely to be precipitated by phenformin in patients when one or several of these are operative.

CLINICAL USE OF ORAL HYPOGLYCAEMIC AGENTS The dose and dose interval of these agents are determined empirically, their effect on symptoms and the blood and urine sugar concentrations being monitored. The short-acting drugs such as tolbutamide and glymidine are administered initially 6 hourly and the long acting agents, e.g. chlorpropamide every 24 hours.

Indications In growth-onset diabetes biguanides may be used in combination with insulin to reduce the insulin requirement but this use is unusual.

In maturity-onset diabetes, oral agents are commonly used when diet alone has been inadequate to control hyperglycaemia. In diabetics who are not overweight, sulphonylureas are usually drugs of first choice, biguanides being the drugs of choice in the obese. In subjects whose response to high doses of either of these groups alone is poor, a combination may be effective.

The ability of oral hypoglycaemic agents to decrease the morbidity and mortality from vascular disease in maturity-onset diabetes has not been established. Indeed, in a prospective multicentre clinical trial carried out by twelve university centres in the USA (University Group Diabetic Program—UGDP) on a predominantly female and coloured population, morbidity and mortality was higher in patients on tolbutamide or phenformin than in those on a placebo or insulin. Although these findings have not been confirmed by other clinical trials, in the absence of evidence that they are beneficial other than in preventing diabetic coma, there are no clear guidelines regarding indications for these drugs and some physicians think they have no place in the treatment of diabetes mellitus. The concensus of clinical opinion in the UK, however, is that they are useful drugs, both improving the well-being and prognosis of maturity-onset diabetics, but they should only be used when dietary measures have failed.

Preparations

Drug	*Adult dose range (mg)*	*Dose interval (h)*
Tolbutamide	500–1000	6–8
Chlorpropamide	100– 500	24
Acetohexamide	500– 750	12–24
Tolazemide	100– 250	12–24
Glibenclamide	2·5– 30	24
Glymidine	500–1000	24
Phenformin	25– 50	8–12
Metformin	500–1000	8–12

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Chapter 32

Iron, Vitamin B_{12} and Folic Acid

Iron, vitamin B_{12} and folic acid (FA) are all constituents of the normal diet and replacement therapy is only required when dietary intake falls short of tissue requirements. This may be due to inadequate dietary intake, malabsorption, an increased tissue requirement or to excessive loss of one or more of these factors. Anaemia is the dominant clinical feature in the deficiency syndromes produced by each of these agents, but as they are all essential for the normal function of all cells, there is often evidence of dysfunction of cells other than those of the bone marrow.

Replacement therapy with iron, B_{12} and FA is usually straightforward and rewarding. However, the causes of deficiency are many, and often more radical therapy than replacement of the deficient factors is required, e.g. resection of a colonic carcinoma in iron deficiency; administration of a gluten-free diet in FA deficiency, etc. A full investigation of the cause of the deficiency therefore is mandatory either before or during replacement therapy. Furthermore, the duration of replacement therapy is determined by the cause of the deficiency and may be short, e.g. iron and FA replacement in pregnancy, or lifelong, as in B_{12} replacement in Addisonian pernicious anaemia.

IRON

ACTION Iron, in the ferrous form, is a component of haem and 60–80% of the total iron in the body (3–4 g) is incorporated into haemoglobin. Anaemia is the principal clinical feature of iron deficiency and is characteristically microcytic and hypochromic. Iron stores are depleted, there is a fall in plasma iron concentration, a rise in the total iron binding capacity (TIBC) of the plasma, and as a consequence, a fall in the extent to which iron-binding sites in the plasma are saturated.

Iron is also a component of myoglobin and of certain enzymes, e.g. the cytochrome enzymes, that are essential for normal cell function. Apart from a microcytic anaemia, chronic iron deficiency is associated with signs of dysfunction of cells of the gastro-intestinal mucosa, e.g. smooth tongue, stomatitis, cheilosis and a post-cricoid web and of epithelial cells, e.g. koilonychia. These signs may be evidence of the essential role of iron in metabolism of these tissues.

DRUG FATE

Absorption Dietary iron is present in high concentrations in egg yolk and organ proteins (liver, heart, kidneys), in intermediate amounts in lean meats, fish, cereals and green vegetables and in low amounts in non-green vegetables and milk. It is absorbed along the length of the small bowel, most readily from the proximal segments. Dietary iron (10–15 mg/day) is absorbed by an active transport system, but for the high doses used in replacement (50–250 mg/day), passive absorption is probably the more important mechanism as active carrier sites are saturated. In the normal state, only 10% of dietary iron is absorbed and the factors influencing absorption are:–

1. Iron status. The rate and extent of iron absorption is inversely related to the amount of iron in the iron stores. In iron-depleted subjects there is an increase in erythropoiesis and, as iron absorption varies with erythropoiesis, 60–80% of an oral dose may be absorbed, amounting to 50–100 mg/day after high doses. This does not occur in haemolytic anaemias as in these conditions there is no net loss of iron.
2. The nature of dietary iron. Inorganic iron is absorbed more readily than organic iron, e.g. iron in haemoglobin or myoglobin. Ferrous iron is absorbed at approximately ten times the rate of ferric iron so that absorption is enhanced by reducing agents, e.g. ascorbic acid and by gastric acidity, as the latter facilitates production of ferrous iron.
3. Food. Food taken at the same time as oral iron decreases the amount of iron absorbed as iron forms stable, non-absorbable complexes with certain food constituents, e.g. phytates and phosphates.

Absorption of iron from intramuscular sites is rapid, most being absorbed by 72 hours. It is not affected by exercise.

Disposition In the plasma iron is bound to a beta globulin, transferrin, and is deposited as ferritin in iron stores in the reticuloendothelial system. Iron stores in the normal male amount to 800–1000 mg, but are usually less for the female. They have no immediate physiological role but supply most of the 25 mg of iron utilised per day in erythropoiesis.

EXCRETION Iron is excreted in small amounts in the urine, bile and sweat, but the major site of iron loss is the gastrointestinal mucosa where it is incorporated into mucosal cells as apoferritin and shed into the bowel lumen as the mucosal cells themselves are desquamated. The mucosal cells of the small bowel have a very rapid rate of turnover, the survival half-life being 18–36 hours, and the amount of iron lost by this route is constant and varies little with changes in either dietary iron or the size of iron stores. Thus if iron absorption is excessive, as in patients with haemochromatosis, or those with impaired pancreatic exocrine function, iron accumulates in excessive amounts in iron stores.

ADVERSE EFFECTS Oral iron invariably causes black motions but is generally well tolerated. Abdominal colic, diarrhoea and constipation are the commonest

side-effects and can usually be ameliorated by taking the iron with meals or by reducing the iron dose.

Acute overdose Acute overdosage is a condition almost exclusive to children, iron tablets, oral contraceptives and salicylates being the agents most common used in accidental poisonings of children. Typically, a child between 1–3 years consumes up to 30 or 40 brightly coloured sugar coated iron tablets prescribed for its mother. Abdominal pain, nausea, vomiting and diarrhoea occur within 6 hours and, if severe, may be followed by hypotension, coma and convulsions. The mortality is directly related to the number of tablets ingested. Strictures in the small bowel may occur as a late complication in survivors.

The principles of treatment of an iron overdose are:–

1. Maintenance of the circulating blood volume by blood transfusion or plasma expander.
2. Gastric lavage with a solution of sodium bicarbonate to remove undissolved tablets.
3. Administration of desferrioxamine, a chelating agent with a high affinity for iron, both via nasogastric tube and intravenously, to bind free iron molecules (*see* Chapter 41).
4. Administration of anticonvulsants if convulsions occur.

Drug interactions: tetracyclines Iron salts given in conjunction with tetracyclines substantially reduces the amount of antibacterial agent absorbed as tetracyclines form stable, insoluble complexes with iron.

PARENTERAL IRON Iron bound to large inert molecules such as dextrans or dextrins may be administered i.m. or i.v. Adverse effects occur much more commonly with these routes of administration and are most common after intravenous therapy. Cardiac dysrhythmias and hypotension may occur and be fatal. Fever, flushing and sweating occurs in the majority of patients during an intravenous infusion, while other symptoms consist of headache, bronchospasm, muscle and joint pains. The pathogenic mechanisms involved are not established but it is almost certain that free iron cations are responsible.

Iron stains the tissues a dark brown and is a local irritant and should be given as a deep intramuscular injection.

CLINICAL USE

Administration Iron replacement, other than by blood transfusion, is preferably by the oral route as the haematological response in most cases is as rapid as after parenteral iron and serious adverse effects are negligible. Parenteral therapy is only indicated in the rare instance when oral iron is not effective and blood transfusion not indicated.

Dose The size of an oral dose is usually limited by gastrointestinal side-effects to 60–120 mg of elimental iron per day. The duration of therapy depends on the extent of the iron deficiency and may be estimated roughly from the plasma haemoglobin concentration (1 ml of blood = 0·5 mg iron).

However, if iron depletion has occurred slowly, iron stores will also be depleted and should be replaced. This takes 4–6 months after the haemoglobin has returned to normal.

For parenteral therapy, the total dose is calculated as follows:–

$$2{\cdot}5\left(1-\frac{\text{plasma Hb conc. (g/100 ml)}}{14{\cdot}8}\right)+0{\cdot}5 \text{ grams}$$

Intravenous iron may be given as a bolus in 5–7 daily injections, each injection being given over 5–10 minutes. Alternatively, it may be given in 500 ml normal saline over 1–2 hours, as a total dose infusion.

Intramuscular iron is given into the gluteal region in divided doses.

INDICATIONS Replacement therapy is indicated in all cases of iron deficiency not requiring blood transfusion. Iron tablets are amongst the most commonly prescribed medicines as iron deficiency is common in women between the menarche and the menopause, due to menstrual losses (15–30 mg/month) and to the increased iron demands of pregnancy (0·5–0·75 g/pregnancy). Iron preparations are available in many forms without prescription and are contained in tonics and many other nostrums of dubious therapeutic efficacy.

Preparations

Oral

	Maximum adult 24 h dose	*Iron content*
Ferrous sulphate	600 mg	120 mg
Ferrous gluconate	400 mg	120 mg
Ferrous fumarate	600 mg	72 mg

Parenteral preparations

	Iron concentration	*Route*
Iron dextran	50 mg/ml	i.m., or i.v. as continuous infusion in 100–500 ml normal saline
Iron sorbitol citrate	50 mg/ml	i.m.
Iron dextrin	50 mg/ml	i.m.

CHOICE OF PREPARATION There are three types of oral iron preparations:

1. Simple iron salts
2. Slow release preparations, e.g. ferrous sulphate imbedded in a porous plastic matrix designed to minimise gastrointestinal side-effects.
3. Combined preparations, containing various compounds such as ascorbic acid, aminoacids (e.g. serine) that increase iron absorption to a small degree, and folic acid for use when there is a coexistent folate deficiency.

In the great majority of cases, the simple iron salt preparations are effective and well tolerated. As they are also much the cheapest they are the preparations of first choice. If these preparations are not tolerated, recourse to the more expensive preparations is indicated.

VITAMIN B_{12} (CYANOCOBALAMIN)

ACTION Vitamin B_{12} is an essential cofactor at several sites in the intermediary metabolism of nucleic acids, proteins, fats and carbohydrates. At one site at least, the conversion of homocysteine to methionine, methyl-tetrahydrofolic acid (THFA) is also a co-factor. There is dependence of these vitamins upon one another and a deficiency of B_{12} causes an accumulation of methyl-THFA and hence a deficiency of THFA for other reactions. The most obvious biochemical change of B_{12} deficiency is a retardation in DNA synthesis and this is most evident in cells with high rates of replication, e.g. the bone marrow and gastrointestinal tract. Anaemia is the commonest clinical sign, the anaemia being macrocytic and megaloblastic, with multinucleated polymorphs in the peripheral blood and a megaloblastic marrow. The delay in DNA synthesis causes RBCs to enter the peripheral circulation later than normal in their development. They have a shorter survival time than normal which results in excess haemolysis and an increase in non-conjugated bilirubin in the plasma. B_{12} is essential for the normal function of the nervous system and a deficiency will cause a peripheral neuropathy, degeneration of the dorsal and cortico-spinal tracts in the spinal cord (subacute combined degeneration of the cord) and degeneration of cortical neurones causing confusion and psychoses. The biochemical mechanisms involved in these neurological abnormalities are not understood.

DRUG FATE

Absorption B_{12} is a large water-soluble molecule (MW 1355) containing a cobalt atom. It is present in all foods of animal origin but not in vegetables. Dietary B_{12} is absorbed by an active transport mechanism. Passive absorption is negligible and even in large doses, is insufficient to sustain the body's needs. The active carrier mechanism is situated in the terminal ileum and requires a glycoprotein cofactor (intrinsic factor) secreted by the mucosa of the fundus of the stomach. The commonest disorder causing B_{12} deficiency in Europe and North America is Addisonian pernicious anaemia in which intrinsic factor is deficient as a consequence of atrophy of the fundal mucosa. In such patients, oral B_{12} replacement therapy is ineffective.

Storage and excretion B_{12} is stored in the liver, 3–5 mg being present in normal subjects. As the daily requirement is very small (2–3 μg/day), symptoms of B_{12} deficiency do not develop for 3–10 years after the development of B_{12} malabsorption. Negligible amounts of dietary B_{12} are excreted unchanged in the urine, except when large amounts are administered parenterally.

ADVERSE EFFECTS Like other water-soluble vitamins, B_{12} is non-toxic at therapeutic doses. Hypersensitivity reactions, urticaria, bronchospasm and anaphylaxis have been reported very rarely.

CLINICAL USE

Administration B_{12} is administered parenterally. There are two preparations, hydroxy-cyanocobalamin and cyanocobalamin. Hydroxy-cyanocobalamin achieves higher peak plasma concentrations after equimolar doses and is inactivated more slowly. It is therefore the preparation of choice. Symptomatic improvement is usually evident within days and sometimes within hours of starting treatment, the reticulocyte response reaching a peak after 5–10 days. A dose of 100 μg of hydroxy-cyanocobalamin is sufficient to maintain a plasma B_{12} concentration above the lower limit of normal for 3–5 weeks, but as the vitamin is cheap and non-toxic, it is common practice to give much higher doses, e.g. 100 μg at weekly intervals for four doses and then at monthly intervals for life.

Indications B_{12} deficiency is the only established use for B_{12} therapy. However, in view of the protean virtues commonly and mistakenly attributed to vitamins, it is sometimes used as a placebo. The dangers of using B_{12} without first assessing the B_{12} status is that if there is a B_{12} deficiency, by correcting the haematological abnormalities, the diagnosis is delayed and the possibility of eventually developing irreversible neurological abnormalities prolonged.

FOLIC ACID

Folic acid (pteroylmonoglutamic acid) has three components, a purine, pteridine, para-aminobenzoic acid (PABA) and glutamic acid as shown in Fig. 1.

It is inactive by itself, but is reduced in the body to tetrahydrofolic acid (THFA) by two steps, the last involving dihydrofolate reductase, hydrogen atoms being added at positions 5, 6, 7 and 8.

ACTION Tetrahydrofolic acid is an essential cofactor in the transfer of one carbon groups (methyl, methylene, formyl and formimino) between metabolites and is essential for purine and pyrimidine synthesis, the interconversion of several aminoacids and for the genesis of formates.

Folic acid deficiency causes a clinical condition identical to that of B_{12} deficiency except that clinical evidence of disordered nervous system function is rare. The biochemical basis for this difference is not understood.

DRUG FATE Dietary folates are polymers of glutamic acid containing several glutamate constituents. Polyglutamates are present in highest concentrations in organ proteins, yeasts and green vegetables, but are present in many foods in small quantities. They are not absorbed themselves, but are hydrolysed enzymatically in the bowel and bowel mucosa to the absorbable pteroylmono-

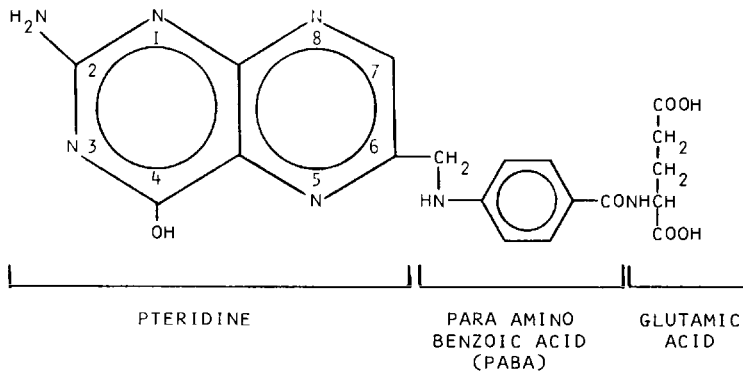

FIG. 1 Structural formula of folic acid

glutamic acid (FA) 80% of dietary folates eventually being absorbed. Prolonged cooking can destroy dietary folates altogether.

Folic acid, like B_{12}, is a large water-soluble molecular (MW 441), that is poorly absorbed by passive diffusion. It is mostly absorbed by an active transport mechanism, situated in the jejunum, very little being absorbed from the ileum. Absorption of FA is slower than hydrolysis of polyglutamates and is the rate-limiting step in folate absorption. After absorption, folic acid is reduced and methylated, principally in the liver and is present in the plasma mostly as methyl-tetrahydrofolic acid. Folate stores amount to 5–10 mg most being present in the liver. The daily requirement in normal circumstances is 50 μg, but increases considerably in pregnancy, and other periods of rapid cell division, e.g. following haemolytic or bleeding episodes, in leukaemias etc. Folate stores are small relative to the daily requirement and unlike B_{12} deficiency, symptoms and signs of folate deficiency occur within 2–3 months of a deficiency developing.

Folates are concentrated inside cells and in the CSF and only very small amounts of dietary folate are excreted unchanged in the urine. However 50% or more of a 5–15 mg oral dose is excreted unchanged in the urine.

ADVERSE EFFECTS Folic acid is very well tolerated and even large doses (15 mg eight-hourly) do not produce symptoms.

In B_{12} deficiency, folate replacement may cause an improvement of the haematological picture, part of which is due to the relative FA deficiency caused by B_{12} deficiency. However, this exacerbates the B_{12} deficiency in the nervous system and may precipitate the neurological syndromes that develop as a result of B_{12} deficiency. Therefore, before starting FA replacement therapy, B_{12} status should be assessed (e.g. by assay of plasma B_{12} concentration) and if, on clinical grounds, such a deficiency is likely, replacement of folic acid should be delayed,

until the biochemical data on B_{12} is available, or both vitamins should be administered.

DRUG INTERACTIONS

Folate analogues The cytotoxic agent and folate analogue, methotrexate (*see* Chapter 38) which has a high affinity for dihydrofolate reductase, may cause folate deficiency and hence antagonise the effects of FA. The antimalarial pyrimethamine and diuretic triampterine are relatively weak human DHFA reductase inhibitors, but may cause FA deficiency if prescribed in large doses or to subjects marginally deficient of FA. Trimethoprim, the antibacterial agent, has a low affinity for human DHFA reductase and rarely causes FA deficiency.

Anticonvulsants Phenytoin, phenobarbitone and primidone may cause FA deficiency, probably by more than one mechanism (*see* Chapter 17).

CLINICAL USE Folic acid is only of established value in the treatment or prevention of folic acid deficiency. As most instances of folate deficiency are reversible, therapy is only required until folate stores are replenished. Therapy is monitored by means of the haemoglobin concentration, the reticulocyte count and by the plasma folic acid concentration, as this is a fair reflection of the state of folic acid stores. Therapy should be continued until these return to normal.

Preparations

	Adult dose	*Dose interval*
Hydroxy-cyanocobalamin	1000 μg	1–4 months
Cyanocobalamin	1000 μg	0·5–2 months
Folic acid	5–15 mg/day (oral)	

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Chapter 33

Anticoagulants

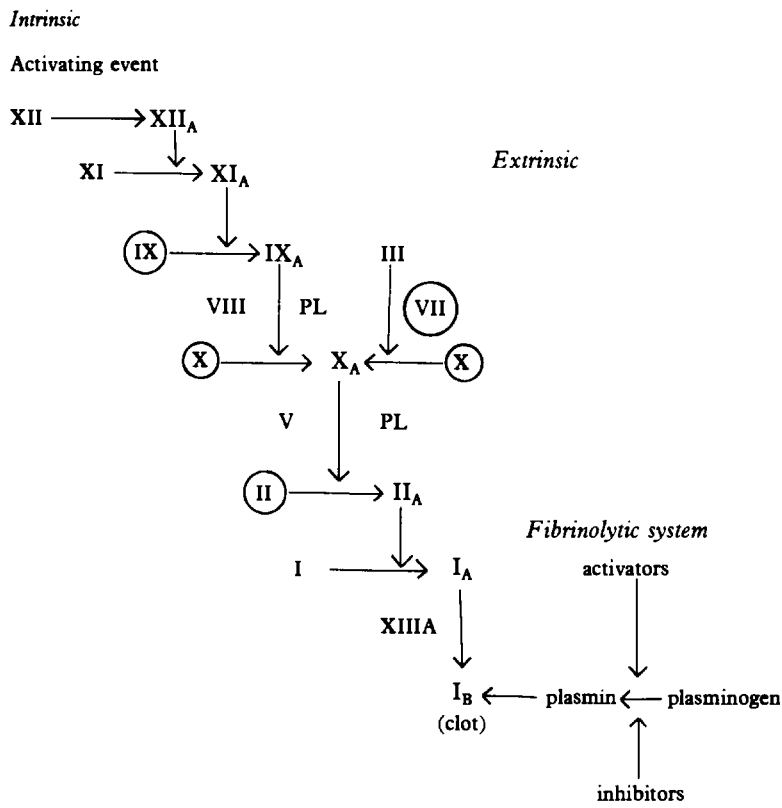
Anticoagulants are drugs that impair clot formation. An understanding of the actions of anticoagulants and their clinical use stems from knowledge of clot formation and degradation.

Clot formation and lysis Blood vessel patency depends on the relative activities of the systems responsible for clot formation and those responsible for clot lysis. Most anticoagulants act by preventing clot formation relying on the normal fibrinolytic mechanisms to lyse formed clots but there are also agents available now that enhance fibrinolysis.

Venous thrombi differ from arterial thrombi in that they are red thrombi, very similar to thrombi that form when blood is placed in a test tube. They consist of red cells immeshed in fibrin and contain very few platelets. Arterial thrombi, by contrast, are white thrombi consisting mostly of platelets and are initiated by platelet aggregation. The available anticoagulants prevent venous thrombi formation, but are generally ineffective against arterial thrombi. There is some promising but inconclusive evidence that drugs that impair platelet aggregation e.g. aspirin and sulphinpyrazone, are of value in preventing arterial thrombi and the major clinical sequelae of such thrombi, myocardial infarction and cerebrovascular disease.

The sequence of events in venous clot formation and clot lysis is shown in Fig. 1. Venous coagulation occurs via two pathways. In the intrinsic system, injury to the endothelial layer exposes subendothelial components that activate factor XII and initiate a cascade of reactions culminating in clot formation. In the extrinsic system, tissue damage exposes tissue thromboplastins that activate factor VII and so initiate clot formation. Clotting factors are circulating proteins and most are enzyme precursors. These enzyme precursors are activated by an activating factor, usually a protease, which detaches part of the protein molecule and so activates the enzyme by revealing its active centre. Factors XII, XI, X, IX and probably VII are all activated by proteases with serine at their active centres. Thrombin is also a protease with serine at its active centre.

Clot lysis is brought about by the fibrinolytic system. Plasminogen is an inactive enzyme precursor that is converted by activators of the proteolytic system to the fibrinolytic enzyme plasmin, which is also a serine protease. There are activators and inhibitors of the fibrinolytic system in the circulation that are normally in dynamic equilibrium. The main physiological substrate for plasmin is fibrin, for which it has a high affinity, but if it is present in sufficient quantities to saturate plasmin inhibitors, it will breakdown fibrinogen and other clotting factors.



Factors that are ringed require vitamin K as a cofactor in their synthesis

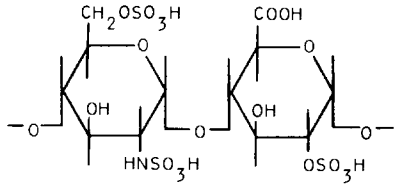
Nomenclature of factors

I	fibrinogen
II	prothrombin
III	tissue thromboplastins
IV	calcium
V	proaccelerin
VII	proconvertin
VIII	antihaemophilic factor
IX	Christmas factor
XI	plasma thromboplastin antecedent
XII	Hageman factor
I_A	unstable (soluble) fibrin
I_B	stable (insoluble) fibrin
$XIII_A$	activated fibrin stabilising factor
PL	platelet phospholipid

FIG. 1 Venous clot formation and degradation

PARENTERAL ANTICOAGULANTS

Heparin



HEPARIN

Heparin is a naturally occurring, acidic mucopolysaccharide with a high molecular weight varying between 6000–20 000, depending on the number of components present. Its acidity is due to sulphate groups. It has a pK of 1·6 so that within the physiological pH range the molecule carries a strong negative charge. For therapeutic purposes, heparin is derived from various sources, usually from the lungs of bullocks or from hog intestine. Only very occasionally does heparin induce antibody formation.

ANTICOAGULANT ACTION Heparin is an effective anticoagulant *in vitro* and *in vivo*. It reacts with a thrombin antagonist in the circulation, anti-thrombin III, and by so doing increases the affinity of the anti-thrombin for thrombin and the other serine proteases. Of these, factor X_A has the highest affinity for the anti-thrombin III—heparin complex and inactivation of this factor is probably responsible for the ability of low doses of heparin to prevent clot formation. To prevent propagation of already formed clot, heparin must inhibit thrombin activity as well and the concentrations at which thrombin is inhibited are considerably higher than those necessary to inhibit factor X_A. Heparin also reduces platelet stickiness at therapeutic concentrations.

The anticoagulant effect of heparin is dependent on its electronegativity as it is antagonised by strongly positively charged molecules such as the arginine rich basic protein protamine.

Heparin also activates the widely distributed enzyme lipoprotein lipase that hydrolyses the triglycerides in chylomicrons to free fatty acids. No therapeutic value has yet been attributed to this action.

DRUG FATE Heparin is inactive by mouth. After a bolus injection, the plasma concentration-time curve is biexponential, the half-life of the slow beta phase being 1·5 hours (range 0·6–2·5 hours). It is removed from the plasma by metabolism, negligible amounts appearing unchanged in the urine, but the sites of metabolism and the metabolic products have not been elucidated. In the plasma, heparin is bound to globulins and fibrinogen, but very little to albumin. The apparent volume of distribution is 6 litres (range 4–7). It does not cross the placental barrier and is a relatively safe anticoagulant to use in pregnancy.

After s.c. administration of 10 000 units, the peak anticoagulant effect occurs at 2 hours and there is appreciable anticoagulant effect at 6 hours.

ADVERSE EFFECTS

Bleeding is the commonest and most serious adverse effect. It may occur when the activated partial thromboplastin time is within therapeutic limits as well as when it is excessively prolonged. It is very much more common in patients who have some impairment of their haemostatic mechanisms and it may also occur during low dose heparin therapy, although in most situations, operations may be safely carried out on subjects on low dose heparin.

Allergic reactions Rarely, heparin administration has been associated with hypotension, asthma or urticaria, presumably due to antibody formation. Alopecia occurs very occasionally.

CLINICAL USE

Administration In the treatment of established thromboembolic disease, heparin is administered i.v. either by a bolus 10 000 u every 4–6 hours or by continuous infusion 30–40 000 u/24 h. To maintain the activated partial thromboplastin time within therapeutic limits throughout therapy, heparin has to be administered by continuous infusion but there is no evidence that this method is more effective at preventing clot formation than intermittent bolus injections, although fewer haemorrhagic side effects occur with continuous infusion.

Subcutaneous heparin, 5000 u 8 hourly or 10 000 u 12 hourly, may be used to prevent clot formation post-operatively or after a myocardial infarction or other events predisposing to clot formation. Bleeding at the site of administration is the commonest adverse effect.

Monitoring Activated partial thromboplastin time is the best means of monitoring heparin therapy, therapeutic limits being when this is 2–3 times that of normal plasma. The whole blood clotting time may also be used but is difficult to standardise and in consequence, the results correlate poorly with the activated partial thromboplastin time.

Antagonism The anticoagulant effect of heparin is rapidly antagonised by basic compounds. The most widely used is protamine, an arginine rich, small molecular weight protein derived from fish sperm. Protamine forms a stable, inactive complex with heparin, 1–1·5 mg antagonising 1·0 mg (120 u) of heparin *in vitro*. The dose requirement of protamine *in vivo* depends on the size of the heparin dose and the time of its administration e.g. 80 mg protamine i.v. is sufficient to antagonise a bolus dose of 10 000 u heparin if given immediately after the heparin, but only half this amount is necessary 1·5 hours later. Protamine is given in 1% solution, the maximum rate being 50 mg/minute. Toxic effects include hypotension, bradycardia and dyspnoea.

Ancrod Ancrod is an alternative intravenous anticoagulant to heparin. It is a purified extract from the venom of the Malayan pit viper. It is effective only when given intravenously and it acts by preventing conversion of an unstable form of fibrin (Fig 1–1a) to the stable (I_B) form. During the first 24 hours of therapy, there is an increase in fibrin degradation products in the plasma which

enhances the anticoagulant effect of ancrod by impairing platelet aggregation. After this early phase, the anticoagulant effect is associated with a low plasma fibrinogen concentration. Resistance to ancrod has been reported after repeated courses of treatment and has been attributed to antibody formation.

Clinical trials comparing ancrod and heparin have not demonstrated that ancrod is superior to heparin.

Fibrinolytic agents Streptokinase and urokinase are enzymes that convert plasminogen to plasmin and so activate the fibrinolytic system which then lyses preformed clot. Streptokinase is an enzyme derived from haemolytic streptococci while urokinase is derived from human urine. They have been shown to cause lysis of deep vein thromboses (DVTs) in the legs and of pulmonary emboli more rapidly than heparin but have not been shown to be more effective at preventing pulmonary emboli or at decreasing the mortality from serious pulmonary emboli.

Both drugs are given intravenously or, in the case of a severe pulmonary embolus, by catheter direct into the pulmonary artery. Adverse reactions are more common with the foreign protein streptokinase than with urokinase, a fever being the most common, but allergic reactions, rashes, broncho-spasm and anaphylaxis may occur. Bleeding may occur and be life-threatening as with other anticoagulants.

These drugs are prohibitively expensive and as they have no established advantages over heparin, are not recommended in the routine management of deep vein thrombosis and minor pulmonary emboli. Streptokinase is used in preference to heparin in many specialist centres in cases of massive pulmonary emboli although there is no conclusive evidence of its superiority in this situation. Since its introduction however, the number of emergency operations to remove pulmonary emboli carried out at such centres has fallen appreciably.

ORAL ANTICOAGULANTS

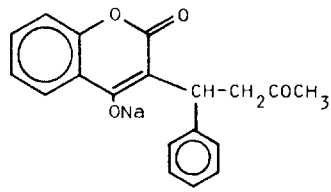
The first oral anticoagulant, bishydroxycoumarin, was derived from spoiled sweet clover following an investigation of a haemorrhagic disease in cattle which was found to have resulted from contamination of the hay eaten by the cattle with spoiled sweet clover. Subsequently, a large number of oral anticoagulants have been developed and on the basis of their chemistry they are classified as two groups:

Coumarins—Warfarin		Indandiones—Phenindione
	Ethyl biscoumacetate	
	Bishydroxycoumarin	
	Nicoumalone (acenocoumarol)	

There is much in common in the clinical pharmacology of these agents and as warfarin is now by far the most widely used oral anticoagulant, only the clinical

pharmacology of warfarin will be discussed in detail, the other agents being contrasted with it.

Warfarin Sodium



Warfarin is a highly lipid-soluble acidic compound. It is racemic, the S (−) enantiomorph being five times as active as the R (+) enantiomorph.

ANTICOAGULANT ACTION Unlike heparin, warfarin has no anticoagulant action *in vitro* and *in vivo*, and its action develops only slowly over a number of hours. Anticoagulation is associated with a fall in the plasma concentration of the vitamin K dependent clotting factors II, VII, IX and X and is antagonised by vitamin K. Vitamin K is an essential cofactor in the elaboration of the peptide precursors of these four clotting factors by liver cells. In the course of its action, vitamin K is converted to an inactive epoxide (K_1-oxide), the active form (K_1) being regenerated by a reductase system present in liver microsomes. Warfarin's anticoagulant action is associated with an accumulation in the plasma of the inactive K_1-oxide and it seems that it acts by inhibiting the conversion of K_1-oxide to the active K_1 form.

The rate of onset of the action of warfarin is determined by the rate of decline of the preformed vitamin K dependent clotting factors and the plasma concentration of warfarin. The plasma concentration of clotting factors decline exponentially after administration of warfarin, factor II falling the slowest with a half-life of 60–120 hours.

DRUG FATE Warfarin is well absorbed from the gut. In the plasma, it is 97% bound to plasma albumin at therapeutic concentrations. The apparent volume of distribution of 6–10 l is determined by the high degree of plasma protein binding, but free drug can readily diffuse into cells, the cerebrospinal fluid and across the placental barrier.

Warfarin is cleared from the plasma by metabolism, negligible amounts of unchanged drug being excreted in the urine or faeces. It is hydroxylated at several sites by liver microsomal enzymes and the hydroxymetabolites are conjugated with sulphate and glucuronic acid and excreted in the urine and bile. Conjugates of warfarin in the bile undergo enterohepatic circulation, very little drug being excreted in the faeces. Mean values for the half-life of warfarin vary between 30–50 hours. The range however is large (17–70 hours) and is mostly genetically determined, although the rate of warfarin metabolism may be both enhanced and retarded by environmental factors (*see* below).

ADVERSE EFFECTS

Bleeding this is the most common and most serious adverse effect and may occur when the prothrombin ratio is within the desired therapeutic range (1·8–3·0). The incidence of bleeding during chronic administration varies with the clinical circumstances, but on occasions is as high as 10%. Haematuria is the most common form of bleeding and bleeding from the gastrointestinal tract the next most common. Fatal haemorrhage, usually due to a massive gastrointestinal or intracranial bleed, occurs in less than 1% of cases in most reported clinical trials.

Other adverse reactions are rare and include rashes and alopecia. Intrauterine death, resulting from intrauterine haemorrhage, has resulted from warfarin therapy during the last trimester of pregnancy but there is no conclusive evidence that it is teratogenic if given during the first trimester.

Drug interactions Coumarin anticoagulants may enhance responsiveness to phenytoin, tolbutamide and chlorpropamide by impairing their metabolism. Phenindione does not have this effect and is the oral anticoagulant of choice in patients on these drugs. For interactions resulting in an enhancement or reduction in the effectiveness of oral anticoagulants see below.

CLINICAL USE

Administration The lag in the onset of action of warfarin means that warfarin is nearly always administered with heparin therapy initially. Heparin is used for 48–72 hours until adequate control of warfarin therapy is established. Warfarin is started with or without a small loading dose of 15 mg, a daily maintenance dose (e.g. 4 mg) being administered on each subsequent day until the prothrombin time reaches the desired value. If this has not occurred within 72 hours of starting therapy, the dose is adjusted until the desired control is achieved.

Monitoring The prothrombin time, in which a standard thromboplastin preparation and calcium are added to a citrated sample of the patient's plasma and the clotting time compared with that of a control plasma, is the best method of monitoring warfarin therapy. A value of 1·8–3 times control value is the therapeutic objective and as patients vary in responsiveness to warfarin and in the rates at which they metabolise the drug, there is a fairly large range of daily doses required to achieve this objective. The degree of anticoagulant control varies between clinics and even in the most scrupulous clinics the prothrombin time is seldom in the therapeutic range for more than 80% of patients. The prothrombin time is not a reliable guide to warfarin dose requirement if patients are receiving high dose heparin therapy and it is best to determine the prothrombin time at least 8 hours after the last dose of heparin or after stopping a continuous infusion.

Antagonism The anticoagulant action of warfarin is most effectively antagonised by vitamin K_1 (phytomenadione) which, after i.v. administration,

reverses the action within a few hours. A high dose (e.g. 25 mg) will prevent further anticoagulation for up to two weeks.

OTHER ORAL ANTICOAGULANTS The time to peak effect and the duration of effect of a therapeutic maintenance dose is shown in Table 1.

Table 1

Drug	*Time to peak effect (h)*	*Duration (days)*
Warfarin sodium	36–48	4–5
Nicoumalone	36–48	2–3
Ethylbiscoumacetate	18–36	2–3
Bishydroxycoumarin	variable	5–6
Phenindione	36–48	2–3

It can be seen from Table 1 that bishydroxycoumarin is not well absorbed and that the onset of action is variable, that ethylbiscoumacetate has the most rapid onset of action and that nicoumalone, ethylbiscoumacetate and phenindione all have a shorter duration of action than warfarin, necessitating a 12 hour rather than 24 hour dose interval.

Phenindione was the most widely used oral anticoagulant for many years, but as it is appreciably more toxic than warfarin, is now seldom used. The serious adverse effects of phenindione include fever and rashes, leucopenia, hepatic and renal dysfunction and malabsorption. The incidence and nature of adverse effects of the other coumarins are similar to those of warfarin.

Factors Altering Responsiveness to Oral Anticoagulants

The widespread use of oral anticoagulants and the ease with which the biological effect can be determined has resulted in the generation of a voluminous literature on factors modifying responsiveness to these drugs.

ENHANCING FACTORS

Vitamin K deficiency In neonates, vitamin K is often deficient before bacteria colonise the large bowel as bowel bacteria are an important source of vitamin K. Vitamin K absorption may be impaired by liquid paraffin and in malabsorption states. Broad spectrum antibacterial agents decrease bowel flora and hence the vitamin K available for absorption and may enhance responsiveness to oral anticoagulants, especially in patients on a vitamin K deficient diet.

Liver disease There is often a prolongation of the prothrombin time in liver disease due to defective hepatocellular function and a fall in the production of vitamin K dependent clotting factors. The response to oral anticoagulants is enhanced and prolonged in these circumstances.

Thyrotoxicosis An enhanced response to oral anticoagulants in this condition

is associated with a more rapid rate of a decline in the plasma concentration of clotting factors.

Drugs Salicylates, phenylbutazone and indomethacin. These drugs cause gastric erosions and increase the bleeding time by reducing platelet stickiness and the risk of haemorrhage is increased by oral anticoagulants. The highly protein bound drugs phenylbutazone and oxyphenbutazone displace warfarin from protein binding sites and increase the amount of free drug in the plasma with a consequent increase in the anticoagulant effect. The same effect has been demonstrated for other acidic drugs, sulphonamides, probenecid, diazoxide, mefenamic acid and nalidixic acid.

Magnesium salts enhance warfarin absorption and monoamine oxidase inhibitors, disulphiram, chloramphenicol and methylphenidate impair its metabolism. Other drugs that may enhance responsiveness to anticoagulants by mechanisms that have not been clearly established include clofibrate, anabolic steroids, quinine, quinidine and allopurinol.

FACTORS REDUCING RESPONSIVENESS

Genetic A small number of cases have been reported in which the dose requirement for warfarin is 10–20 times the average dose. Such subjects are very sensitive to vitamin K and metabolise warfarin at normal rates. This decreased sensitivity to oral anticoagulants is carried on an autosomal dominant gene (*see* Chapter 5).

An increase in vitamin K ingestion decreases responsiveness to oral anticoagulants. Oestrogens, but not progestogens, stimulate synthesis of vitamin K dependent clotting factors and also factors I and VIII, increase platelet stickiness and decrease fibrinolytic activity. In pregnancy, and in subjects on oestrogens, including those on oral contraceptives, there is a reduction in responsiveness to oral anticoagulants.

Microsomal enzyme inducing agents increase the rate of warfarin metabolism and decrease responsiveness to warfarin and other oral anticoagulants (*see* Chapter 3).

INDICATIONS FOR ANTICOAGULANT THERAPY

Venous thrombi Anticoagulation decreases the incidence of pulmonary emboli in patients with deep venous thrombosis and in this situation is normally administered for three months.

Pulmonary emboli As for venous thrombosis. Anticoagulants, other than streptokinase and urokinase, do not increase the rate of lysis of the embolus but prevent further emboli.

Atrial and ventricular emboli The incidence of systemic emboli in patients with a left atrial thrombus due to mitral stenosis or a ventricular thrombus following a myocardial infarction is reduced by anticoagulants.

Arterial thromboembolic disease Myocardial infarction—despite widespread

use of these agents in the secondary prevention of myocardial infarction, anticoagulants have no established place in the routine management of this condition. However there is clinical trial evidence indicating that the incidence of reinfaraction in males under the age of 55 is reduced in patients receiving these drugs for two years after a first infarct.

Cerebrovascular disease In patients with intermittent cerebrovascular ischaemic episodes without an established stroke, anticoagulants decrease the incidence of cerebrovascular accidents. They are of no value in other forms of cerebrovascular disease.

CONTRA-INDICATIONS The following is a summary of the main contra-indications to the use of anticoagulants—

1. Failure of the patient to cooperate with instructions on drug taking.
2. Inadequate facilities for monitoring drug therapy.
3. Impaired haemostasis, e.g. liver disease.
4. Increased liability to bleed due to any factor whether it be social, e.g. a job with increased liability to trauma, diseases in which bleeding may be a complication, e.g. epilepsy, hypertension, peptic ulceration or concurrent drug therapy, e.g. anti-inflammatory agents.

Haemostatic agents

These are drugs that either prevent or reduce bleeding. They are much less frequently used in therapeutics than anticlotting agents and may be classified as topical and systemic haemostatic agents.

Topical Haemostatic agents include adrenaline, calcium alginate, oxidised cellulose and absorbable gelatin sponge. They are administered to superficial bleeding sites and encourage clot formation.

Systemic Haemostatics include aminocaproic acid, tranexamic acid and ethamsylate. These agents inhibit activators of the endogenous fibrinolytic agent plasmin and hence favour clot formation. Their most serious adverse effect is thus clot formation and they should not be administered in bleeding states associated with enhanced clot formation e.g. disseminated intravascular coagulation.

Aminocaproic acid and tranexamic acid are of established value in the reduction of bleeding following prostatectomy, as they are mostly excreted unchanged in the urine where they inhibit the endogenous fibrinolytic agent urokinase. They should not be administered to patients with seriously impaired renal function.

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Chapter 34

Vitamins A, D, K, B Complex and C

In the wealthy nations of the world, vitamin deficiency syndromes are rare, occurring most commonly as a consequence of dietary neglect, ethanol dependence, psychiatric illness or gastrointestinal disorders. Notwithstanding this, preparations containing vitamins are among the most commonly consumed medicines, the majority being available without prescription. This is due to the still widely held notion that vitamins possess medicinal virtues other than in the treatment and prevention of deficiency states, a notion that is not supported by scientific evidence. Furthermore, while the majority of vitamins are safe in large doses, this is not so for vitamins D and A, and the indiscriminate use of multivitamin preparations containing these agents is potentially dangerous.

There is a great deal of information on the essential role that individual vitamins play in various cellular biochemical events, but there is frequently no explanation of the sequence of events that links the biochemical role to the clinical features in deficiency syndromes. In this chapter, stress is laid on those aspects of the pharmacology of the vitamins that are essential for their correct clinical use.

Vitamin A

Vitamin A is present in nature in a variety of forms of which β-carotene, a precursor of vitamin A, is the most abundant. The foods most rich in the vitamin are egg yolk, fish liver oil, dairy products, carrots, spinach and watercress.

ACTIONS

Vision Vitamin A is an essential component of the photosensitive retinal pigment rhodopsin. This pigment is located in the rods and is broken down on exposure to low intensity light with the initiation of a nerve impulse. It is essential for dark adaption and in its absence night blindness develops.

Epithelial integrity Vitamin A is an important factor in the development of epithelial cells. In the deficiency syndrome, dysfunction of the corneal epithelium is the dominant clinical feature with ulceration and necrosis of the cornea and conjunctiva (keratomalacia) which may progress to xerophthalmia and blindness. There is also an increase in respiratory tract infections and renal calculi and a dry, rough skin develops. These are features of epithelial abnormalities.

DRUG FATE Vitamin A and β-carotene are fat soluble and are readily absorbed from the bowel. Absorption is impaired in all forms of steatorrhoea. Most of the vitamin is stored in the liver and there is a high concentration in the adrenal cortex where it is a cofactor in glucocorticoid biosynthesis. In the plasma, most of the vitamin is protein bound and is cleared from the plasma by metabolism, negligible amounts being excreted unchanged in the urine.

ADVERSE EFFECTS

Overdose This results from the ingestion of more than 50 000 units/day for periods of weeks to months, the normal daily requirement being 4000–5000 units. Clinical signs consist of roughening of the skin, rhagades (fissures of the mouth) and hyperostosis of bones, with the development of hard, tender swellings in the occipital region and on the bones of the arms and legs. Intracranial pressure may be raised and be associated with headache and papilloedema. The plasma vitamin A concentration is grossly elevated and the signs and symptoms resolve within weeks of stopping the drug.

CLINICAL USES

Deficiency The only clinical situation in which vitamin A is of any proven value is in the treatment and prophylaxis of vitamin A deficiency. There is an increased requirement during pregnancy, lactation and periods of rapid growth when dietary sources may be inadequate and prophylaxis therefore justified. Vitamin A replacement therapy may also be of value in malabsorption syndromes.

Vitamin D

The D vitamins are all steroids and are present in various foods as the precursors ergesterol (yeasts, fungi, ergot) and 7-dehydrocholesterol (fish liver oils), the latter also being present in the epidermis. Both precursors are converted to the three forms of the vitamin by irradiation (Fig. 1).

All three forms of the vitamin are available commercially. Cholecalciferol is the most potent and dihydrotachysterol the least potent on a weight basis.

ACTIONS

Calcium absorption Calcium is poorly absorbed from the gastrointestinal tract by passive diffusion and is mostly absorbed by an active carrier mechanism. This mechanism requires vitamin D as a cofactor and is inhibited by cortisol. Vitamin D therefore, facilitates calcium absorption and to a lesser extent increases phosphate absorption.

Calcium mobilisation In conjunction with parathyroid hormone, vitamin D mobilises calcium from the bone to blood, so maintaining plasma calcium concentrations within normal limits. The vitamin probably has a direct effect on renal tubular reabsorption mechanisms and in the absence of parathyroid hormone, enhances calcium and phosphate reabsorption, but the nature of its effect in the presence of the hormone is uncertain.

Deficiency syndrome Vitamin D acts to maintain the calcium and phosphate

plasma concentrations at supersaturation levels as these are necessary for normal bone mineralisation. In deficiency states bone mineralisation is inadequate. In children there is a failure of mineralisation of newly formed osteoid bone which remains soft and deformities, bowing etc., develop in bones undergoing most rapid growth, e.g. the skull during first year and bones of the legs during second and third years. In adults, osteomalacia develops, in which there is a generalised reduction in bone mineralisation with no change in protein bone matrix.

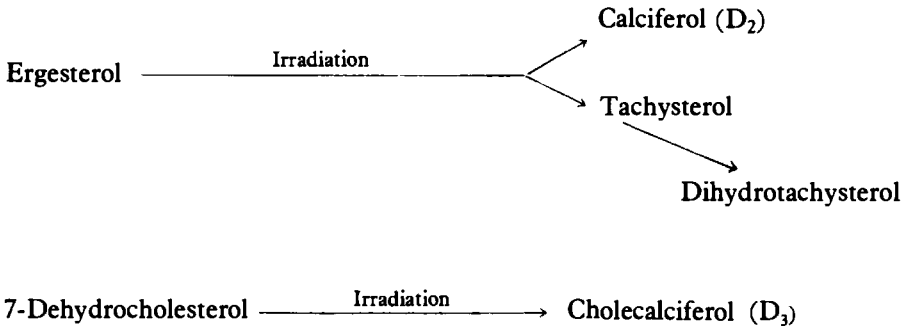

FIG. 1 Conversion of vitamin D precursors by irradiation to the three forms in which the vitamin is available for clinical use

DRUG FATE All forms of the vitamin are readily absorbed, mostly from the jejunum and in the plasma are partially bound to albumin and globulin.

Both D_2 and D_3 forms of the vitamin are hydroxylated by liver microsomal enzymes (but not by those responsible for hydroxylation of most drugs) to 25-hydroxyergocalciferol and 25-hydroxycholecalciferol (25-HCC) respectively. Both are more active than the parent compounds and are present in the blood in higher concentrations than other forms of the vitamin. Both are further hydroxylated in the C_1 position by the kidney and this conversion is modulated by parathyroid hormone which facilitates the conversion. 1,25-dihydroxycholecalciferol (1,25-HCC) is by far the most active form of the vitamin and is physiologically the most important. The kidney also forms another metabolite, 1,24,25-trihydroxycholecalciferol which, though less active than 1,25-HCC, stimulates calcium absorption but has little effect on bone. In physiological circumstances, production of 1,25-HCC by the kidney is determined by the plasma calcium concentration by a negative feedback control mechanism, but the details of how this mechanism operates are not established. In severe renal disease, there is usually a reduction in the rate of 1,25-HCC production and this is responsible for the vitamin D resistant rickets that may develop.

Vitamin D is excreted only in the bile, approximately half an oral dose

appearing in the faeces, negligible amounts of unchanged vitamin being detected in the urine. It is also partly metabolised to inactive metabolites by the liver and this process may be enhanced by enzyme inducing drugs (*see* below). Vitamin D has a long duration of action. The plasma half-life of cholecalciferol and 1,25-HCC is 18–30 hours, but that for 25-HCC is 25–30 days. Hence the duration of action of the vitamin is determined by the rate at which 25-HCC is converted to 1,25-HCC by the kidney.

ADVERSE EFFECTS

Overdose is the only adverse effect of vitamin D and this may develop if doses of 25 000 u/day or greater are continued for long periods in subjects with normal vitamin D metabolism. Overdose causes hypercalcaemia, the presenting clinical symptoms usually being nausea, vomiting and diarrhoea and central symptoms of confusion, psychotic episodes, coma and convulsions. Renal failure and hypertension are also common, the renal failure initially being reversible. Prolonged hypercalcaemia however, causes nephrocalcinosis and irreversible renal failure and soft tissue calcification of the heart, blood vessels and other organs. Pancreatitis may also develop.

Treatment of overdose is to stop the vitamin, correct the fluid and electrolyte abnormalities, which commonly result from the vomiting and defective renal function, and to reduce the plasma calcium. This is achieved within a few days by glucocorticoids.

Clinical signs of hypercalcaemia are an unreliable guide to the plasma calcium and it is mandatory to monitor the plasma calcium, phosphate and alkaline phosphatase in patients on doses of the vitamin above the physiological range (i.e. 400 u/day) and especially in those on doses of 25 000 u/day or more,

Drug interaction: anticonvulsants Prolonged use of phenobarbitone, phenytoin and primidone, alone or in combination may cause osteomalacia (*see* Chapter 17). This condition is associated with a shorter plasma half-life of vitamin D_3 and a lower plasma concentration of 25-HCC and is probably the consequence of an enhanced rate of metabolism of the active to inactive forms of the vitamin.

CLINICAL USE

Dietary deficiency In rickets or osteomalacia, vitamin D is administered in doses of 3000–4000 u/day. It may also be given prophylactically in smaller doses (400 u/day) in conditions in which there is an increased requirement for the vitamin, e.g. during rapid growth, pregnancy and lactation when vitamin requirements cannot be obtained from exposure to sunlight.

Malabsorption In steatorrhoea due to gastrointestinal liver or pancreatic disease, vitamin D may be given in high oral doses or in lower doses parenterally. The dose requirement is determined by the response of the blood calcium and alkaline phosphatase.

In renal failure Vitamin resistance may be present due to failure of the

kidney to synthesise 1,25-HCC, and osteomalacia may develop. In this situation, high doses of vitamin D are usually required, 50–500 000 u/day, but treatment is preferably by the synthetic analogue 1α-hydroxycholecalciferol or by 1,25-dihydroxycholecalciferol itself. 1α-HCC is rapidly hydroxylated by the liver to 1,25-dihydroxycholecalciferol and hence does not require activation by the kidney.

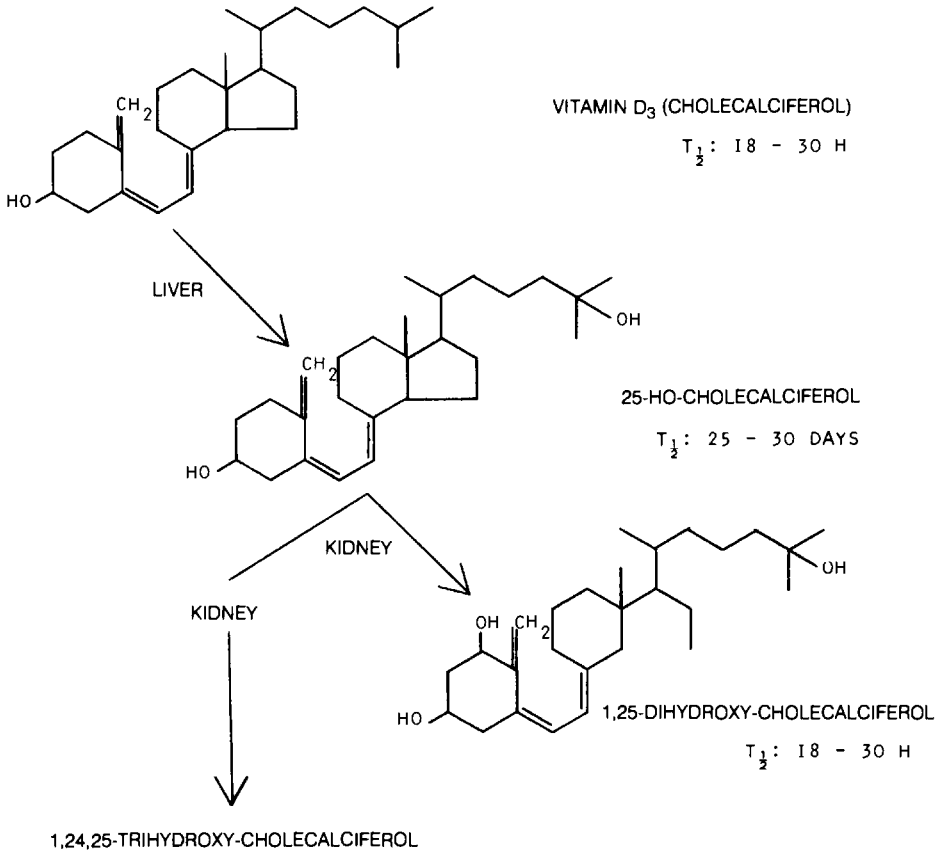

FIG. 2 Metabolism of vitamin D_3

As 1,25-HCC also has a much shorter $t_{\frac{1}{2}}$ (Fig. 2) than 25-hydroxycholecalciferol dosage adjustment is much easier with this preparation. Hypercalcaemia and a rise in plasma creatinine result from overdosage so that great care should be taken while establishing the correct dose to monitor both plasma calcium and creatinine.

Hypoparathyroidism—high doses (50–5000 000 u/day) of vitamin D are usually required to treat hypocalcaemia resulting from hypoparathyroidism but as only small doses (0·5–1 μg/day) of 1α- or 1,25-HCC are required, obviously these are the preparations of choice in this condition.

Hypophosphataemia Vitamin D is often effective at raising the plasma phosphate in idiopathic hypophosphataemia.

Vitamin K

Vitamin K is present in two forms in nature, vitamin K_1 (phytomenadione) and vitamin K_2. Both are quinones and are lipid-soluble, the principal sources of the vitamins being photosynthesising plants, fruit, vegetable oils and egg yolk. Vitamin K is also present in high concentrations in bacteria and hence in faeces and rotting matter.

Vitamin K_3 (menaphthone) is a synthetic analogue of vitamin K which also has a quinone structure, is fat-soluble and has the same actions as the naturally occurring vitamins. There are water soluble derivatives of menaphthone with highly polar side chains, e.g. acetomenaphthone, menaphthone sodium biphosphate and menadiol sodium bisulphite.

NOMENCLATURE Only vitamins K_1 and K_3 and analogues are available commercially. There is a difference between the official names of both K_1 and K_3 in the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP) which may lead to confusion, e.g. phytomenadione (BP) = phytonadione (USP), menaphthone (BP) = menadione (USP). Certain forms, e.g. menadiol diphosphate, are only available from the USA when the USP nomenclature is used universally.

ACTIONS

Synthesis of clotting factors Vitamin K is an essential cofactor in the synthesis by the liver of peptide precursors of clotting factors II, VII, IX and X. The vitamin is converted in the course of this action to the inactive form K_1 oxide by a hepatic epoxidase and the active form regenerated by another enzyme, a reductase. The latter enzyme is inhibited by oral anticoagulants.

Deficiency syndrome A deficiency of vitamin K causes a fall in the plasma concentration of factors II, VII, IX and X and a corresponding increase in prothrombin time (*see* Chapter 33). The prolongation of clotting time which results may cause clinical evidence of haemorrhage, e.g. haematuria, bruising, gastrointestinal haemorrhage or intracranial haemorrhage.

DRUG FATE Both the fat-soluble and water-soluble forms of the vitamin are readily absorbed from the gut. In malabsorption states due to biliary obstruction or gastrointestinal dysfunction (e.g. gluten sensitivity) the fat-soluble forms of the vitamin are poorly absorbed. Water-soluble forms may be adequately absorbed in malabsorption syndromes and are the drugs of choice if oral replacement is required.

Very little vitamin K is stored in the body so that evidence of deficiency becomes evident within weeks of its development. The routes of metabolism of the vitamin are unknown but negligible amounts are excreted unchanged in the urine. Large amounts are present in the faeces however and are probably derived from faecal bacteria. The amount falls in patients treated with antibacterial agents as these drugs reduce the number of organisms in the colon.

ADVERSE EFFECTS The fat-soluble forms of vitamin K have a negligible toxicity even in large doses.

Haemolytic anaemia Water soluble analogues of vitamin K may cause haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency, and in high doses may do so in normal subjects. They are highly active redox compounds. They are readily oxidised themselves and may then oxidise ferrous iron of haemoglobin to ferric iron so forming the less stable methaemoglobin and sulfhaemoglobin and causing haemolysis. The water-soluble forms of vitamin K are dangerous to neonates, who are less able to conjugate the increased bilirubin that results from haemolysis (*see* Chapter 42). Unconjugated bilirubin will accumulate in the plasma in this situation and causes kernicterus if present in sufficient concentration.

Drug interactions Oral anticoagulants antagonise the actions of vitamin K (*see* Chapter 33). Broad-spectrum antibacterial agents decrease vitamin K absorption by reducing faecal bacteria. Vitamin K deficiency however does not usually develop unless there is also a dietary deficiency or vitamin K malabsorption but these agents often enhance responsiveness to oral anticoagulants. Liquid paraffin may reduce vitamin K absorption.

CLINICAL USE Vitamin K is only of established value in the treatment or prophylaxis of vitamin K deficiency states.

Haemorrhagic disease of the newborn The plasma concentrations of vitamin K dependent clotting factors are low in neonates and especially in premature babies. This is due to the absence of colonic bacteria which only colonise the bowel in the first two weeks of life. When vitamin K deficiency is severe, haemorrhagic disease of the newborn develops. Vitamin K therapy to the mother shortly before birth, or to the child at birth, usually takes several days to take effect, while clotting factors are being synthesised. Prophylaxis with vitamin K orally to the mother for two weeks before delivery however is effective at preventing deficiency in the neonate.

Liver disease Parenteral vitamin K_1 is effective at correcting the vitamin K deficiency that develops due to prolonged biliary obstruction or to gastrointestinal disorders. However, it is seldom effective when the fall in the concentration of clotting factors in the plasma is due to hepatocellular damage.

Antagonism of oral anticoagulants If haemorrhage occurs during therapy with oral anticoagulants, vitamin K_1 given intravenously (5–20 mg) causes a detect-

able increase in plasma clotting factors within 8–10 hours and is a more effective antagonist of these drugs than the water-soluble forms of the vitamin. The actions of oral anticoagulants are antagonised for a period up to two weeks after vitamin K_1 administration, depending on the dose of the vitamin administered. If continued anticoagulant therapy is required it is advisable to administer a small dose (5–10 mg) initially and to repeat this if necessary.

Vitamin B complex

There are a number of agents usually considered under the heading of the vitamin B complex, but only those commonly used in therapy will be considered. Vitamin B_{12} is discussed in Chapter 32.

Thiamine (anuerine B_1)

ACTION Thiamine is converted in the body to its active form thiamine pyrophosphate, ATP being the source of pyrophosphate. Thiamine pyrophosphate (TPP) is a coenzyme in the decarboxylation of pyruvic and α-ketoglutaric acids and hence is essential for the normal metabolism of carbohydrates. The requirement for thiamine increases with an increase in the carbohydrate content of the diet and with an increase in the metabolic rate as in hyperthyroidism.

Deficiency syndrome Thiamine is present in a wide range of foods and deficiency syndromes are only seen in Western communities as a consequence of dietary neglect (e.g. ethanol dependence, psychotic states), as a consequence of prolonged vomiting (e.g. hyperemesis gravidarum) or of malabsorption. Biochemical evidence of deficiency can be obtained by determining red blood corpuscle (RBC) transketolase as this enzyme requires TPP as a cofactor. Deficiency is judged to be present when addition of TPP causes an increase of more than 15% in the enzymes activity. This test gives evidence of deficiency within two weeks if B_1 intake ceases altogether.

Clinical evidence of thiamine deficiency does not usually develop for some weeks. Deficiency may be evidenced by Wernicke's encephalopathy (external ophthalmoplegia, ptosis, nystagmus and ataxia) and mental disturbances (e.g. Korsakov's psychosis in which there is a loss of recent memory and gross confabulation) and a peripheral neuropathy. A high output form of congestive heart failure (beri) occurs as a late manifestation of deficiency.

DRUG FATE

Thiamine, which has a quaternary nitrogen, is only slowly absorbed from the bowel and its absorption is retarded by ethanol. It is widely distributed in the tissues, the concentration being highest in the liver, kidney, heart and brain. It is metabolised fairly rapidly and the amount present in the body falls within days if a diet deficient in thiamine is administered.

ADVERSE EFFECTS

Thiamine causes no adverse effects, even in high doses (400 mg) orally and only very rarely if such doses are given intravenously.

CLINICAL USE

Thiamine is only of established value in the prophylaxis and therapy of deficiency states. In severe deficiency states, e.g. Wernicke's encephalopathy, 50 mg i.v. causes an improvement in nystagmus, ataxia and ophthalmoplegia in 1–6 hours. There is usually only a partial improvement in the confusion state and peripheral neuropathy and this only occurs slowly, over a period of weeks.

Nicotinic acid Nicotinic acid or its precursors, nicotinamide and tryptophan, are present in many foods, but are low in corn and its products. Nicotinamide and tryptophan are converted in the liver to nicotinic acid.

ACTION

Nutritional Nicotinic acid is converted in the body to its active forms, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These are coenzymes to dehydrogenases and as such, are essential for normal cell respiration.

Deficiency syndrome (pellagra) the syndrome is characterised by an erythematous rash, similar in appearance and distribution to sunburn, in areas exposed to daylight; gastrointestinal disorders, stomatitis, sialorrhoea, nausea, diarrhoea; mental disturbances and a peripheral neuropathy.

Vasodilatation Nicotinic acid, but not nicotinamide, causes vasodilatation for 1–3 hours after ingestion. Blood vessels of the skin are principally affected, and there is no significant increase in cerebral or myocardial blood flow or that in peripheral arteries. Symptoms of vasodilatation, flushing and pruritus, wear off in 2–3 weeks if treatment is continued.

Hypolipidaemia In large doses (0·3–9 g/day) nicotinic acid inhibits adipose tissue lipolysis, depresses plasma free fatty acid concentration and decreases very low density lipoprotein (VLDL) synthesis (*see* Chapter 24).

DRUG FATE Nicotinic acid and nicotinamide are water soluble, are readily absorbed from the small bowel and are widely distributed in the tissues. In low doses, most of the vitamin is metabolised but in high doses a large amount is excreted unchanged in the urine.

ADVERSE EFFECTS Nicotinic acid and its amide are safe in very high doses. Side-effects are common however, when nicotinic acid is used as a hypolipidaemic agent. Flushing and itching occur in the majority of patients but wear off after 2–3 weeks. Impaired liver function tests occur but are reversible on stopping the drug. Diabetes mellitus may be exacerbated and this is related to the effect of nicotinic acid on lipid metabolism. Hyperuricaemia and clinical attacks of gout may also occur.

Drug interactions Nicotinic acid antagonises the action of hypoglycaemic agents and enhances those of hypotensive agents.

CLINICAL USE

Pellagra Nicotinic acid in high doses (0·5 g/day) corrects the clinical manifestation of pellagra within days.

Hyperlipidaemia Nicotinic acid (0·3–9 g/day) lowers VLDL and LDL in hyperlipidaemia states. In normal people there is no evidence that it prevents arterial disease or its complications (*see* Chapter 24).

Peripheral vascular disease Although nicotinic acid is commonly given to relieve the symptoms of peripheral vascular disease, there is no convincing evidence to show that it is of benefit in either Raynaud's disease or intermittent claudication.

Pyridoxine (vitamin B_6)

ACTION Pyridoxine, pyridoxal and pyridoxamine are present in many foods. They are all converted in the body by pyridoxal phosphatase to the active form of the vitamin, pyridoxal phosphate, which is a coenzyme in the metabolism of tryptophan and other amino acids.

Deficiency syndrome is characterised by glossitis, stomatitis, a seborrhoeic dermatitis of the face, and a peripheral neuropathy.

All forms of vitamin B_6 are readily absorbed from the bowel and are excreted as metabolites in the urine.

There are no adverse effects attributable to pyridoxine.

CLINICAL USE

Deficiency The deficiency syndrome rarely, if ever, occurs alone and pyridoxine is usually included in multivitamin preparations used in patients suffering from malnutrition.

Drug interactions Pyridoxine is effective at preventing and treating the peripheral neuropathy that may occur when high doses of isoniazid are used. Isoniazid is a potent inhibitor of pyridoxal phosphatase and it is assumed that this is responsible for its peripheral neuropathic effects. Pyridoxal phosphate is also a coenzyme to aromatic amino acid decarboxylase. This enzyme converts L-dopa to dopamine and if pyridoxine is given with L-dopa there is a fall in the amount of L-dopa in the plasma and hence in the amount that penetrates the blood-brain barrier. Thus pyridoxine antagonises the actions of L-dopa alone, but not when that drug is administered with a dopa decarboxylase inhibitor (Chapter 16).

Affective disorders Pyridoxine is a coenzyme in the synthesis of 5-hydroxytryptamine, a deficiency of which has been implicated in depressive illness. It has been used in the treatment of depression but its effectiveness has not been substantiated, neither has the relationship between pyridoxine deficiency and depressive illness.

Oxalate stones In subjects who form oxalate renal stones, pyridoxine decreases stone formation and the clinical consequences of renal stones. Such subjects have an enzyme defect in the metabolic pathway of glyoxylate

metabolism and pyridoxine probably acts by expediting the transamination of glyoxylate to glycine, hence decreasing the oxylate in the plasma and urine.

Riboflavine

ACTIONS Riboflavine is present in a wide variety of foods. It is active in the body as flavine mononucleotide and flavine adenine dinucleotide, which act as coenzymes in the electron transfer systems of cells. A deficiency causes vascularisation of the cornea, cheilosis and glossitis, but rarely occurs without evidence of deficiency of other vitamins.

Riboflavine is readily absorbed from the bowel and is excreted in the urine as metabolites. It is elaborated by gut bacteria and is present in the faeces, but in a non-absorbable form.

There are no toxic effects attributable to riboflavine.

CLINICAL USE Riboflavine is used only in the prevention and treatment of deficiency states, usually in multivitamin preparations.

Vitamin C

Ascorbic acid (vitamin C) is present in fruit and fresh vegetables including potatoes. It is also present in most preserved foods where it is used as a reducing agent so that a deficiency syndrome (scurvy) is now rare except in the elderly.

ACTIONS Ascorbic acid is a highly active redox compound being readily oxidised to dehydroascorbic acid. The relationship between this property and its biological action is uncertain but it is possible that it may be important in maintaining adequate amounts of reduced sulphydryl groups in the tissues. It is a cofactor in the hydroxylation of proline by collagen proline hydroxylase and as collagen is an important component of ground substance, when the vitamin is deficient the physical properties of ground substance are changed and its supportive function impaired.

Deficiency syndrome The clinical features of scurvy are the consequence of increased capillary fragility and consists of haemorrhages at the diaphyseal junction and subperiosteally in growing children, causing diaphyseal dysunion. In both adults and children, bleeding gums and haemorrhages around hair follicles and into subcutaneous tissues occur. Wound healing is slowed and resistance to infection reduced. Anaemia is common, the ascorbic acid concentration in the plasma and white blood corpuscles is reduced and there is a reduction in the urine concentration of ascorbic acid and hydroxyproline.

DRUG FATE Ascorbic acid is readily absorbed from the bowel, is widely distributed in the tissues and is present in high concentrations in white blood corpuscles and platelets. It is partly excreted unchanged in the urine, the amount varying with the plasma concentration and partly metabolised, urinary oxalate being an important metabolite.

ADVERSE EFFECTS Ascorbic acid causes no adverse effects, even in large doses.

CLINICAL USE

Scurvy In western communities, vitamin C deficiency occurs most in old people living alone on a diet deficient in fruit and vegetables. Replacement therapy with fruit juice etc., is usually sufficient and corrects the deficiency syndrome in 1–2 weeks.

Reducing agent The vitamin may be used for its reducing properties in methaemoglobinaemia, although methylene blue is generally more effective.

Oral iron preparations commonly contain ascorbic acid as the reducing properties of the vitamin help to maintain iron in the ferrous state, in which form it is most readily absorbed (*see* Chapter 32).

Prophylaxis against colds Large doses of vitamin C (1–3 g/day) have been widely held to prevent colds. This effect however has not been substantiated by prospective controlled clinical trials, although there is some evidence that large doses may ameliorate and reduce the duration of colds.

Other conditions Although vitamin C has been used in a large number of clinical conditions, there is no convincing evidence in patients who are not suffering from vitamin C deficiency that the vitamin is of any value.

Some vitamin preparations

	Adult daily dose	
	Therapy	*Prophylaxis*
Vitamin A	10–50 000 u	4–10 000 u
Calciferol (D_2)	50–200 000 u 1·25–5·0 mg	4–800 u
Activated dehydrocholesterol (D_3)	0·125–1·25 mg	20 μg
Phytomenadione (K_1)	5–20 mg	
Menaphthone (K_3)	5–20 mg	
Menaphtone sodium bisulphite	5–20 mg	
Menadiol sodium diphosphate	5–20 mg	
Thiamine hydrochloride	25–100 mg	2–5 mg
Nicotinic acid	50–250 mg	15–30 mg
Nicotinamide	50–250 mg	15–30 mg
Pyridoxine hydrochloride	50–150 mg	2 mg
Riboflavine	5–10 mg	1–4 mg
Ascorbic acid	200–600 mg	25–75 mg

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Chapter 35

Chemotherapy with Antibacterial Agents

GENERAL PRINCIPLES

The concept that chemicals could be selectively toxic to bacteria was introduced by Paul Ehrlich in 1904 while he was studying the tissue binding properties of dyes and he used the term chemotherapy to describe the use of selectively toxic chemicals in the treatment of bacterial infections. The first successful chemotherapeutic agents, the sulphonamides, resulted from studies carried out in Germany on the biological properties of azo-dyes, which culminated in the introduction to clinical medicine of the first sulphonamide, prontosil, by Domagk in 1935. Independent of the development of the sulphonamides, Fleming, in 1929 at St. Mary's Hospital, London, observed that a fungal extract, which he named penicillin, was capable of killing bacteria in culture media and the successful use of penicillin in the treatment of a bacterial infection in man was achieved by Chain and Florey and co-workers in Oxford in 1940.

Penicillin was the first antibiotic, i.e. chemotherapeutic agent elaborated by a micro-organism, and it was soon followed by many others such as tetracycline, streptomycin, chloramphenicol, most of which were discovered by massive screening operations carried out by the pharmaceutical industry, The distinction between chemotherapeutic agent and antibiotic has become blurred with methods of synthesising some antibiotics, such as chloramphenicol, and the development of semi-synthetic antibacterial agents, such as the new penicillins and cephalosporins, in which a synthetic substrate is incorporated into a precursor molecule by micro-organisms. In this text, the term antibacterial agent will be used for any chemical used in the treatment of bacterial infections.

There are now available a large number of antibacterial agents and all known pathogenic bacteria are sensitive to one or more of these agents. However, bacterial infections are still common causes of morbidity and mortality indicating that there is more to the treatment and prevention of bacterial infections than the availability of large numbers of highly effective antibacterial agents.

The Objective of Antibacterial Therapy Unlike the situation in most diseases, in those due to bacteria, the cause of the disease is known and the objective of therapy is therefore obvious, to eliminate invading bacteria without harming host tissues. The success of drugs used for this purpose depends on the

degree to which they are selectively toxic to bacteria and as this depends largely on structural and biochemical differences between bacterial and mammalian cells, these differences will be briefly summarised.

Bacteria—structure and function A prototype bacterium is shown in Fig. 1. Although pathogenic bacteria differ considerably in structure and function the major features common to all are shown in the figure. The major differences between the bacterial and the mammalian cell are, therefore, the possession of a cell wall and, in some cases, a capsule in addition to the cytoplasmic membrane.

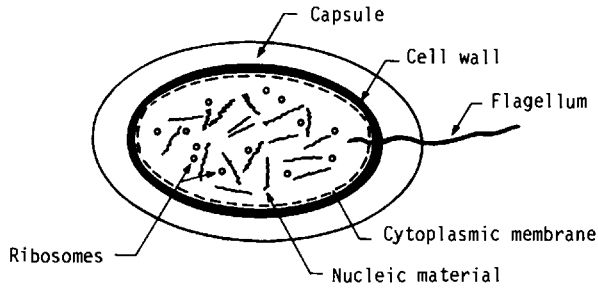


FIG. 1 Prototype bacterium.

Capsule Is gelatinous in nature and usually composed of polysaccharides and is of variable thickness.

Cell wall Is a rigid structure that maintains the shape and volume of the bacteria, despite changes in environmental osmolarity, the rigidity being due to a layer of glycoprotein in the cell wall. The cell wall of Gram-positive organisms is thicker than that of Gram-negative organisms, but the latter is more complex and has an outer layer of lipoprotein. These differences account for some of the differences in susceptibility to antibacterial agents of Gram-positive and Gram-negative organisms.

Cytoplasmic membrane Is a lipoprotein structure similar in its permeability characteristics to mammalian cell membranes and possessing active transport systems for specific molecules. It is responsible for maintaining the hyperosmolarity of bacterial cytoplasm relative to that of host tissue water, the osmolarity of the cytoplasm of Gram-positive organisms being greater than that of Gram-negative organisms.

Cytoplasm and nucleus The cytoplasmic organelles are similar to those in mammalian cells but the nuclear material in bacteria is less aggregated.

The mode of action of antibacterial agents The antibacterial agents can be divided into three broad categories in terms of the principal toxic effects on bacteria.

1. Agents that impair cell wall synthesis.

e.g. Penicillins
Cephalosporins
Cycloserine
Vancomycin
Bacitracin

All agents in this group impair synthesis of the glycoprotein layer in the cell wall. Synthesis of this layer takes place in three steps.

Step 1. Formation of uridine nucleotide precursors.
Step 2. Addition of pentapeptides.
Step 3. Cross linking of linear peptide strands.

Steps 1 and 2 take place in the bacterial cytoplasm and during these stages, wall precursors are soluble. Step 3 takes place outside the cytoplasmic membrane and converts the layer into an insoluble, rigid structure.

Bacteria grown in the presence of the agents listed above lack a rigid cell wall and lyse in the hypo-osmolar environment such as exists in most host tissues. In an iso-osmolar environment, bacteria continue to grow and multiply, albeit with an abnormal cell wall, when they are known as spheroplasts or L-forms.

2. Agents that impair cytoplasmic membrane synthesis and function.

e.g. Polymyxin
Bacitracin

Agents with surface-active properties such as the polypeptides polymyxin and bacitracin, become incorporated into the lipoprotein cytoplasmic membrane and cause an increase in its permeability and a leak of intracellular contents. Such agents are unique in being toxic to bacteria in their dormant phase, i.e. when they are not undergoing cell growth and cell division. Bacitracin also affects cell wall formation. Other agents, such as streptomycin, which also impair cytoplasmic membrane function, probably do so as a secondary effect.

3. Agents that impair nucleic acid and protein synthesis.

e.g. Sulphonamides
Trimethoprim
Tetracyclines
Chloramphenicol
Aminoglycosides
Macrolides
Rifampicin

Agents in this group may impair any step or steps in the synthesis of DNA and its replication in cell division, DNA-dependent RNA synthesis, or any site in the various steps in protein synthesis. For example, sulphonamides and trimethoprim inhibit the synthesis of nucleotide precursors ((a) in Fig. 2); the antituberculous agent rifampicin, inhibits DNA-dependent RNA polymerase (b); tetracyclines and chloramphenicol prevent the link up of ribosomes, messenger-RNA and transfer-RNA with attached amino acid (c); aminoglycosides cause misreading or the codon by transfer-RNA, so that an inappropriate amino acid is added to the growing peptide chain (d) (mismatching);

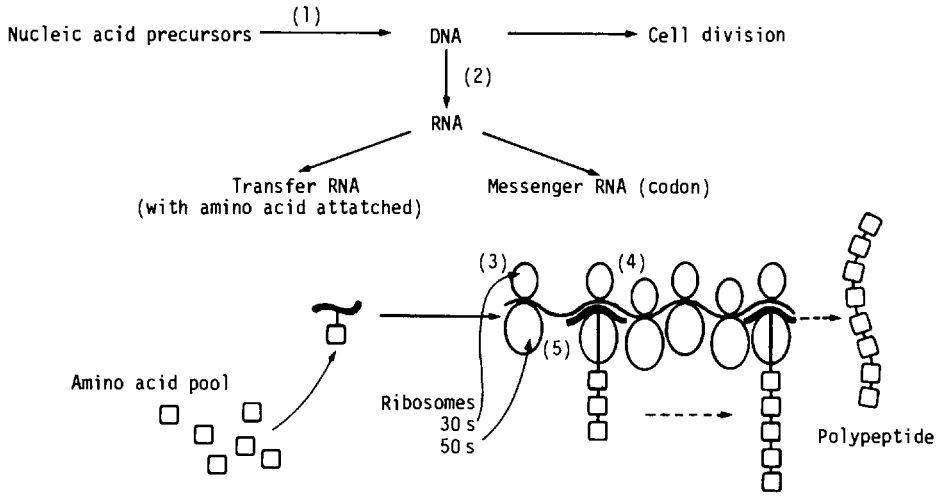


FIG. 2 Sites of action of antibacterial agents that impair nucleic acid and protein synthesis.
(1) Block nucleic acid synthesis e.g. sulphonamides, co-trimoxazole, nalidixic acid.
(2) Block RNA synthesis e.g. rifampicin.
(3) Prevent the link up of messenger RNA with ribosomes and transfer RNA e.g. tetracycline, chloramphenicol.
(4) Misreading of codon and synthesis of faulty proteins (site of action 30S ribosomes) e.g. aminoglycosides, streptomycin etc.
(5) Block protein synthesis (site of action 50S ribosomes) e.g. macrolides, erythromycin etc.

macrolides impair protein synthesis by competing with amino acids for ribosomal binding sites (e).

The selective toxicity of antibacterial agents of class 1 is based on a major structural difference between bacterial and mammalian cells, that is the possession of a cell wall by the former and not the latter. The selective toxicity of agents of classes 2 and 3 is not based on major differences in structure but rather on functional differences, e.g. the mammalian cell membrane is permeable to folic acid (FA) and it can therefore use FA in the diet; bacterial cell walls however are impermeable and the bacteria must therefore synthesise their own FA and are thus susceptible to sulphonamides which inhibit FA synthesis. The enzyme dihydrofolate reductase of bacterial origin, the site of antibacterial activity of trimethoprim, has a 50 000 times greater affinity for trimethoprim than the enzyme with the same function in mammalian cells. Chloramphenicol is much more readily bound to messenger RNA of bacterial origin than to RNA of mammalian origin.

The effects of antibacterial agents on bacteria *in vitro* Bacteria grown in culture media (*in vitro*) in the presence of antibacterial agents will respond in one of the ways shown in Fig. 3.

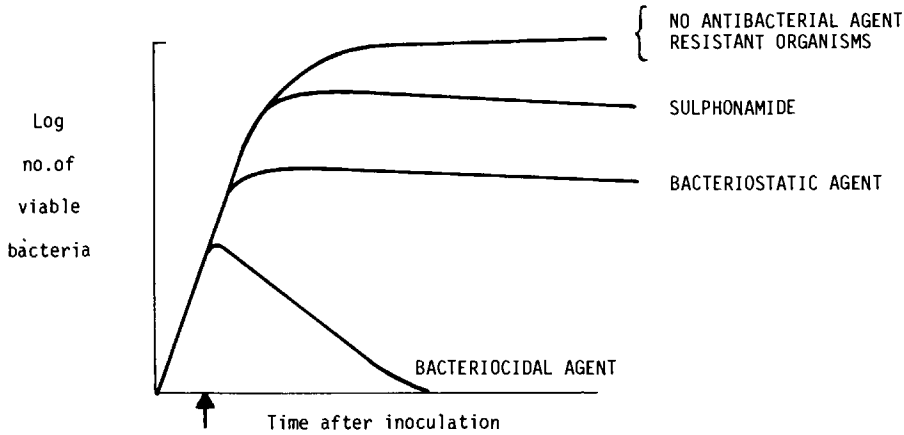


FIG. 3 Schematic representation of the effects of antibacterial agents *in vitro*. At zero time, culture medium was inoculated. The arrow depicts the time that the antibacterial agents were applied.

Resistant organisms Bacterial growing *in vitro*, in the absence of antibacterial agents or in the presence of an agent to which the bacteria are resistant, divide rapidly initially, cell replication exceeding cell death but after a time, these processes equilibrate.

Bacteriostatic agents These agents, e.g. sulphonamides, tetracyclines, chloramphenicol, prevent cell division but do not kill the bacteria. The lag between onset of action of sulphonamides is due to the availability of folic acid synthesised prior to the addition of sulphonamide.

Bacteriocidal agents Agents of this type, e.g. penicillins, cephalosporins, aminoglycosides, trimethoprim-sulphonamide combination (co-trimoxazole), kill bacteria during the stage of rapid cell division and cause a rapid fall in the number of viable bacteria present.

In common with all other drugs, the effects of antibacterial agents both *in vitro* and *in vivo* are dose-dependent and the terms resistant, bacteriostatic and bacteriocidal, refer to the effects of agents at the maximal concentrations *in vivo* that do not cause adverse effects. The minimal inhibitory concentration *in vitro* (MIC), i.e. the lowest concentration of antibacterial agent that stops cell division, is a guide to the antibacterial effect of a given agent against a specific pathogen. The probability that the agent will be of value clinically depends on the ratio of the MIC to the plasma concentration at which adverse reactions commonly occur.

The effects of antibacterial agents on bacteria *in vivo* The response of bacteria at a site of infection *in vivo* is subject to many more variables than are operative *in vitro*. The most important of these are—

1. The body's defence mechanism Invading bacteria are subject to attack by both humoral and cellular immune mechanisms and by polymorphonuclear leukocytes and macrophages. The integrity of these defence mechanisms enhances the response to all antibacterial agents and is essential for the effectiveness of those that are only bacteriostatic, as with these agents, elimination of existing bacteria is left entirely to the body's defence mechanisms.

The site of infection may determine the effectiveness of these defence mechanisms. Thus, intracellular organisms such as the tubercle bacillus, *Brucella abortus,* and *Salmonella typhi,* are not affected by humoral immune mechanisms but only by the slow cellular mechanisms. This partly explains the slowness with which these infections respond to antibacterial agents. Infections at sites where the concentration of polymorphs and macrophages is low, such as on heart valves and the meninges, are more resistant to antibacterial agents than infections elsewhere.

2. Concentration of antibacterial agent at sites of infection In culture media, the concentrations of antibacterial agent remains constant unless the agent is metabolised by the bacteria but *in vivo* the concentration of the agent at a site of infection is determined by the concentration in the plasma, the blood supply of the infected site and the facility with which the drugs can diffuse to the infected site. In general, the higher the plasma concentration and the longer the plasma half-life of the agent, the higher the drug-tissue concentration. Most antibacterial agents are large polar molecules and diffuse slowly across cell membranes and the concentrations they achieve at intracellular sites, in cerebrospinal fluid and in the extracellular space in the central nervous system, are very much lower than those achieved in the plasma. This explains, in part, the ineffectiveness of some agents against intracellular pathogens and in meningitis. Drug concentrations may also be affected by disease, e.g. in severe renal disease, antibacterial agents such as the cephalosporins, penicillins and aminoglycosides accumulate in the plasma as they are mostly excreted unchanged in the urine, but their concentration in the urine falls.

3. Host tissue environment The effect of antibacterial agents may be profoundly altered by conditions at the site of infection. The various factors antagonising the antibacterial agents are dealt with under constitutive factors determining bacterial resistance.

Resistance to antibacterial agents Resistance to antibacterial agents may be due to environmental factors at sites of infection (constitutive factors) or to genetic factors. In the former case, the bacteria are not resistant to the antibacterial agent in culture media but in the latter they are.

1. Constitutive factors All antibacterial agents are most effective against rapidly dividing organisms and bacteria in the dormant phase are relatively resistant. In pus, most bacteria are in a dormant phase; bacteriostatic drugs, by preventing

cell division, induce a dormant phase; the greater the number of organisms at sites of infection the higher the concentration in the dormant phase.

Salts such as phosphates and magnesium ions, antagonise the actions of aminoglycoside antibacterial agents and the hydrogen ion concentration also effects antibacterial activity, presumably by altering binding of drugs to tissues. Basic agents such as aminoglycosides, erythromycin and lincomycin are antagonised in acid media and tetracyclines and acidic agents such as novobiocin and mandelic acid are less effective in alkaline media.

Folic acid, para-aminobenzoic acid and the presence of 1-carbon donors and recipients, such as may exist in pus and tissue breakdown products, antagonise the action of sulphonamides.

2. Genetic factors There is considerable variation in susceptibility of bacteria to antibacterial agents, even within a given strain. Resistance to an agent may exist prior to the time when the bacteria are exposed to it or it may be acquired during exposure to the agent. These two patterns of resistance are shown in Fig. 4. In both cases resistance is determined genetically; in (b) it has resulted from a random mutation, the antibacterial agent acting as an agent of selection.

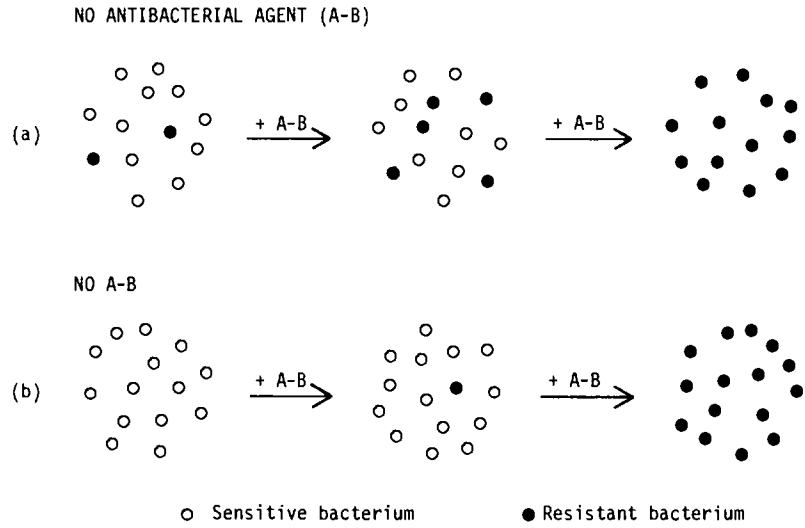


FIG. 4 Schematic representation of two patterns of emergence of resistance during antibacterial therapy. (a) resistant organisms are present in small numbers prior to antibacterial therapy. (b) resistance occurs during therapy a the consequence of a random mutation.

Emergence of resistance Resistance to an antibacterial agent may emerge rapidly or slowly. Rapid emergence results from a single mutation and occurs with some aminoglycosides, e.g. streptomycin. Slow emergence occurs as the

consequence of a series of mutations, each resulting in a slight decrease in the susceptibility of the organisms to the antibacterial agent and such a pattern of emergence of resistance occurs with tetracyclines and chloramphenicol.

The pattern of emergence of resistance also varies between bacteria. Staphylococci, the tubercle bacillus and many Gram-negative organisms readily develop resistance to various antibacterial agents, whereas organisms such as the haemolytic streptococcus and *Treponema pallidum* do so much less readily.

Mechanisms of resistance In many instances, the mechanism determining bacterial resistance to an antibacterial agent are not known but there are several mechanisms of clinical importance that are understood.

1. Metabolism of the antibacterial agent by bacteria The most important example is the inactivation of benzylpenicillin by β-lactamase-producing strains of *Staphylococcus aureus*. This enzyme may be present in the cytoplasm and be released on bacterial cell death or may be secreted by the live bacteria. Several types of β-lactamase (penicillinase and cephalosporinase) have been identified. The enzyme is elaborated by several species of *E. coli* and pseudomonas as well as by staphylococci. Some species of *E. coli* and staphylococci may also be able to inactivate chloramphenicol by means of the enzyme chloramphenicol acetyltransferase.

2. Altered affinity of receptor site The intracellular site of streptomycin is the 30S ribosome. The 30S ribosome of resistant organisms has a greatly reduced affinity for streptomycin and this correlates with the degree of resistance to its antibacterial effect.

Similarly, bacteria that have acquired resistance to sulphonamides have a para-aminobenzoic acid binding enzyme with a much lower affinity for sulphonamides than do sensitive organisms.

3. Alterations in cell wall permeability A few bacteria, such as *Strep. faecalis*, can utilise folic acid present in the environment, presumably because their cell walls are permeable to folic acid. Such bacteria are therefore resistant to sulphonamides.

Staphylococci resistant to methicillin have a thicker capsule than sensitive organisms and this may confer resistance by impairing diffusion of the antibacterial agents to their site of action in the cell wall.

4. Genetically determined resistance The genes determining resistance to antibacterial agents may be transferred in two ways:

(a) Genes may be carried on chromosomes and passed on to subsequent generations by means of cell division.

(b) Genes may be carried on extra chromosomal pieces of DNA known as plasmids. Such extra chromosomal resistance factors (R-factors) may be transferred by contact between organisms (conjugation) and may occur

between organisms of the same or different species. R-factors have been found of clinical importance in the treatment of infections by many Gram-negative organisms, especially enteric infections, e.g. shigella dysentery, as these organisms commonly conjugate, unlike Gram-positive organisms which are not known to do so. R-factors usually confer resistance to several antibacterial agents at the same time such as chloramphenicol, tetracyclines, streptomycin and gentamicin.

Administration of antibacterial agents The objective of antibacterial therapy is to eliminate all pathogens at the site of infection. The success of an antibacterial agent against a specific pathogen depends on many factors, of which the *in vitro* susceptibility of the organism to the particular agent is the only one that can be determined. Thus for each agent, the dose and dose interval, route of administration and duration of therapy is established empirically. In the individual patient, the response to a given agent is determined in terms of the patient's symptoms and signs, temperature, white cell count, X-rays, etc. In general, as all antibacterial agents are most effective against rapidly dividing organisms, the shorter the doubling time, the shorter the course of therapy, e.g. a course of antibacterial therapy in staphylococcal infections (doubling time 20 minutes) lasts 5–10 days, that for infections due to *Mycobacterium tuberculosis* (doubling time 30 hours) last 6–18 months.

THE PENICILLINS

The penicillins are amongst the most widely used antibacterial agents, their popularity being based on their effectiveness as antibacterial agents and the very low incidence of the serious adverse effects they cause.

Source and Chemistry The mold, *Penicillium chrysogenum*, elaborates a number of penicillins of which only benzylpenicillin is commonly used clinically. If the mold is grown in a medium lacking an *acyl* side chain donor, a precursor of penicillin *6-aminopenicillanic acid* is produced. This may be condensed chemically with many acids producing a wide range of 'semi-synthetic' penicillins which differ only in their side chains and antibacterial properties (Table 1).

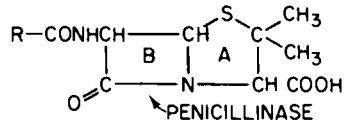
Penicillins have molecular weights of 350–500; they are acidic (the pK for benzylpenicillin being 2·76) and are nearly fully-ionised in the physiological pH range. They are highly water soluble and vary in the degree to which they are susceptible to acid hydrolysis, the half-time for hydrolysis of benzylpenicillin or methicillin at pH 1·3 is 2–3 minutes, but for ampicillin is 660 minutes. The pH range of maximal stability is 5·5–7·5.

Antibacterial Action

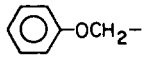
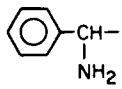
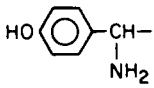
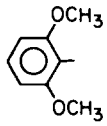
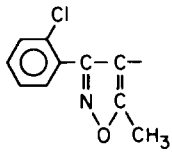
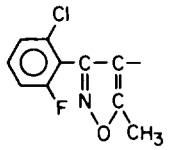
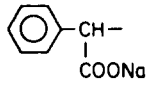
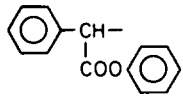
The penicillins and cephalosporins have a common mode of action and effect on bacteria but differ in relative potency and antibacterial spectrum. They impair formation of the rigid glycoprotein layer of bacterial cell walls by inhibiting an enzyme, a transpeptidase, responsible for the final step in the formation of the

Table 1
The penicillins

Basic structure



A = THIAZOLIDINE RING
B = BETA LACTAM RING

SIDE CHAIN (R)	APPROVED NAME	ADULT DOSE (g)	ROUTE	DOSE INTERVAL (h)
	BENZYLPENICILLIN	0.25–10 MILLION UNITS	i.m., i.v.	4–6
	SEMISYNTHETIC PENICILLINS			
	PHENOXYMETHYL-PENICILLIN	0.25–2 (g)	Oral, i.m., i.v.	4–6
	AMPICILLIN	0.25–2	Oral, i.m., i.v.	4–6
	AMOXYCILLIN	0.25–1	Oral, i.m., i.v.	4–6
	METHICILLIN	1–4	i.m., i.v.	4–6
	CLOXACILLIN	0.50–2	Oral, i.m., i.v.	4–6
	FLUCLOXACILLIN	0.25–1	Oral, i.m., i.v.	4–6
	CARBENICILLIN	1–6	i.m., i.v.	4–6
	CARFECILLIN	1–6	Oral, i.m., i.v.	4–6

rigid glycoprotein layer, the cross linking of two peptide chains. The cell walls of susceptible organisms, grown in the presence of penicillin, lack rigidity, and as the bacterial cytoplasm is hyperosmolar to the surrounding environment, the

organisms swell up and lyse. Penicillins and cephalosporins are therefore generally bacteriocidal and are most effective when bacteria are rapidly dividing, having little effect on bacteria in a dormant phase. They are as effective *in vivo* as *in vitro*, and are not antagonised by pus or tissue breakdown products. A higher plasma concentration is necessary to cure infections *in vivo* compared to those that are bacteriocidal *in vitro*, but this is probably due to binding by plasma proteins.

Individual Agents

Benzylpenicillin One of the first penicillins produced commercially, benzylpenicillin, still has an important place in therapy. It has a narrow spectrum, is acid-labile and is readily hydrolysed by β-lactamase.

SPECTRUM

Staph. aureus	*Bacillus anthracis*
Strep. pyogenes	*Clostridium welchii*
Streptococcus viridans	*tetani*
Strep. faecalis	*Corynebacterium diphtherii*
Enterococci	*Actinomyces*
Pneumococcus	*Treponema pallidum*
	Leptospira spp.
Gonococcus	
Meningococcus	

The spectrum of benzylpenicillin is described as being narrow, as it is relatively ineffective against Gram-negative bacilli. It is amongst the most effective antibacterial agents, some organisms being susceptible *in vitro* to as low a concentration as 20 μg/ml.

RESISTANCE Naturally resistant organisms, such as Gram-negative bacilli, have cell walls that are relatively impermeable to benzylpenicillin, preventing it reaching its site of action when applied in the usual therapeutic concentrations.

Acquired resistance No important degree of resistance to benzylpenicillin has been acquired by *Streptococcus pyogenes* or the pneumococcus; a variable degree has been acquired by the meningococcus and the gonococcus. A component of the latter is probably the low plasma concentration of benzylpenicillin achieved when it is administered as a depot preparation (e.g. procaine penicillin) which is the custom in many venereal disease clinics.

Staphylococcal resistance A very high proportion of *Staph. aureus* strains, cultured from patients or personnel working in hospital, are resistant to benzylpenicillin. Resistance is due to production by such organisms of β-lactamase (penicillinase), an enzyme that facilitates the hydrolysis of the β-lactam ring at the position shown in Table 1, converting benzylpenicillin to

the inactive penicilloic acid. Semi-synthetic penicillins such as methicillin, possess bulky side chains that shield the β-lactam ring from enzymic hydrolysis. Penicillin resistance does not arise during treatment of susceptible organisms and as penicillinase-producing staphs may be in a minority in some staphylococcal infections, benzylpenicillin may still be an effective antibacterial agent if administered with a penicillinase resistant penicillin, e.g. cloxacillin, fucidin or a cephalosporin. Rarely, apparent resistance of susceptible organisms, such as *Strep. pyogenes,* is attributable to penicillinase producing staphs at the site of infection.

DRUG FATE Only 20–25% of an oral dose reaches the blood stream due to rapid hydrolysis of benzylpenicillin in the acid gastric secretions. Benzylpenicillin is rapidly absorbed from intramuscular injection sites reaching a peak plasma concentration in 30–60 minutes.

The apparent volume of distribution approximates to the extracellular space, presumably as its high water-solubility impairs its diffusion through lipid cell membranes. Tissue concentrations are low compared to that in the plasma and are low in pleural, peritoneal and pericardial spaces and in the synovial fluid and abscess cavities. In plasma, 35–60% is bound to albumin and part of this can be displaced by other acidic drugs such as probenecid and sulphonamides.

Blood-brain barrier In normal patients and experimental animals, the concentration in the cerebrospinal fluid (CSF) varies between 0·5–6% that in the plasma due to the impermeability of the lipid blood-brain barrier to benzylpenicillin. Benzylpenicillin is also actively transported out of the CSF by the choroid plexus. In meningitis, the permeability of the meninges is increased and CSF/plasma concentration ratio may be 3–4 times that of normal patients.

The half-life of benzylpenicillin after i.v. bolus injection is 30–40 minutes, 58–85% being eliminated in the urine and a small proportion in the bile. There is no evidence that benzylpenicillin is metabolised to an important extent. Renal clearance is by glomerular filtration and active tubular secretion, clearance rates being as high as 500–1000 ml/min. The tubular active secretory mechanism may be inhibited by acidic compounds, notably probenecid and phenylbutazone, which in therapeutic doses, may increase the $t_{\frac{1}{2}}$ 2–3 times. In renal failure the $t_{\frac{1}{2}}$ of benzylpenicillin varies with the creatinine clearance and at values of 10 ml/min may be 10 hours or longer.

ADVERSE EFFECTS The toxicity of benzylpenicillin to human tissues is very low after systemic administration. The central nervous system is the most sensitive tissue to this drug and if administered intravenously in very high doses (50–100 mega units/24 hours) or intrathecally, penicillin may cause an encephalopathy with confusion, hyper-reflexia, myoclonic and grand mal seizures and occasionally coma. Central nervous system toxicity is more common in the presence of renal failure and very rare after i.m. or oral administration. The impermeability of the blood-brain barrier accounts for the very low toxicity of penicillin after systemic injection, and when administered intrathecally no more than 20 000

units should be administered to an adult in a single injection, 10 000 units being the upper limit in children. The administration intrathecally of ordinary parenteral doses of penicillin has proved fatal on many occasions.

Hypersensitivity reactions Reactions ascribed to an immune mechanism are the commonest adverse effect of benzylpenicillin. Skin rashes of various types are the most common allergic response occurring in approximately 3% of cases. More serious responses include anaphylaxis, asthma, urticaria, serum sickness and drug fever which may occasionally be fatal. Penicillins are the drugs most commonly implicated in anaphylactic reactions. Haemolytic anaemia and acute tubular necrosis, which occur very rarely after large doses of penicillin, have been shown to have an immune basis. A preformed highly reactive antigen present in penicillin may be responsible for hypersensitivity reactions. Penicilloic acid, a hydrolysis product of 6-aminopenicillanic acid, has been suggested as a likely hapten as it readily reacts with protein residues such as lysine to form antigenic amides (*see* Chapter 8). Polymers of benzylpenicillin have also been implicated, as removal of contaminants from benzylpenicillin reduces the incidence of hypersensitivity reactions, but does not abolish them altogether.

Hypersensitivity reactions occur most commonly in atopic subjects (i.e. those giving a history of eczema, asthma and hay fever) and much more commonly when applied topically than by other routes. Skin tests are of little value in predicting hypersensitive subjects, as only a small proportion of patients who develop a positive response to topically applied penicillin, or to penicilloyl-polylysine, develop a clinical immune syndrome and a few develop a potentially (*see* Chapter 8) life-threatening response to the skin test.

A history of prior exposure to penicillin is the most useful determinant of hypersensitivity reactions, as a high percentage of patients reacting to penicillin, give a history of a previous reaction, although a negative history does not rule out the possibility. There is cross sensitivity between all penicillins and in a small number of patients with cephalosporins as well.

Semisynthetic Penicillins

These agents have much in common with benzylpenicillin so that only those aspects of their clinical pharmacology that differ from benzylpenicillin will be described.

Phenoxymethyl Penicillin is an acid-stable penicillin and is therefore effective after oral administration. The spectrum is the same as benzylpenicillin but it is slightly less potent on a molar basis *in vitro*. Phenoxymethyl penicillin is used against susceptible organisms when the infection is not sufficiently serious to justify parenteral benzylpenicillin. It is readily hydrolysed by β-lactamase.

Ampicillin and Amoxycillin are acid-stable agents, are orally-active and have a broad spectrum of antibacterial activity. They are less water-soluble than other penicillins.

SPECTRUM As for benzylpenicillin plus

H. influenzae	*Salmonella* spp.
E. coli	*Shigella* spp.
Proteus mirabilis	

In vitro ampicillin is half as active as benzylpenicillin against benzylpenicillin sensitive organisms, but is much more effective against Gram-negative organisms. Ampicillin and amoxycillin are readily hydrolysed by β-lactamase.

DRUG FATE Forty–50% of an oral dose of ampicillin and a much higher proportion of amoxycillin is absorbed, the latter drug attaining twice the peak plasma concentrations of ampicillin when administered in similar doses. In the plasma, less than 20% is protein-bound. The apparent volume of distribution is similar to benzylpenicillin, the concentration in the CSF being approximately 4% that in the plasma, rising to over 40% in the presence of meningitis. Approximately 90% of the absorbed drug is excreted in the urine unchanged. A considerable proportion is excreted in the bile, undergoing enterohepatic circulation, and it reaches a concentration in the gall bladder 8–9 times that in the plasma. The half-life is approximately 1 hour and rises 8–10 times this value with creatinine clearance of less than 10 ml/min. The concentration of ampicillin in the renal parenchyma falls with impaired renal function but it reaches effective antibacterial concentrations in the urine at creatinine clearances of less than 5 ml/min.

ADVERSE EFFECTS A maculo-papular skin rash occurs in approximately 7–10% of all patients treated with ampicillin and in over 90% of patients with glandular fever or lymphatic leukaemia. It is also common in patients with viral infections. The pathological mechanism responsible for this rash is not established and until it is, the same precautions taken in established instances of penicillin hypersensitivity should be observed. Super-infections with *Candida albicans* and other organisms, occur more commonly than with other penicillins on account of the broad spectrum of ampicillin.

CLINICAL USE Ampicillin and amoxycillin are used very widely as broad spectrum antibacterial agents of first choice and have proved effective in treating infections with sensitive bacteria of the respiratory, gastrointestinal and urinary tracts and also bacterial meningitides. Amoxycillin has the advantage that only half the dose of ampicillin is required. Both drugs are susceptible to β-lactamase and should be administered with a β-lactamase resistant agent if there is a possibility that a β-lactamase producing organism is present at the site of infection.

Methicillin is relatively resistant to β-lactamase.

SPECTRUM Similar to benzylpenicillin but only 1/30th as potent on a weight basis *in vitro*.

It is inactive orally being administered i.v. or i.m. and has a distribution and half-life similar to benzylpenicillin.

Cloxacillin and Flucloxacillin are chemically closely related and are orally-active, β-lactamase resistant penicillins.

SPECTRUM As for benzylpenicillin but including β-lactamase-producing staphylococci.

They are an eighth to a quarter as effective as benzylpenicillin *in vitro* and are therefore less effective in all infections other than those by penicillinase-producing organisms. Flucloxacillin is better absorbed than cloxacillin and both are over 90% protein-bound, in contrast to the low degree of protein binding of methicillin.

Staphylococcal resistance to methicillin and cloxacillin has emerged since the introduction of methicillin in 1960. By 1969, a number of laboratories reported that approximately 5%of all strains of staphylococci were resistant to methicillin but the figure now is lower. Nearly all resistant organisms were penicillinase producing organisms resistant to a wide range of antibacterial agents and the increased rate of emergence of methicillin resistance correlated with the increased use of all penicillins. Penicillinase resistant penicillins should only be used in infections that are, or could be, caused by staphylococci.

Carbenicillin and Carfecillin Carbenicillin has a broader spectrum than ampicillin.

SPECTRUM As for ampicillin plus

Proteus organisms and

Pseudomonas pyocyanea

Carbenicillin is much less active than ampicillin against Gram-positive organisms and most strains of *E. coli*. High concentrations are necessary for pseudomonas infections (5–100 μg/ml) and many pseudomonas organisms are resistant to even these concentrations. Carbenicillin is hydrolysed by β-lactamase; it is not orally-active; it has a similar distribution and excretion to benzylpenicillin. Carfecillin is orally-active and is rapidly hydrolysed in the plasma to carbenicillin. The concentration of carbenicillin in the urine falls in renal failure. Both drugs are used in urinary tract infections caused by sensitive strains of pseudomonas and proteus organisms.

CLINICAL USE OF PENICILLINS The bactericidal action of penicillins, their high degree of antibacterial activity, and their very low toxicity has resulted in their being used as antibacterial agents of first choice in infections due to sensitive organisms.

Orally-active preparations are used in all but the most serious infections as intramuscular injections are painful. Penicillins may be given by bolus or continuous infusion i.v. as they are fairly stable in 5% dextrose or normal saline at room temperature. They should not be mixed in solution with other drugs, especially aminoglycosides, macrolide antibacterial agents or tetracyclines, as they form visible deposits or react with such agents resulting in loss of activity of one or both drugs.

The usual adult doses and dose interval are shown in Table 1. These vary with the nature and severity of the infection, e.g. a single dose of 1 g amoxycillin plus 1 g of probenecid is effective in eliminating gonococcal infection in over 90% of patients, but in subacute bacterial endocarditis due to *Streptococcus viridans* up to 80 mega units/day of benzylpenicillin may be necessary, given by continuous infusion for six weeks. In most infections it is only necessary to maintain a plasma concentration of penicillin above the MIC for 6 hours/24 hours to attain a satisfactory clinical response.

The principle limitation to the use of penicillins are the high incidence of immunologically mediated adverse effects. A careful history of previous penicillin use is advisable before prescribing these drugs and they are best avoided in atopic subjects.

PREPARATIONS *See* Table 1. The doses are adult doses. The sodium salt of benzylpenicillin contains 0·3 mmol Na/mega unit, the potassium salt containing 1·7 mmol K/mega unit.

SLOW RELEASE PREPARATIONS Procaine penicillin contains an equimolar concentration of benzylpenicillin and procaine. The salt precipitates out at i.m. injection sites and benzylpenicillin is released into the blood stream, reaching a peak height at 4 hours, with detectable amounts being present in plasma at 24 hours. Procaine concentrations in the plasma are also appreciable and may be responsible for drowsiness and abnormal behaviour that occasionally follows injections. Benzathine penicillin maintains a low blood concentration of benzylpenicillin for several weeks.

CEPHALOSPORINS

Source and Chemistry Naturally occurring cephalosporins are derived from the mold Cephalosporium. All clinically used cephalosporins are semi-synthetic and are manufactured by a method analogous to that of the semi-synthetic penicillins.

The cephalosporin nucleus, 7-aminocephalosporanic acid, is very similar to the penicillin nucleus, both containing a β-lactam ring (Table 2). Cephalosporins are weak acids and very soluble in water.

ANTIBACTERIAL ACTION The mode of antibacterial action of the cephalosporins and their effect on bacteria are identical to those of the penicillins but they are less effective on a weight basis *in vitro*. They are bacteriocidal at therapeutic concentrations and most effective against rapidly multiplying organisms.

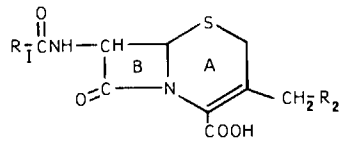
SPECTRUM

Strep. pyogenes
pneumoniae
viridans
Staph. aureus
Neisseria gonorrhoeae
Neisseria meningitidis
E. coli
Proteus mirabilis
Klebsiella spp.
Shigella spp.

Table 2

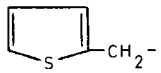
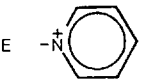
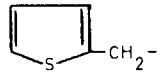
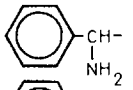
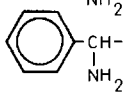
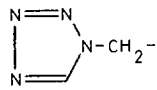
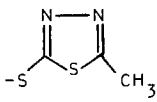
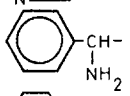
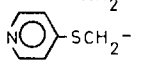
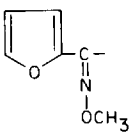
The cephalosporins

Basic structure



A = DIHYDROTHIAZINE RING

B = BETA LACTAM RING

R_1	APPROVED NAME	R_2	ADULT DOSE* (G)	ROUTE	DOSE INTERVAL
	CEPHALORIDINE		I-I.5	i.m., i.v.	6
	CEPHALOTHIN	$-OCCH_3$ (O)	I-I.5	i.m., i.v.	6
	CEPHALOGLYCINE	$-OCCH_3$ (O)	I-I.5	Oral	6
	CEPHALEXIN	-H	0.5	Oral	6
	CEPHAZOLIN		I-I.5	i.m., i.v.	6
	CEPHRADINE	-H	0.5	Oral	6
	CEPHAPIRIN	$-OCCH_3$ (O)	I-I.5	i.m., i.v.	6
$N{\equiv}C-CH_2-$	CEPHACETRILE	$-OCCH_3$ (O)	I-I.5	i.m., i.v.	6
	CEFUROXIME	$-OCNH_2$ (O)	0.75-I.5	i.m., i.v.	6-8

*ADULT DOSES FOR SUBJECTS WITH NORMAL RENAL FUNCTION.

The spectrum is similar to that of ampicillin but cephalosporins are less effective against *Strep. faecalis*, *H. influenzae* and *Salmonella typhi* and more effective against Klebsiellae. They are effective against penicillinase-producing staphylococci and *Proteus mirabilis* but are ineffective against *Pseudomonas*

aeruginosa. With most sensitive Gram-positive organisms, the order of *in vitro* effectiveness is cephaloridine, cephalothin and cephalexin. With Gram-negative organisms, cephaloglycine is relatively more effective.

RESISTANCE Acquired resistance to cephalosporins, as with the penicillins, occurs slowly by multiple steps, resistance to cephalexin being acquired more readily than to cephaloridine and cephalothin. A component of both natural and acquired resistance to enterobacteria is due to breakdown of cephalosporins by a β-lactamase. Cephalosporins are relatively resistant to hydrolysis by staphylococcal β-lactamase but there are several types of β-lactamase produced by enterobacteria some of which hydrolyse cephalosporins more readily than penicillins though cefuroxime is usually β-lactamase resistant. Methicillin resistant staphs are nearly always resistant to cephalosporins, and synergism between kanamycin and cephalosporins has been demonstrated against these organisms.

Individual Cephalosporins

Parenteral agents

Cephalothin is acid-labile and negligible amounts are absorbed after oral administration. After intramuscular injection, a peak plasma level is obtained by 30 minutes. The apparent volume of distribution approximates to the extracellular space, 65–80% of the drug being bound to proteins in the plasma. The concentration attained in the CSF is approximately 10% of the plasma concentration. The plasma half-life is 30–50 minutes and at therapeutic doses 60–70% of the drug is excreted unchanged in the urine by glomerular filtration and tubular secretion, the renal clearance rate being 2·5 that of creatinine. The remainder of the drug is deacetylated by esterases in the liver and tissues, to the deacetyl metabolite which has appreciably less antibacterial effectiveness than the parent compound and a plasma half-life of 8 hours. In patients with impaired renal function, cephalothin in normal doses accumulates to a lesser degree than penicillins and cephaloridine, the half-life only increasing appreciably with creatinine clearance values of 5 ml/min or less.

Cephaloridine is slightly more effective as an antibacterial agent than cephalothin *in vitro* but is more susceptible to β-lactamase. Cephaloridine is inactive orally. After i.m. injection, it is better absorbed than cephalothin, achieving a higher peak plasma concentration. It has a similar apparent volume of distribution but only 10–30% is protein-bound. The CSF concentration is 4–5% the plasma concentration. The half-life is 60–90 minutes, over 70% being excreted unchanged in the urine, the renal clearance rate being identical with that of creatinine. Cephaloridine is not metabolised and in renal failure, the half-life varies inversely with the creatinine clearance and with values less than 10 ml/min it is 20–23 hours.

Cefuroxime is the most resistant cephalosporin to hydrolysis by β-lactamase and is hence the cephalosporin of choice in the treatment of infections due to multiresistant Gram-negative organisms. It is also a useful agent in the treatment of infections due to *Haemophilus influenzae* and in those due to penicillin resistant gonococci.

Cefuroxime is administered i.m. or i.v. and is removed from the plasma solely by renal excretion, its half-life in normal subjects being 75 mins and in anephric patients 24 hours. When the creatinine clearance is 10 ml/min or less, 0·5 g is administered 24 hourly, the dose increasing in proportion to the creatinine clearance, reaching normal doses at clearance values greater than 50 ml/min. Cefuroxime is well tolerated with a very low degree of nephrotoxicity.

Other parenteral cephalosporins Cefazolin, cephapirin and cephacetrile are similar to cephalothin, but are probably less nephrotoxic.

Orally Active Agents

Cephaloglycine, the first orally active cephalosporin has now been superceded by cephalexin and cephradine which are better absorbed. Cephaloglycine is as effective as cephaloridine *in vitro* against Gram-negative but less effective against Gram-positive organisms. Cephalexin is the least effective cephalosporin against both groups *in vivo*.

Cephalexin over 80% of an oral dose is rapidly absorbed, peak plasma concentrations occurring after 1 hour. It is effective against systemic infections and urinary tract infections.

ADVERSE EFFECTS OF THE CEPHALOSPORINS

Pain at the site of injection and phlebitis, especially with cephalothin, occurs with the parenteral preparations but is least frequent with cephaloridine. Diarrhoea is also quite common as with all broad-spectrum antibacterial agents. A positive Coombs test occurs occasionally but haemolytic anaemia is rare.

Hypersensitivity reactions Hypersensitivity reactions to cephalosporins occur in less than 3% of patients not sensitive to penicillin but are much more common in penicillin-sensitive patients, the incidence varying between 5 and 16%. Skin rashes are the most common manifestation but anaphylactic reactions have occurred in penicillin-sensitive subjects so that precautions should be taken to treat serious reactions before giving such patients cephalosporins.

Nephrotoxicity Cephaloridine, in therapeutic doses, may cause renal tubular damage with an increase in plasma creatinine, protein and casts in the urine and eventually acute tubular necrosis. Nephrotoxicity is most common when the drug is administered in normal doses, to patients with impaired renal function or when given in conjunction with frusemide or ethacrynic acid or with an aminoglycoside, e.g. gentamicin. Cephalothin is also nephrotoxic, as are the newer cephalosporins, but much less so than cephaloridine. Renal function

should be assessed at commencement of therapy and the dose or dose frequency reduced in accordance with the reduction in creatinine clearance.

Neurotoxicity High systemic doses and intrathecal cephaloridine and cephalothin have produced clinical evidence of an encephalopathy. No more than 50 mg of intrathecal cephalosporin should be administered in a single dose.

CLINICAL USE

Cephalosporins are drugs of first choice in klebsiella infections when they are most effective given with an aminoglycoside, e.g. gentamicin. They are useful alternatives to penicillinase-resistant penicillins in the treatment of penicillinase producing staphylococcal infections and to all penicillins in penicillin-sensitive patients. As a proportion of these patients will also be sensitive to cephalosporins, it is best to avoid them in patients with a history of a serious allergic response to penicillin. Cephalothin is the preferred agent for parenteral therapy in staphylococcal infections and in the presence of poor renal function but for all other circumstances cephaloridine is preferable. Cephalosporins penetrate the blood-brain barrier poorly and are not of established value used alone in bacterial meningitis.

ALTERNATIVES TO BENZYLPENICILLIN

The antibacterial agents described in this section have antibacterial spectrums similar to benzylpenicillin and are used mostly to treat penicillinase-producing staphylococcal infections and patients who are allergic to penicillins.

Erythromycin

Erythromycin is derived from a strain of streptomyces. It is a large basic molecule (pK 8·8) and is unstable in acid solution. It is the most commonly used of a family of chemically related antibacterial agents which includes oleandomycin, carbomycin and spiromycin known as 'the macrolides' as their structure contains a macrocyclic lactone ring. The clinical pharmacology of erythromycin only will be described.

SPECTRUM As for benzylpenicillin plus
H. influenzae
Campylobacter
Chlamydia trachomatis
Mycoplasma pneumoniae
Legionella pneumophila

Erythromycin is not as effective as benzylpenicillin on a weight basis against susceptible organisms, but is similarly effective against penicillinase-producing staphylococci. It is bacteriostatic at therapeutic concentrations, but may be bacteriocidal to the most sensitive organisms.

MODE OF ACTION Erythromycin becomes attached to the ribosomes of sensitive organisms and impairs protein synthesis by competing with amino acids for ribosomal binding sites. Other macrolides, lincomycin and clindamycin, occupy identical ribosomal binding sites.

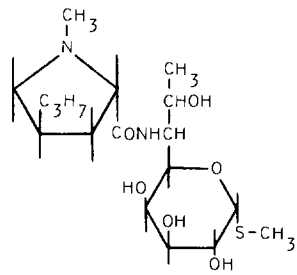
RESISTANCE Natural resistance is probably due to the inability of erythromycin to penetrate cell walls of Gram-negative organisms. Resistance is acquired rapidly *in vitro* by a series of large steps and occurs clinically in courses of treatment longer than a few days. It is not due to metabolism of the drug by bacteria and there is cross-resistance with other macrolides.

DRUG FATE Erythromycin is poorly absorbed after oral administration as it is unstable in gastric acid. Salts of erythromycin, notably the stearate and propionate, release the free base slowly in the small bowel and are orally active. Less than 20% of the drug is bound to plasma proteins. The concentration in most tissues is similar to or greater than that in the blood except in the CSF where it is very low, although this rises in meningitis. Less than 5% is excreted unchanged in the urine being cleared by the kidney at a rate less than creatinine and the concentration in the urine is low. An appreciable amount is excreted in the bile where it reaches a concentration many times that in the plasma. A proportion of the drug is metabolised, but the metabolic pathways are not established. The half-life of the drug is 1·4 hours in the presence of normal renal function and increases to 4–6 hours in oliguric patients.

ADVERSE EFFECTS Gastrointestinal symptoms, especially nausea, are the most common. Erythromycin has a very low toxicity but the estolate salt, which is no longer available on the UK market, may cause jaundice if administered for longer than ten days.

CLINICAL USE Erythromycin is a useful alternative to benzylpenicillin and phenoxymethylpenicillin in penicillin-sensitive patients with relatively mild infections. It is also the antibiotic of choice in the treatment of atypical pneumonias, including Legionnaire's disease.

Lincomycin, Clindamycin



Lincomycin

Lincomycin is derived from a strain of streptomyces and clindamycin is its

7-chloro-7-deoxy derivative. They are basic compounds, soluble in both water and organic solvents.

ANTIBACTERIAL ACTION They impair protein synthesis in the same manner as erythromycin.

SPECTRUM

Staph. aureus	*B. anthracis*
Strep. pyogenes	*Clostridia* spp.
Strep. pneumoniae	*Bacteroides* spp.
Strep. viridans	*Veillonella* spp.

The spectrum is narrower than for benzylpenicillin as these agents are relatively ineffective against *Strep. faecalis*, *Neisseria* organisms and *Haemophilus influenzae*. They are effective against the anaerobes, bacteroides and *Veillonella*. Gram-positive cocci are the most sensitive organisms. Clindamycin is appreciably more effective than lincomycin.

RESISTANCE Resistance is acquired slowly to these agents and does not occur during a course of treatment. Resistant staphylococci and other Gram-positive organisms occur quite commonly at centres where lincomycin and clindamycin are widely used. There is no cross-resistance with the macrolides. However erythromycin may antagonise lincomycin if the two agents are given together in the treatment of a staphylococcal infection with organisms resistant to erythromycin but sensitive to lincomycin, as the two drugs compete for the same ribosomal binding sites.

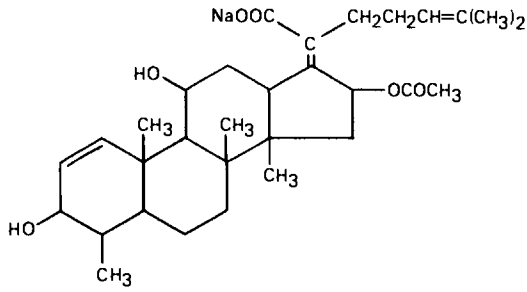
DRUG FATE Both are orally active, the absorption of lincomycin but not clindamycin, being impaired by food. Clindamycin is better absorbed, attaining twice the peak plasma level of lincomycin after a similar oral dose. Eighty–90% of the drugs are protein bound and they are widely distributed, having apparent volumes of distribution equal to that of total body water. Concentrations in bone and CSF are lower than that in the plasma but after the usual therapeutic doses, may exceed the minimal inhibitory concentration of some Gram-positive organisms. The half-life of clindamycin is 1·5–3·5 hours and for lincomycin 4–5 hours. Less than 10% of either agents is excreted unchanged in the urine. The half-lives increase only 2–3 fold in oliguric patients making these safe agents to use in renal failure. The concentrations achieved in the urine are low, appreciable amounts appearing in the faeces, in part due to bilary excretion. The proportion of these drugs that is metabolised and the metabolic pathways involved have not been established.

ADVERSE EFFECTS *Diarrhoea* occurs in approximately 20% of cases. In a small proportion, the diarrhoea is severe and often bloody and is associated with abdominal pain and fever. The symptoms develop 3–25 days from the start of therapy, the sigmoidoscopic and histological changes being those of a pseudomembranous colitis. The condition is treated similarly to an acute attack

of ulcerative colitis and usually resolves on glucocorticosteroids orally and topically. However, on a number of occasions, the condition has proved fatal or a total colectomy has been necessary. The pathogenesis of the condition is not understood although recent evidence has implicated a toxin produced by *Clostridium difficile*. It is probably similar to the pseudomembranous colitis that may occur with broad-spectrum antibiotics, e.g. tetracyclines and ampicillin. Vancomycin is probably the drug of choice in the treatment of pseudomembranous colitis.

CLINICAL USE Clindamycin is preferable to lincomycin as it is a more effective antibacterial agent *in vitro* and is better absorbed from the gut. Clindamycin is a useful alternative to metronidazole in bacteroides infections and to penicillins in staphylococcal infections in subjects allergic to penicillin. It has proved useful in the treatment of osteomyelitis as it diffuses to sites of infection in bone more readily than most antibacterial agents.

Sodium Fusidate



Sodium fusidate has a steroid structure and is derived from the fungus *Fusidium coccineum*.

ANTIBACTERIAL ACTION. It impairs protein synthesis of susceptible organisms and at therapeutic concentrations is bacteriocidal to the most susceptible organisms.

SPECTRUM

Staph. aureus	*Neisseria meningitidis*
Neisseria gonorrhoeae	*Clostridia* spp.

The spectrum is narrower than that of benzylpenicillin but it is effective against penicillinase producing staphylococci. Streptococci are relatively resistant.

RESISTANCE Staphylococci develop resistance rapidly. This is due to the presence of resistant mutants which occur more commonly the larger the culture.

DRUG FATE Sodium fusidate is rapidly absorbed after oral administration, is highly protein-bound and is widely distributed, reaching effective concentra-

tions in all tissues other than the brain and CSF. It is slowly removed from the blood stream, mostly by metabolism, and if given in repeated doses reaches a steady plasma concentration after 2–6 days. An appreciable amount is excreted in the bile. Some unchanged drug is present in the faeces but trivial amounts in the urine. The metabolic pathways responsible for its degradation have not been established.

ADVERSE EFFECTS Mild gastrointestinal effects are the only side effects and no serious toxic effects have been reported. Sodium fusidate has no detectable mineralocorticoid or glucocorticoid activity.

CLINICAL USE It is a useful alternative to penicillin in the treatment of staphylococcal infections. Its chief drawback is the rapidity with which resistance develops although this can be avoided by administering the drug in combination with other antibacterial agents to delay the emergence of resistant organisms. *In vitro*, a degree of antagonism has been observed between sodium fusidate and benzylpenicillin against non-penicillinase producing staphylococci and between fucidin and methicillin against penicillinase producing organisms. This has not been observed *in vivo*.

Vancomycin Vancomycin is derived from *Streptomyces orientalis*. It impairs cell wall synthesis and cytoplasmic membrane function of susceptible organisms to whom it is bactericidal at therapeutic concentrations.

SPECTRUM

Staph. spp.
Strep. spp.
Clostridia spp.

The spectrum is narrower than that of benzylpenicillin. Resistance is not readily acquired and is not a problem clinically.

DRUG FATE Vancomycin is not absorbed after oral administration, is painful to give i.m. and is therefore commonly given i.v. It is widely distributed, very little is protein bound and is mostly excreted unchanged in the urine. The half-life is 6–8 hours but in oliguria may increase to 9–14 days.

ADVERSE EFFECTS Vancomycin is an irritant and may cause thrombophlebitis. Drug induced fever is also common but the most serious toxic effect is deafness which has most commonly occurred when vancomycin has been given in normal doses in the presence of renal failure.

CLINICAL USE It is an alternative agent to benzylpenicillin and has been used most commonly in infections due to penicillinase-producing staphylococci. It is also effective taken orally 2 g/day in the treatment of pseudomembranous colitis.

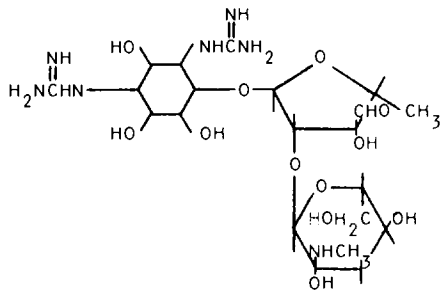
Preparations

Drug		*Adult dose (g)*	*Route*	*Dose interval (h)*
Erythromycin	stearate propionate	0·25–0·5	Oral	6
Erythromycin	ethylsuccinate lactobionate gluceptate	0·25–0·5	i.m., i.v.	6
Lincomycin	hydrochloride	0·5	Oral	8–12
		0·3 –0·6	i.m., i.v.	8–12
Clindamycin		0·15–0·3	Oral	6
Sodium fusidate		0·25–0·5	Oral	8
Vancomycin		0·5	i.v.	6

AMINOGLYCOSIDE ANTIBACTERIAL AGENTS

The aminoglycosides are a family of antibacterial agents having in common the possession of a sugar moiety containing an amine group (*see* streptomycin). They are large, water soluble basic compounds, almost wholly ionised at physiological pH, having similar but not identical antibacterial actions, a similar fate in the body and similar adverse effects.

Streptomycin



Streptomycin is a large basic molecule produced by the mold *Streptomyces griseus*. It was the first antibacterial agent to be produced as the consequence of a systematic screening programme and was the first antibacterial agent effective against *M. tuberculosis*.

SPECTRUM

Staph. aureus
Pasteurella pestis
Pasteurella tulurensis
Brucella abortus
H. influenzae
M. tuberculosis
E. coli
K. pneumoniae
Proteus vulgaris
Pseudomonas aeruginosa
Salmonella spp.
Shigella spp.

Streptomycin has a broad-spectrum of antibacterial activity. It is very active against *M. tuberculosis* but relatively ineffective against *Streptococci*. The sensitivity of Gram-negative organisms varies very considerably.

MODE OF ACTION Streptomycin is bactericidal at therapeutic concentrations and is most effective against rapidly multiplying organisms. It becomes attached to the 30S ribosomes of susceptible bacteria, in common with messenger RNA and prevents the initiation of peptide chains. The proteins synthesised in the presence of streptomycin, do not function normally with the result that there is impaired cell membrane function, nucleic acid synthesis and eventually cell death. Streptomycin is most effective in an alkaline environment and its activity is appreciably reduced at pH values less than 6, in anaerobic conditions and in the presence of polyvalent ions such as phosphates and magnesium.

RESISTANCE Resistance to streptomycin develops very rapidly *in vitro* and *in vivo* in nearly all susceptible organisms and is probably due to a single mutation. Resistant organisms do not bind streptomycin to the 30S ribosomes. In urinary tract infections treated with streptomycin the MIC increases upwards of one thousand times in 2–5 days of starting therapy and if the drug is used alone in tuberculosis, resistant organisms emerge within a few weeks of starting therapy. The emergence of resistant organisms can be delayed, often indefinitely, by administering a second antibacterial agent to which the bacteria are susceptible.

DRUG FATE Streptomycin is very poorly absorbed from the bowel as it is virtually fully ionised at intraluminal pH values and when given orally most of the drug is excreted unchanged in the faeces. After i.m. injection peak plasma concentrations are achieved by 0·5–1·5 hours. Only 30–40% of the drug is protein-bound and its apparent volume of distribution is similar to that of the extracellular space as it does not readily diffuse into cells. After the usual therapeutic doses it achieves effective antibacterial concentrations in tuberculous abscess cavities, pleural and peritoneal spaces and in the fetus, but not in the brain or CSF. Streptomycin is not appreciably metabolised, 70% or more of an i.m. dose being excreted unchanged in the urine by glomerular filtration and a small proportion is excreted in the bile. In subjects with normal renal function the plasma half-life is 2–3 hours, but this varies with the creatinine clearance. It is usually increased in infants and in the elderly and in oliguric renal failure it may be as long as 100 hours.

ADVERSE EFFECTS

Ototoxicity The most common adverse effect of streptomycin apart from pain at the site of injection, is ataxia due to a toxic effect of the drug on the hair cells of the vestibular sensory epithelium. The earliest sign of vestibular dysfunction is an impaired caloric response but clinical symptoms and signs of ataxia, nystagmus and a positive Romberg's sign appear in over 50% of patients on long-term therapy with 2g/day. There are wide interindividual

differences in susceptibility to these effects which may occur with doses of as little as 0·5g/day. Vestibular dysfunction is reversible in the early stages but may be irreversible if treatment is continued in the presence of symptoms. Impaired renal function, leading to accumulation of the drug in the plasma, is the commonest predisposing factor to the development of ototoxicity. Renal function should be evaluated at the beginning of therapy and dose size or frequency should be reduced in accordance with any reduction of creatinine clearance. In a small proportion of patients streptomycin may cause high tone deafness.

Neuromuscular blockade Streptomycin has a neuromuscular blocking action similar to that of curare and magnesium ions. This is of clinical importance post-operatively when there may be an additive effect with neuromuscular blocking drugs and in patients with myasthenia gravis, who are especially sensitive to neuromuscular blocking drugs.

Hypersensitivity reactions Skin rashes, fever and eosinophilia develop in approximately 5% of patients, symptoms occurring within one day to six months of starting therapy. Rarely, anaphylaxis or exfoliative dermatitis have occurred.

CLINICAL USE The most important role for streptomycin is in the treatment of *M. tuberculosis* infections in which it is a drug of first choice (*see* treatment of tuberculosis). In no instance should it be given alone in view of the rapidity with which resistant organisms emerge. Streptomycin is effective in plague and in tuluraemia and, given with tetracycline, in brucelosis. In subacute bacterial endocarditis due to *Strep. faecalis*, it may act synergistically with high doses of benzylpenicillin.

The other aminoglycosides are not effective antituberculous agents, but have many properties in common with streptomycin. Only the ways in which they differ from streptomycin will be stressed.

Gentamicin Gentamicin is derived from certain strains of microspora. Its mode of action and antibacterial effects are similar to streptomycin.

SPECTRUM

Staph. aureus	*Proteus* spp.
Strep. faecalis	*Ps. aruginosa*
E. coli	*Salmonella* spp.
K. pneumoniae	*Shigella* spp.

It is more effective on a weight basis against staphs. and Gram-negative bacilli than streptomycin, neomycin and kanamycin. It is effective against many species of pseudomonas and has a synergistic effect against this organism *in vitro* with carbenicillin. It is active against penicillinase producing *Staph. aureus* but not against most streptococci or *Providencia stuartii*.

RESISTANCE Resistance is not acquired rapidly as it is with streptomycin and

there is usually cross resistance with tobromycin but seldom with other aminoglycosides. R-factor mediated resistance to gentamicin and other aminoglycosides and broad-spectrum antibacterial agents, has been reported from specialist units and the frequency with which resistant organisms occur is directly related to the frequency with which it is used.

DRUG FATE The fate of gentamicin is similar to that of streptomycin and it is inactive orally. The half-life is 2–3 hours in the presence of normal renal function, increasing to 13 hours with a creatinine clearance of 10 ml/min and 40 hours when the latter has fallen to 3 ml/min.

ADVERSE EFFECTS

Ototoxicity On a weight basis gentamicin is over twice as toxic as streptomycin to the hair cells of the vestibule and cochlea. In clinical use, vestibular dysfunction occurs at plasma concentrations greater than 12 μg/ml and may be irreversible, but high tone deafness is much less frequent. Ototoxicity has occurred most commonly when gentamicin is given in normal doses to patients with impaired renal function.

Nephrotoxicity Used alone, gentamicin occasionally causes impaired renal function, but this increases in frequency when it is given in conjunction with cephalorodine or frusemide.

CLINICAL USE In severe infections with Gram-negative organisms, gentamicin alone or in combination with a cephalosporin is the most effective antibacterial agent available. In pseudomonas infections, it is most effective when given with high doses of carbenicillin, but these drugs should not be mixed in intravenous infusions, as high concentrations of carbenicillin rapidly inactivate gentamicin.

Gentamicin is administered either intramuscularly or intravenously as a bolus or by continuous infusion. Most organisms are susceptible to plasma concentrations of 2 μg/ml or less, but the concentration above which ototoxic effects are common (12 μg/ml) is close to the plasma concentration necessary to eradicate some Gram-negative organisms and it is advisable to monitor the plasma level of gentamicin during a course of therapy. The objective of therapy is to maintain a plasma concentration above the MIC for the particular bacteria 1 hour after i.m. or 15 minutes after a bolus i.v. injection and not to exceed at any time a concentration of 12 μg/ml.

Neomycin Neomycin has a similar spectrum to gentamicin but is less effective on a weight basis. As with gentamicin resistance emerges slowly and there is often cross-resistance between neomycin and kanamycin which may be R-factor mediated.

DRUG FATE After oral administration or rectal infusion, approximately 1% of the dose is excreted in the urine and this is not increased by gastrointestinal disease. If neomycin is applied in quantity to the peritoneal or pleural surfaces or to the surface of large wounds, sufficient may be absorbed for toxic concentrations to be achieved in the plasma.

ADVERSE EFFECTS After parenteral administration adverse effects occur more frequently with neomycin than with other aminoglycosides and as a consequence it is only used orally or topically. It may cause acute tubular necrosis at plasma concentrations close to therapeutic concentrations. It is toxic to both vestibular and cochlear hair cells inducing deafness often weeks after withdrawal of the drug. Like streptomycin and kanamycin, neomycin may cause neuromuscular blockade and, after oral administration, may also cause steatorrhoea.

CLINICAL USE Neomycin is not given parenterally on account of its toxic side effects.

Topical administration Alone or in combination with other poorly absorbed antibacterial agents, e.g. bacitracin and polymyxin, neomycin is commonly used topically for skin, eye and wound infections due to staphylococci or Gram-negative bacilli.

Oral administration Neomycin is used in gastrointestinal infections due to *E. coli* but is less effective against salmonella and shigella infections. It has proved effective at reducing gut bacteria and is used for this purpose in the symptomatic treatment of hepatic encephalopathy.

Preparations

Drug	*Adult dose (g)*	*Route*	*Dose interval (h)*
Streptomycin	0·5–1·0	i.m.	24
Gentamicin	0·8 mg/kg	i.m., i.v.	8
Tobramycin	0·8 mg/kg	i.m., i.v.	8
Kanamycin	0·25–0·5	i.m., i.v.	6
Neomycin	1–2	Oral	6

Other aminoglycosides Kanamycin is very similar to gentamicin but is less effective on a weight basis and is more nephrotoxic. Consequently it has been largely replaced by gentamicin in clinical practice.

Tobramycin and amikacin are the most recent aminoglycosides to be introduced. Tobramycin appears to differ little from gentamicin and is often ineffective against gentamicin resistant organisms. Amikacin, on the other hand, is similar to kanamycin and is often effective against gentamicin-resistant organisms.

ANTITUBERCULOUS AGENTS

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*. This organism, like *Mycobacterium leprae*, contrasts with other bacteria in that it multiplys slowly (the doubling time for *M. tuberculosis* being 12–30 hours, that for *Staphylococcus*

aureus being 20 minutes) and causes chronic, rather than acute, inflammatory changes. Tuberculosis affects the lungs most commonly but may affect any organ. It usually runs a chronic course and the histological changes are of caseating necrosis and are quite characteristic.

A number of antituberculous agents, e.g. para-aminosalicylic acid, isoniazid and ethambutol, are not effective as antibacterial agents against other organisms, probably on account of morphological and biochemical differences between *M. tuberculosis* and other bacteria. Courses of therapy against TB are very long, lasting 6 months–2 years usually, and this is probably due to the slow doubling time of the mycobacterium. *M. tuberculosis* develops resistance readily to any of the known antituberculous agents used alone, and as the rate of emergence of resistance can be delayed or prevented by administering two or more agents at the same time, therapy is always carried out with at least two agents.

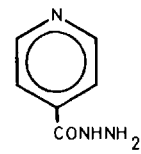
There are a number of antituberculous agents available for clinical use and the clinical pharmacology of the most widely used agents will be considered.

Streptomycin

(*See* aminoglycosides) Streptomycin was the first antituberculous drug available for clinical use and is still one of the most effective. It is used in moderately severe and severe cases, being administered i.m. once daily or every other day. It is excreted unchanged in the urine and renal function should be determined before drug administration. The maintenance dose is 0·5–1 g/24 hours in subjects with normal renal function and in renal failure should be adjusted accordingly to the creatinine clearance.

The disadvantages of streptomycin are that it has to be administered i.m.; it does not reach intracellular sites; resistant organisms emerge rapidly and it is toxic to the vestibular apparatus.

Isoniazid (isonicotinic acid hydrazide, INAH)



Isoniazid is a synthetic pyridine derivative. It is very soluble in water and to a much lesser extent in organic solvents.

ANTIBACTERIAL ACTIVITY Isoniazid is one of the most effective antituberculous agents *in vitro*, but is ineffective against all other pathogens. It inhibits bacterial cell division and kills rapidly dividing organisms. Unlike streptomycin, it readily penetrates cell walls and can penetrate the cell wall of *M. tuberculosis*. It impairs lipid metabolism and cell wall function as a consequence. It also interferes with DNA and to a lesser extent RNA synthesis, but the precise mechanisms responsible for its antibacterial effect have not yet been established.

RESISTANCE *In vitro* resistance emerges rapidly by a series of small steps. *In vivo* it emerges less rapidly than with streptomycin but when given alone to patients with pulmonary tuberculosis, 75% of organisms isolated from patients after three months are resistant. The emergence of resistant mutants is delayed by the co-administration of another antituberculous agent.

DRUG FATE Isoniazid is rapidly and completely absorbed from the gut. Very little is protein-bound in the plasma and it is widely distributed, reaching effective concentrations inside cells, in tuberculous cavities and in the CSF, where the concentration is less than that in the plasma.

Metabolism Isoniazid is acetylated by a hepatic cytoplasmic enzyme system, the acetylated metabolite having much less antituberculous activity than the parent drug. If the rate of isoniazid acetylation is determined in a population, the frequency-distribution is found to be bimodal indicating that the rate of acetylation is determined by a single genetic factor and that this factor displays polymorphism (*see* Chapter 5). In Europeans and American negroes, approximately half the population are fast acetylators, but the proportion of those that are fast acetylators varies round the world, being highest amongst the Eskimos (95%). It is higher in Japan (88%) and the Far East than in Europe, but lower in Indians and lowest of all in Egyptians (10%). The half-life for fast acetylators is approximately 1 hour and for slow acetylators is 3 hours, but there is considerable scatter around these mean values. If the acetylator type is not taken into account in deciding the dose of isoniazid, slow acetylators respond better than fast acetylators to the antituberculous effects, but also develop adverse effects more commonly. Five–27% of the drug is excreted in the urine unchanged and in renal failure, with a creatinine clearance of 10 ml/min or less, there is only a small increase in isoniazid half-life. In severe liver disease isoniazid acetylation may be impaired, especially when bilirubin is 34 μM (2 mg%) or greater

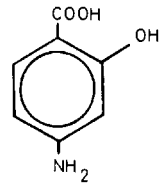
ADVERSE EFFECTS

Neurotoxicity Peripheral neuropathy is the most common serious adverse effect. It is dose related and at high doses (14 mg/kg/day) it occurs in approximately 5% of cases. The neuropathy is abolished by pyridoxine and is prevented by giving this vitamin prophylactically with isoniazid. Pyridoxine does not antagonise the antituberculous action of isoniazid. Isoniazid is a potent inhibitor of pyridoxal kinase, the enzyme which converts the inactive pyridoxine to its active form pyridoxal phosphate (*see* Chapter 34) and it is assumed that its neurotoxic effect is due to this action. Convulsions and, less commonly, psychoses, also occur after high doses of isoniazid but their relationship to pyridoxine is not clear.

Hepatocellular damage is a rare complication of isoniazid given alone and is much less common than with para-aminosalicyclic acid. Rashes and drug fever are also occasional adverse effects.

CLINICAL USE Isoniazid is the most widely used of all antituberculous agents on account of its ease of administration, cheapness, wide distribution, high antituberculous activity and low toxicity. It is always given in conjunction with another antituberculous agent, usually para-aminosalicyclic acid, ethambutol or rifampicin.

Para-aminosalicylic Acid (PAS; sodium aminosalicylate)



Para-aminosalicylic acid is a synthetic highly water-soluble compound.

ANTIBACTERIAL ACTIVITY PAS is bacteriostatic to *M. tuberculosis*. Its antibacterial action is probably similar to that of the sulphonamides in that it is antagonised by para-aminobenzoic acid. Given alone it is much less effective than streptomycin or isoniazid, but resistant organisms emerge more slowly than with either of these agents and in combination with them it appreciably delays the emergence of resistant organisms.

DRUG FATE PAS and its sodium salt are rapidly absorbed from the bowel. 45–75% of the drug is bound to plasma protein and the apparent volume of distribution is similar to the extracellular space. The blood-brain barrier is impermeable to PAS which only achieves therapeutic concentrations in the CSF when the meninges are inflamed. A small proportion of the drug is acetylated by the liver and when given with isoniazid, PAS may delay the latter's rate of acetylation. However, the rate of PAS acetylation is not determined by the same genetic mechanism as is isoniazid, the frequency distribution of PAS acetylation showing a unimodal distribution. PAS has a half-life of 40–50 minutes. Approximately 80% is excreted unchanged in the urine by glomerular filtration and tubular secretion and probenecid delays its excretion. Very high concentrations of both PAS and its acetylated metabolite are achieved in the urine and rarely, this may precipitate out in acid urine producing crystaluria.

ADVERSE EFFECTS PAS is used in very large daily doses (10–15 g/day) and symptoms of gastrointestinal intolerance, anorexia, nausea, epigastric pain and gastrointestinal haemorrhage are common, especially in patients with peptic ulceration. Symptoms are relieved if PAS is taken with meals or antacids. Rarely PAS may cause steatorrhoea.

Mild reactions include rashes, fever, eosinophilia and lymphadenopathy and severe reactions, hepatocellular damage and agranulocytosis. Loeffler's syndrome with pulmonary radiological opacities not due to an exacerbation of

pulmonary TB, has also been reported, as has a syndrome similar to glandular fever.

PAS is a weak anionic inhibitor of iodide uptake by the thyroid gland and goitre with or without hypothyroidism may occur in patients on long-term therapy.

PAS/isoniazid combination may impair phenytoin metabolism causing phenytoin accumulation in the blood and overdose effects when these drugs are prescribed together.

CLINICAL USE PAS has an important place in the chemotherapy of tuberculosis in preventing the emergence of strains of *M. tuberculosis* resistant to the more potent antituberculous agents, isoniazid, streptomycin and rifampicin. It is widely-used, often in combination with isoniazid ± streptomycin, in severe cases of TB and with isoniazid alone in less severe cases. The high frequency of gastrointestinal side effects and the large bulk of preparations containing PAS, make them unpopular and poor patient compliance is common in patients on this drug. Though well tried, PAS is used less frequently than formerly, being replaced by equally effective agents with fewer adverse effects.

Rifampicin Rifampicin is the most widely used of the rifamycins, a group of antibacterial agents derived from *Streptomyces mediterranei*. It is a large molecule (MW 822) and is soluble in both water and some organic solvents. It is a very potent antituberculous agent and is also effective against Gram-positive organisms and to a much lesser degree against Gram-negative organisms. It acts by inhibiting DNA-dependent RNA polymerase and so impairs RNA synthesis. There is no cross resistance with other antituberculous agents. In most cultures *in vitro*, there are a small number of resistant organisms and the effectiveness of rifampicin decreases appreciably with an increase in the size of the culture. When used against Gram-positive organisms or *M. tuberculosis in vivo*, resistant organisms emerge rapidly so that rifampicin should not be used alone.

DRUG FATE Rifampicin is absorbed from the gut and achieves effective concentrations in all tissues including neuronal tissue, fetal tissue and the CSF after oral administration. It is metabolised in the liver partly by deacetylation, less than 15% being excreted as unchanged drug in the urine. Rifampicin is excreted in the bile and undergoes enterohepatic circulation. Probenecid impairs its bilary excretion but when given concurrently only causes a small rise in its plasma concentration. Rifampicin induces liver microsomal enzymes and this may account for a decrease in the effectiveness of oral contraceptives when taken in conjunction with rifampicin. The half-life of rifampicin varies between 2–6 hours and increases in subjects with severe hepatocellular damage but not in those with impaired renal function.

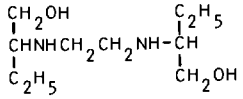
ADVERSE EFFECTS

Hepatic dysfunction Rifampicin impairs bilirubin excretion by the hepatocyte and may cause a rise in plasma bilirubin concentration. The frequency

with which it causes hepatotoxicity is uncertain as it is most commonly administered with isoniazid which may itself damage liver cells. When these two drugs are given in combination there is often a rise in serum aspartate transaminase (AST) concentration and rarely clinical evidence of liver cell damage. Fever, rashes and thrombocytopenia also occur and may be serious if rifampicin is prescribed in high doses once or twice weekly. Teratogenic effects have been reported in animal studies and the drug should be avoided in the first trimester of pregnancy. Patients on rifampicin occasionally develop red urine, faeces, tears or sweat.

CLINICAL USE Rifampicin is a highly effective antituberculous agent. It has been used with success as a first line antituberculous drug in combination with isoniazid or ethambutol. An alternative use has been to reserve rifampicin for patients who do not tolerate streptomycin or isoniazid or to treat infections due to organisms resistant to these drugs. Rifampicin is also a useful alternative to sulphones in the treatment of leprosy (*see* page 481).

Ethambutol



Ethambutol is a less potent antituberculous drug than streptomycin, rifampicin or isoniazid. It is as effective as PAS when given in conjunction with any of these three drugs except in severe cavitating disease in which PAS is probably more effective. Resistance to ethambutol emerges more slowly than to most other antituberculous drugs and there is no cross-resistance to streptomycin, isoniazid or rifampicin.

Ethambutol is orally-active and readily penetrates all membranes. Over 70% of an oral dose is excreted in the urine, mostly as unchanged drug, oxidation products being the principal metabolites. It has a mean plasma half-life of 8 hours.

ADVERSE EFFECTS

Optic neuritis with high doses (15 mg/kg/24 hours or more), a small number of patients develop blurred vision, impaired colour perception, especially to red and green, and central and peripheral visual field defects. These are due to optic neuritis and resolve on stopping the drug. It is advisable to warn patients to stop ethambutol in the event of visual symptoms occurring.

CLINICAL USE Ethambutol is better tolerated than PAS and, as it is as effective, is a useful alternative to this drug in all but severe cavitating disease.

Thiacetazone Thiacetazone, a sulphonamide derivative, is a widely used antituberculous agent in underdeveloped countries, on account of its cheapness and the fact that it is effective at a low dose. The susceptibility of *M. tuberculosis* to thiacetazone varies round the world, strains in the Far East being more

resistant than those in Britain or Africa. It is active orally and the commonest side-effects are gastrointestinal symptoms. Severe reactions, which are not uncommon in high doses, include hepatocellular damage and bone marrow depression. In combination with isoniazid it is an acceptable alternative to PAS/isoniazid therapy, especially in countries where the cost of drugs is of great importance.

Other Drugs There are a number of other antituberculous drugs, pyrazinamide, ethionamide and cycloserine, that are used in cases due to organisms resistant to the agents already described. Their more widespread use is limited by their potentially serious adverse effects which are appreciably more common than with the agents already considered. Pyrazinamide may cause hepatocellular damage, ethionamide gastrointestinal symptoms, abnormal liver function tests, convulsions and peripheral neuropathy, and cycloserine convulsions and psychoses.

DRUG THERAPY IN TUBERCULOSIS In severe and moderately severe cases, therapy is usually initiated with three antituberculous drugs, traditionally streptomycin, isoniazid and PAS, having first checked renal and hepatic function. In less severe cases, isoniazid and PAS or ethambutol only may be used. This regime is usually adopted in severe cases when recovery is established, or after three months triple therapy. Treatment is continued for at least one year and in severe cases for 18 months to two years, depending on the course of the disease. Progress is monitored by means of sputum microscopy and culture, clinical examination, radiological and biochemical data. Patient compliance is a common cause of failure of therapy and the simpler the drug regime the better the compliance, and, for this reason a fixed-dose combination of PAS and isoniazid is commonly used. Patients not tolerating streptomycin or

Preparations

Drug	*Adult dose range*	*Route*	*Dose interval (h)*
Streptomycin	0·5–1·0 g	i.m.	24
Isoniazid	50–100 mg	Oral	8
PAS	3–5 g	Oral	8
Rifampicin	450–600 mg	Oral	24
Ethambutol	15–25 mg/kg	Oral	24
Thiacetazone	150 mg	Oral	24

PAS are treated with rifampicin and ethambutol and in many clinics isoniazid, rifampicin and ethambutol is the initial regime. In developing countries, in which drug costs are a primary consideration, isoniazid/PAS or thiacetazone are the most widely used drug combinations.

The present trend in antituberculous therapy is for shorter courses using rifampicin and isoniazid in combination. Initial clinical experience suggests that

such a regime with or without a third agent may be curative if given for only 6–12 months. Clinical trial confirmation of this impression is awaited.

TETRACYCLINES AND CHLORAMPHENICOL

The tetracyclines are a group of antibacterial agents elaborated by certain species of streptomyces, that contain a four ringed chemical nucleus after which they are named. The first tetracyclines, chlortetracycline, oxytetracycline and tetracycline were discovered shortly after chloramphenicol, and throughout the 1950s and most of the 1960s were the most widely-used of all antibacterial agents by virtue of their broad-spectrum and low toxicity. They are still widely-used, but are not as popular as formerly (*see* Table 3).

There are a number of tetracyclines of which tetracycline and the newer agents methacycline, doxycycline and minocycline are semisynthetic. The tetracyclines are amphoteric and are water-soluble. They are stable as salts such as hydrochlorides.

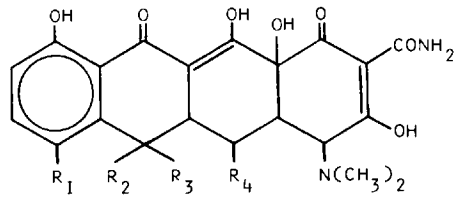
ANTIBACTERIAL ACTION

Staph. aureus
Strep. pyogenes
Strep. pneumoniae
N. gonorrhoeae, meningitidis
Cl. welchii, tetani
Bacillus anthrax
Listeria monocytogenes
Haemophilus influenzae
Escherichia coli
Klebsiella pneumoniae
Salmonella spp.
Shigella spp.
Brucella
Yesinia pestis
Treponema
Leptospira
Borrelia
Chlamydia
Rickettsiae
Mycoplasma pneumoniae
Entamoeba histolytica

The tetracyclines have the broadest spectrum of all antibacterial agents being active against chlamydia, rickettsiae and *Entamoeba histolytica* as well as both Gram-positive and a large number of Gram-negative species. Proteus and pseudomonas organisms are usually resistant, as are fungi and viruses, with the exception of nocardiasis. Minocycline is the most potent tetracycline *in vitro* followed by doxycycline, but between the other agents there is no more than a twofold range in potency.

The tetracyclines are bacteriostatic at therapeutic concentrations. They prevent cell division as a consequence of impaired protein synthesis. They do this by blocking the link up of messenger RNA with ribosomes and the binding of aminoacyl transfer-RNA to the messenger RNA-ribosome complex. Bacteria so affected can survive but not divide and their elimination from the body is dependent upon the normal cellular and humoral defence mechanisms. These agents do not affect DNA and RNA synthesis in bacteria or protein synthesis in host cells, at therapeutic concentrations.

Table 3
Tetracyclines



BASIC STRUCTURE

APPROVED NAME	R_1	R_2	R_3	R_4
TETRACYCLINE	-H	$-CH_3$	-OH	-H
OXYTETRACYCLINE	-H	$-CH_3$	-OH	-OH
CHLORTETRACYCLINE	-Cl	$-CH_3$	-OH	-H
DESMETHYLCHLORTETRACYCLINE	-Cl	-H	-OH	-H
METHACYCLINE	-H	$=CH_2$		-OH
MINOCYCLINE	$-N(CH_3)_2$	-H	-H	-H
DOXYCYCLINE	-H	$-CH_3$	-H	-OH

RESISTANCE Resistant mutants emerge slowly *in vitro* by a series of small steps on repeated subculturing. The concentration of tetracycline necessary to block protein synthesis in homogenates of resistant organisms is similar to that for sensitive organisms, suggesting that the cell membranes of resistant organisms are less permeable than those of sensitive organisms. In Gram-negative organisms, resistance is commonly R-factor mediated. *In vivo* resistance to tetracyclines has emerged very slowly but is now quite common amongst haemolytic streptococci, pneumococci, *H. influenzae* and *Clostridium welchii*. This has

reduced the usefulness of these agents considerably in the treatment of upper and lower respiratory tract infections.

DRUG FATE

Absorption All tetracyclines are orally active, peak plasma levels being achieved 2–3 hours after administration. Apart from minocycline and doxycycline, which are well absorbed, absorption of tetracyclines is poor, parenteral doses usually being only one-third to one-half those of oral doses. They form insoluble chelates with di- and trivalent cations and the amount absorbed is substantially reduced by coadministration of calcium ions, milk, antacids and iron salts. Absorption can be enhanced however by administration with phosphate or citric acid.

Distribution The degree to which tetracyclines are protein bound varies between agents being 70–80% for methacycline and minocycline, 40–70% for chlor- and demethylchlortetracycline (DMCT) and 20–30% with tetracycline, oxytetracycline and doxycycline. Tetracyclines achieve therapeutic concentrations in most tissues including the CSF in which, after multiple doses, the concentration approaches that in the plasma. The apparent volume of distribution of these agents exceeds that of total body water (100–128 l) indicating that they are concentrated in tissues. The plasma half-life in the presence of normal renal function is longest for minocycline and doxycycline (14–20 hours) intermediate for DMCT and methacycline (11–13 hours) and for tetracycline and oxytetracycline (8–9 hours) and shortest for chlortetracycline (5–6 hours).

Excretion Tetracyclines are removed from the plasma by both renal and biliary excretion. There is little information on metabolism of these drugs, but it appears that only minocycline and doxycycline are appreciably metabolised. For all tetracyclines other than doxycycline and minocycline after parenteral administration, the majority of a dose is excreted unchanged in the urine, renal excretion being by glomerular filtration at a rate lower than that for creatinine. Minocycline is excreted in the urine to a lesser degree than other tetracyclines as it is partially metabolised and over 80% of a dose of doxycycline is excreted as an inactive conjugate in the faeces.

Tetracyclines are excreted in the bile where they achieve a concentration many times that in the plasma. Chlortetracycline is the most rapidly excreted by this route.

In renal failure, all tetracyclines other than doxycycline accumulate in the plasma. In oliguric patients the $t_{\frac{1}{2}}$ for tetracycline and oxytetracycline is 50–100 hours. Chlortetracycline accumulates to a lesser degree, the half-life in oliguric patients being 6–12 hours, and doxycycline does not accumulate at all.

ADVERSE EFFECTS

Gastrointestinal symptoms, nausea, vomiting, loose stools, epigastric pain, dysphagia and stomatitis are common symptoms, but are seldom troublesome.

Superinfection The broad spectrum of antibacterial activity of tetracyclines causes profound changes in commensal flora, especially in the gut and this probably accounts for the side-effects of loose stools and diarrhoea. More serious, the removal of commensal organisms predisposes to invasion of the bowel lumen by resistant pathogens. Of these the most serious is the staphylococcus which may cause a staphylococcal enteritis, a condition that can be rapidly fatal. Infection with the fungus *Candida albicans* or with *Pseudomonas* or *Proteus* may cause a pseudomembranous colitis, and occasionally a pseudomembranous colitis develops with no pathogen being cultured from the stool.

Hepatotoxicity With oral doses of 2g or less per day, tetracyclines rarely cause an increase in aspartate transaminase and occasionally clinical evidence of hepatocellular damage. In high parenteral doses (2–6g/day), tetracyclines may cause severe and sometimes fatal hepatocellular damage with fine vacuolar fatty changes on liver histology.

Nephrotoxicity In renal failure, all tetracyclines, with the exception of doxycycline, may cause weight loss and an increase in blood urea and occasionally a fall in glomerular filtration rate. These effects which are usually reversible, are partly due to an impairment of anabolic events in the tissues by high concentrations of tetracycline. Occasionally, the detrimental effects on renal function may be irreversible and result in a serious reduction in renal function. Doxycycline does not cause this syndrome and is therefore the only tetracycline which is safe to use in patients with renal failure.

Tetracyclines have a weak diuretic action, but do not cause renal damage except in the presence of renal failure. A reversible Fanconi-like syndrome with renal tubular acidosis, glycosuria and amino aciduria has been attributed to a degradation product of tetracycline, anhydro-4-epitetracycline, present only in substandard tetracyclines.

Staining of teeth Tetracyclines form chelates with divalent and trivalent cations and are taken up in bones and teeth. If administered to pregnant women or neonates they may cause brown discoloration to the primary dentition and, less commonly, hypoplasia of the enamel. Staining of the secondary dentition may occur if they are prescribed to children under the age of 7. Oxytetracycline has less effect on the teeth than other tetracyclines but, if possible, these agents should not be prescribed to children under the age of 7.

CLINICAL USE Despite the long list of potential adverse effects, tetracyclines are generally well-tolerated and safe drugs. For many years they were the most widely used antibacterial agents and their fall in popularity in recent years resulted from the introduction of the bactericidal, broad-spectrum agents ampicillin, the cephalosporins and co-trimoxazole and the emergence of tetracycline resistant strains of the important pathogens *Staph. aureus*, haemolytic streptococci, the pneumococcus and *Haemophilus influenzae*. They are now seldom the antibacterial agent of first choice in respiratory tract or urinary tract

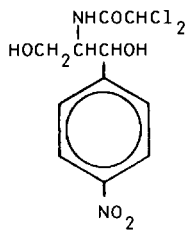
infections, but they are in rickettsial infections, in *Mycoplasma pneumoniae* infections and those due to chlamidia, trachoma, psittacosis and lymphogranuloma venereum. They are also useful alternatives to penicillin in a number of infections, including syphilis, actinomycosis, anthrax and plague and alone, or with streptomycin, in brucellosis and glanders.

Despite the large number of tetracyclines, there is little to choose between them on pharmacological grounds. Minocycline is the most potent *in vitro* but causes dizziness and vertigo in some patients through an effect on the vestibular apparatus. Minocycline and doxycycline have the longest half lives and doxycycline is the only safe tetracycline in patients with renal failure. In patients with normal renal function the choice is commonly made on the basis of cost, oxytetracycline being the cheapest preparation.

Preparations

	Adult dose (mg)	*Route*	*Dose interval*
Demethychlortetracycline	150	Oral	6–8
Methacycline	150	Oral	6–8
Doxycycline	100	Oral	24
Minocycline			
Tetracycline hydrochloride	250–500	Oral	8
Chlortetracycline			
Oxytetracycline			

Chloramphenicol



Chloramphenicol was the first broad-spectrum antibacterial agent to be discovered and was very widely-used for over ten years after its discovery, until the rare, but sometimes fatal adverse effect of bone marrow depression became apparent. It was originally isolated from *Streptomyces venezuelae*, but shortly afterwards its chemical structure and synthesis was achieved and now only the synthetic form is available.

SPECTRUM As for tetracycline.

The spectrum of chloramphenicol differs little from the tetracyclines. It is one of the most effective agents against all species of *Salmonella*, *H. influenzae* and *B. pertussis*. It is ineffective against *Pseudomonas aeruginosa*, some species of *Proteus*, fungi and viruses.

Chloramphenicol is bacteriostatic, acting by impairing protein synthesis. It becomes attached to the 50S ribosomes of sensitive organisms and prevents the link up of ribosomes and messenger RNA, and of this complex with aminoacyl transfer-RNA, in a similar fashion to tetracycline.

RESISTANCE Mutants resistant to chloramphenicol emerge slowly *in vitro*. *In vivo* resistance also emerges slowly. Until 1962, no chloramphenicol resistant strains of *S. typhi* were reported but since then, they have become increasingly common and in 1972 80% of all organisms isolated from one centre were resistant. Resistance is often R-factor mediated and may be due to a variety of mechanisms including the elaboration of chloramphenicol metabolising enzymes such as chloramphenicol acetyl transferase, by resistant bacteria e.g. *Staph. aureus* or *E. coli*.

DRUG FATE Chloramphenicol is orally active 33–85% of an oral dose being absorbed. Peak plasma levels are achieved by 2–4 hours. It is 60% protein-bound in plasma, diffuses readily across cell membranes and rapidly achieves a concentration in the CSF 40–50% that in the blood. It is removed from the blood by metabolism being conjugated with glucuronic acid in the liver. Only 10–15% of an i.v. dose is excreted unchanged in the urine, the rest being excreted in the bile, where it undergoes enterohepatic circulation. In adults, with normal renal and hepatic function, the $t_{\frac{1}{2}}$ is 1·6–3·3 hours, that of the major metabolites being longer, and it is not increased in severe renal failure. In renal disease, the concentration of unchanged drug in the urine falls with the creatinine clearance and with values 20 ml/min or less is only one-tenth that when renal function is normal. In neonates, chloramphenicol is excreted less rapidly than in adults as the hepatic drug conjugating mechanisms are poorly developed and the glomerular filtration rate and effective renal plasma flow are below adult values. The effect on the $t_{\frac{1}{2}}$ of chloramphenicol is shown in Table 4.

Table 4

Age	$t_{\frac{1}{2}}$ *(h)*
1–2 days	26
10–16 days	10
5 years	4–5

ADVERSE EFFECTS

Super infection As with tetracycline the broad-spectrum of chloramphenicol predisposes to super infection.

Bone marrow depression Chloramphenicol has been implicated as the drug that most commonly induces bone marrow depression. The true incidence of this serious effect has not been clearly established, but it is clear that the risk of developing it increases with the size of the dose and the duration of therapy, suggesting that bone marrow depression is a direct toxic effect of drug or a metabolite. The haematological changes are variable but in the

majority of cases, there is a reduction in all cellular elements in the peripheral blood and a hypoplastic bone marrow. The onset of these changes may occur weeks or months after the first dose and often a long time after stopping the drug so that routine blood counts during therapy give little or no warning of bone marrow toxicity. The condition may be reversible but the overall mortality is of the order of 50%. Chloramphenicol impairs the incorporation of iron into haemoglobin and may cause a reversible anaemia associated with a rise in serum iron and vacuolisation of red cell precursors.

'Grey baby syndrome' Given in high doses (100 mg/kg or greater) to neonates, chloramphenicol may cause abdominal distension, vomiting, irregular breathing, profound cyanosis and vasomotor collapse, a syndrome described as the 'grey baby syndrome' on account of the appearance of the babies in the terminal stages. The syndrome is usually fatal and is associated with very high blood levels of unconjugated chloramphenicol which accumulates over 2–4 days if the drug is given in high doses (*see* Drug fate).

CLINICAL USE

Chloramphenicol is a drug of first choice in the treatment of typhoid, except in areas with a high incidence of chloramphenicol-resistant organisms. It has reduced the mortality from 12% to less than 5% but is ineffective against *S. typhi* carriers. Its effectiveness against *H. influenzae* and its ability to diffuse readily across the blood-brain barrier, makes it also a drug of first choice in the treatment of *H. influenzae* meningitis.

In other infections, with the slight but definite risk of bone marrow depression and the availability of alternate broad-spectrum antibacterial agents, chloramphenicol should seldom, if ever, be used. It may however be used in potentially dangerous infections when less toxic agents have proved ineffective and in topical preparations for use in eye and ear infections. It is still widely used in proprietary antibacterial preparations in combination with other agents in many parts of the world. Its use in this way is to be deprecated.

Preparations

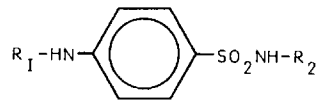
		Dose (g)	*Route*	*Dose interval*
Adults	chloramphenicol	0·5–1·0	Oral	6–8 h
Children	chloramphenicol palmitate	15–30 mg/kg	Oral	8
	chloramphenicol succinate	15–30 mg/kg	i.m., i.v.	8

SULPHONAMIDES

Sulphonamides were the first effective systemic antibacterial agents and were introduced to clinical medicine by Domagk in 1935. The introduction of penicillin in 1940, which heralded the era of antibiotics, and the early emergence of sulphonamide-resistant strains amongst a number of common

pathogens, severely restricted their use. Recently, however, the introduction of the trimethoprim-sulphonamide combination has re-established sulphonamides as useful antibacterial agents effective against a wide spectrum of bacteria and the malarial parasite (*see* Chapter 36).

The sulphonamides are synthetic compounds having the common structure.



They are weak acids and hence are more soluble in an alkaline than acid environment, e.g. the solubility of sulphadiazine increases over 20-fold between pH 5·5 and pH 7·5.

SPECTRUM

Staph. aureus	*E. coli*
Strep. pyogenes	*Proteus mirabilis*
Strep. pneumoniae	*Klebsiella* spp.
N. gonorrhoeae	*Shigella* spp.
N. meningitidis	*Salmonella* spp.
H. influenzae	

They have a broad-spectrum and are bacteriostatic at therapeutic concentrations. They are most effective against *Strep. pyogenes* and *N. meningitidis*, their effectiveness against Gram-negative bacilli being highly variable. *Proteus* species, other than *mirabilis* and *Pseudomonas* organisms, are resistant. There is some variability in antibacterial activity between sulphonamides, and in general the rapidly absorbed agents with short half-lives are the most potent.

MODE OF ACTION Sulphonamides impair folic acid (FA) synthesis in bacteria. Folic acid (for formula *see* Chapter 32) is synthesised from the nucleic acid pteridine, para-aminobenzoic acid (PABA) and glutamic acid by a series of enzymatically mediated steps (*see* Fig. 5).

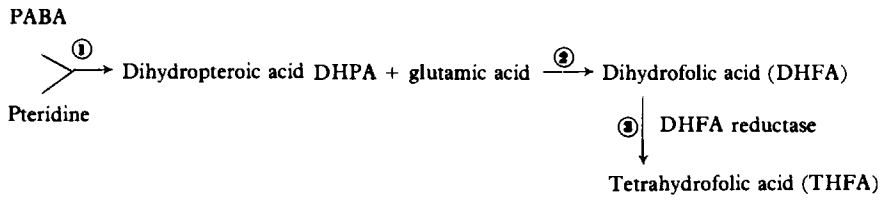


FIG. 5 Steps in the biosynthesis of tetrahydrofolic acid in bacteria.

The sulphonamide nucleus is similar in structure to PABA and sulphonamides compete with PABA for the enzyme responsible for step 1 in tetrahydrofolic acid (THFA) synthesis with the result that sensitive organisms become THFA deficient. THFA is a cofactor in the transport of 1-carbon atom metabolites and is essential for nucleic acid synthesis. In the presence of

sulphonamides, sensitive bacteria do not generate sufficient nucleic acids for cell division and cell division ceases. The selective toxicity of the sulphonamides is based on the fact that the mammalian cell membrane, but not the bacterial cell wall, is permeable to dihydrofolic acid (DHFA), so that the metabolic requirements of mammalian cells for DHFA are satisfied from the diet, DHFA reaching its site of action by diffusion from the extracellular space.

RESISTANCE Resistance emerges slowly both *in vitro* and *in vivo*. Resistant strains of *Strep. pyogenes* and *pneumoniae* and *N. gonorrhoeae* were reported within a few years of the introduction of sulphonamides. Resistant strains of *Shigella* are common and more recently, resistant strains of *N. meningitidis* have occurred. There is cross-resistance between sulphonamides. The mechanisms of resistance are not always clear. Resistant organisms may produce more PABA than sensitive species or may possess enzymes responsible for DHFA synthesis with a lowered affinity for sulphonamides. Sulphonamides are generally less effective *in vivo* than *in vitro*, as they are antagonised by tissue breakdown products and are less effective in the presence of plasma, presumably on account of drug-protein binding.

DRUG FATE Most sulphonamides are rapidly and completely absorbed from the gut. The relatively water insoluble compounds, succinylsulphathiazole and phthalylsulphathiazole, are very poorly absorbed and their antibacterial effect is confined to the bowel lumen and gut wall. In the plasma, sulphonamides are partially protein-bound and in general the duration of action increases with the extent of protein binding, the long-acting preparations, e.g. sulphadimethoxine (95% bound) and sulphamethoxypyridazine (85% bound) being the most highly protein-bound. They rapidly diffuse across cell membranes and the blood-brain barrier, the concentration of the CSF being determined by the drug plasma albumin binding e.g. the sulphadiazine which is 50% protein-bound the CSF/plasma concentration ratio is 0·5. The apparent volume of distribution of sulphonamides is close to that of total body water.

Sulphonamides are metabolised in the liver, partly by oxidation and conjugation, and partly by acetylation. The acetylated form is the major metabolite for a number of sulphonamides, e.g. sulphadiazine, sulphathiazole and sulphamethoxazole and the rate at which these drugs are acetylated is determined by a single genetic factor which displays polymorphism (*see* isoniazid). The acetylated metabolite accounts for 10–60% of the total drug in the urine for these agents.

Excretion of sulphonamides and metabolites is via the urine by both glomerular filtration and tubular secretion, the rate of excretion increasing with urine pH and urine volume, and varying inversely with the degree to which the drug is protein-bound. Most orally-active sulphonamides achieve effective antibacterial concentrations in the urine even in subjects with renal failure.

ADVERSE EFFECTS Sulphonamides are generally less well-tolerated than the penicillins and tetracyclines. The short acting preparations are used in high

doses (*see* Preparations) and commonly cause nausea and vomiting. Allergic reactions are also quite common, rashes (including the Stevens-Johnson syndrome) being the most frequent manifestation and are most common with long-acting agents.

Bone marrow depression When sulphonamides were widely used, the frequency with which they caused bone marrow depression was second only to chloramphenicol. In patients with glucose-6-phosphate dehydrogenase deficiency, they may cause methaemaglobinaemia and a haemolytic anaemia.

Nephrotoxicity Many sulphonamides and their acetylated metabolites are poorly soluble in acid urine and may precipitate out causing renal tubular damage, crystaluria and, in some cases, renal tubular necrosis and acute renal failure. This complication is avoided by maintaining an alkaline urine and a urine volume greater than 2l/24 hours.

CHOICE OF SULPHONAMIDE There are a large number of sulphonamides and choice of a suitable agent is usually made on the extent to which it is absorbed from the gut, the plasma half-life and its solubility in the urine. On these criteria sulphonamides may be classified as follows:

1. Well absorbed

(a) Short half-lives (12 hours or less)
   (i) low urine solubility, e.g. sulphadiazine, sulphadimidine, sulphathiazole, sulphamethoxazole.
   These agents are suitable for the treatment of systemic infections e.g. meningococcal menigitis and urinary tract infections.
   (ii) high urine solubility, e.g. sulphafurazole and sulphamethiazole.
   These agents do not cause crystaluria and are used most commonly in the treatment of urinary tract infections.

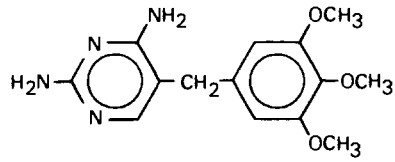
(b) Long half-lives (24 hours or greater) e.g. sulphamethoxazine, sulphamethoxypyridazine. These agents are highly protein bound and are slowly metabolised and excreted. They are rarely used in bacterial infections at present but with trimethoprim are occasionally used in malaria (*see* Chapter 36). Adverse effects occur more commonly with these agents than with those with shorter half-lives.

2. Poorly absorbed e.g. succinylsulphathiazole, phthalysulphathiazole. These agents do not attain therapeutic plasma concentrations after oral administration and are only used to treat intestinal infections and to decrease the number of bacteria in the bowel lumen.

CLINICAL USE Sulphonamides alone are most commonly used in urinary tract infections, their cheapness being their chief recommendation. They are also used (e.g. sulphadiazine) in the treatment of meningococcal meningitis, usually in combination with benzylpenicillin. In most other circumstances, sulphonamides are less effective than a number of other antibacterial agents and

cause more adverse effects. In most instances, their effectiveness can be greatly increased by trimethoprim. It is seldom justified, therefore, to use a sulphonamide alone, except for urinary tract infections.

Trimethoprim



Trimethoprim is a diaminopyrimidine, a weak base (pK 7·3) and is sparingly soluble in water.

ANTIBACTERIAL ACTIVITY Trimethoprim alone is bacteriostatic and has a similar spectrum to the sulphonamides, but is slightly more potent on a weight basis. Like sulphonamides, trimethoprim impairs THFA synthesis, but its site of action is different as it is an inhibitor of dihydrofolic acid reductase, the enzyme that converts the metabolically inactive DHFA to its active form as THFA (site 3 Fig. 5). Trimethoprim's selective toxicity for bacteria is due to its greater affinity for bacterial DHFA reductase which it inhibits at a concentration 1/50,000 of that necessary to produce the same degree of inhibition in mammalian cell DHFA reductase.

SYNERGISM WITH SULPHONAMIDES The double block of THFA synthesis produced by the sulphonamides and trimethoprim in combination renders these agents synergistic. The sum of the minimal inhibitory concentrations (MICS) of sulphamethoxazole and trimethoprim for a number of pathogens is very much less than the sum of the MICS of each drug alone. This is illustrated in Table 5.

Table 5 (Bushby 1969)
MIC μg/ml

	Sulphamethoxazole	*Trimethoprim*	*Bacteria*
Alone	100	1	*Strep. pyogenes*
Combination	1	0·05	
Alone	30	2	*Strep. pneumoniae*
Combination	2	0·01	
Alone	3	1	*Staph. aureus*
Combination	0·3	0·015	
Alone	10	1	*H. influenzae*
Combination	0·3	0·015	

The consequence of the synergism between these agents is that the sulphamethoxazole-trimethoprim combination is bacteriocidal at therapeutic

concentrations. As less sulphamethoxazole is required, adverse effects due to the sulphonamide component are much less common.

Trimethoprim is only available commercially in combination with sulphamethoxazole, and the rational basis for the choice of this sulphonamide is that as it has a similar plasma half-life, the ratio of trimethoprim/sulphamethoxazole should remain the same throughout a course of therapy.

Co-trimoxazole Co-trimoxazole is a combined preparation of trimethoprim and sulphamethoxazole in a ratio of 1 to 5 by weight. The maximum degree of synergism between these agents *in vitro* against most bacteria is obtained when they are present in the ratio of their MICS, and for many organisms this is around a trimethoprim-sulphamethoxazole ratio of 1/20. The volume of distribution of trimethoprim (1·5 l/kg) is greater than that of sulphamethoxazole (0·4 l/kg) and a concentration ratio in the plasma of 1 to 20–30 is best achieved when given in a dose ratio of 1 to 5.

ANTIBACTERIAL ACTIVITY Co-trimoxazole has a similar spectrum to the sulphonamides and is effective against salmonella species and penicillinase producing staphs. It is bacteriocidal in most instances at therapeutic tissue concentrations and resistance *in vitro* emerges slowly. *In vivo,* resistant strains of *H. influenzae* and *K. pneumoniae* have been reported and appear most commonly in patients treated with long term courses of co-trimoxazole.

DRUG FATE Both drugs are rapidly and completely absorbed from the bowel reaching peak plasma concentrations 2–4 hours after ingestion. Sulphamethoxazole is 65% and trimethoprim 40% protein-bound. Trimethoprim is concentrated in the tissues to a greater extent than sulphamethoxazole and both agents can reach the CSF in effective concentrations. Fifty to 70% of a dose of both drugs is excreted as unchanged drug in the urine and the half-life of both compounds in the plasma is around 10 hours. Sulphamethoxazole is a weak acid (pK 5·7) and trimethoprim a weak base and they are not excreted by the kidney by the same mechanisms, the trimethoprim/sulphamethoxazole ratio usually being less than 1/20. Sulphamethoxazole is excreted in the urine more slowly than trimethoprim, the rate being dependent on urine flow rate but not pH below pH values of 7·0 whereas the trimethoprim excretion rate varies inversely with pH but little with urine flow. The ratio of concentration of these agents in the urine therefore varies considerably with urine pH, but even with severe renal impairment both agents are present in effective concentrations in the urine. In severe renal failure the half-lives of both agents increase approximately three-fold.

ADVERSE EFFECTS Co-trimoxazole is generally much better tolerated than sulphonamides alone, although most of the adverse effects of sulphonamides may occur, of which the most common are gastrointestinal symptoms and rashes. The low dose of sulphonamide used has greatly reduced the incidence of renal complications, although acute tubular necrosis has been attributed to

co-trimoxazole. Aplastic anaemia, neutropenia and thrombocytopenia may occur, probably as a result of a reaction to sulphamethoxazole. Signs of folic acid deficiency, megaloblastic anaemia and thrombocytopenia have rarely occurred, even in patients on long courses of co-trimoxazole, although co-trimoxazole may exacerbate the effects of folic acid deficiency from other causes.

CLINICAL USE Co-trimoxazole is a highly effective broad spectrum antibacterial agent against infections at any site with sensitive organisms. It is effective in the treatment of typhoid and is a possible alternative therapy to chloramphenicol. It is also effective as a prophylactic agent against *Pneumocystis carini*. Although it has not been proved to have a teratogenic effect, the antifolate action of trimethoprim suggests that it should not be used during pregnancy. It is only available as an oral preparation.

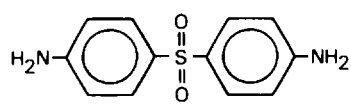
Preparations

	Adult dose (g) *Loading*	*Maintenance (g)*	*Route*	*Dose interval (h)*
Sulphadiazine	2–4	1	Oral	4–6
Sulphadimidine	3	1–1·5	Oral	4–6
Sulphafurazole	3	1–1·5	Oral	4
Sulphamethiazole	–	0·15–0·2	Oral	4
Succinylsulphathiazole / Phthalysulphthiazole	–	2	Oral	6
Co-trimoxazole trimethoprim / sulphamethoxazole		80–160 mg / 400–800 mg	Oral	8–12

Sulphones

The sulphones are structurally similar to the sulphonamides and their antibacterial activity was demonstrated in man only shortly after that of the sulphonamides. All sulphones in clinical use are derivatives of dapsone. As dapsone is the most widely used sulphone only the clinical pharmacology of this agent will be discussed in detail.

Dapsone (diaminodiphenylsulphone DDS)



ACTION Dapsone is bacteriostatic to *Mycobacterium leprae* and *M. tuberculosis*. It is also effective against many bacteria susceptible to sulphonamides. Its clinical use however is limited to the treatment of leprosy as it is less effective in TB than the established anti-tuberculous drugs and is less well tolerated than

sulphonamides or alternate antibacterial agents in other bacterial infections. The mode of action of sulphones is not clearly established but they probably act in a similar way to the sulphonamides as their antibacterial action is antagonised by para-amino benzoic acid.

Dapsone is effective in the majority of cases of leprosy, 50 mg/day being sufficient to reduce symptoms and to render skin smears virtually free of *M. leprae* within three months of starting therapy. A small number of viable bacteria may remain dormant in tissues for years and as dapsone is not bacteriocidal to such organisms, therapy must usually be continued for several years.

DRUG FATE Dapsone is well absorbed from the gut. In the plasma 70–80% of the drug is protein-bound. It is distributed in total body water, readily diffusing across cell membranes, into the CSF and into peripheral nerves. It is metabolised in the liver, less than 15% of an oral dose being excreted as unchanged drug in the urine. It undergoes N-oxidation to monohydroxylamine dapsone, which is probably responsible for its haemolytic activity (*see* below). It is also acetylated in the liver and as with other drugs that undergo hepatic acetylation (e.g. isoniazid) the rate of acetylation is determined by a single genetic factor which displays genetic polymorphism. However, as the acetylated metabolite reacetylates dapsone there is no difference in the rate of plasma clearance of dapsone between fast and slow acetylators, the $t_{\frac{1}{2}}$ being 17–25 hours.

ADVERSE EFFECTS

Haemolysis The incidence of haemolysis increases with the dose of dapsone and is probably due to the oxidation of haemoglobin to methaemaglobin and sulphaemaglobin by the metabolite monohydroxylamine dapsone. Haemolysis is rare at doses of 50 mg/day or 100 mg twice weekly and is more common in subjects with glucose-6-phosphate dehydrogenase deficiency.

Erythema nodosum leprosum Some patients, during the first year of dapsone therapy, develop crops of subcutaneous nodules consisting of infiltrations of polymorphonuclear leucocytes, IgG and complement but not *M. leprae*. Such crops usually last 2–3 weeks but may last longer and are associated with fever and malaise. Symptomatic relief is obtained with analgesics and anti-inflammatory drugs and dapsone can be continued. Other side effects include gastrointestinal symptoms, skin rashes, drug-induced fever and hepatocellular damage.

CLINICAL USE

Dapsone is the drug of choice in most cases of leprosy being effective, cheap and well tolerated at low doses. Therapy is initiated with 25 mg twice weekly and the dose increased by increments of 25 mg every two weeks, to a maintenance dose of 50 mg/day or 100 mg twice weekly. Treatment is continued for 5–10 years but may be discontinued after 3 years in tuberculoid leprosy.

Dapsone resistance may be treated with rifampicin which, in a dose of 600 mg/day, is effective against dapsone resistant organisms. Rifampicin is bacteriocidal to *M. leprae* and is much more rapidly effective than dapsone in relieving symptoms and sterilising skin lesions, although its high cost precludes its widespread use in this disease. An alternative drug is thiambutosine (0·5–2·5 g/day) which is also effective against dapsone resistant organisms, and is well tolerated but causes a blue-black discoloration of skin lesions.

Dapsone is also used in the treatment of dermatitis herpetiformis as it is effective at eliminating the skin lesions and, taken continuously, at suppressing their reappearance.

Other Sulphones Sulphoxone and sulphetrone differ little from dapsone. Long acting preparations diformyldapsone with a $t_{\frac{1}{2}}$ of 85 hours and acedapsone with a $t_{\frac{1}{2}}$ of 7 weeks are repository preparations which may be given once weekly and once monthly respectively. They are currently undergoing clinical evaluation.

MISCELLANEOUS ANTIBACTERIAL AGENTS

Polymyxins There are two polymyxins in clinical use, polymyxin B and E (colistin). They are basic polypeptides and their clinical pharmacology is very similar. They are available as sulphates and as sulphomethyl derivatives.

SPECTRUM

H. influenzae
E. coli
K. pneumoniae
Ps. aeruginosa
Salmonella spp.
Shigella spp.
A. aerogenes

Polymyxins are highly effective against most Gram-negative organisms including pseudomonas species, but are ineffective against Gram-positive organisms, Gram-negative cocci and against proteus species. They are bactericidal, impairing the function of the cytoplasmic membrane and causing a leak of intracellular contents.

Resistance does not emerge rapidly *in vitro* or *in vivo*.

DRUG FATE Polymyxins are not absorbed from the gut or from the skin but are slowly absorbed from intramuscular sites. Very little is excreted unchanged in the urine within 12 hours of an i.m. injection, but an appreciable urinary concentration is obtained by 24 hours. The sulphomethyl derivative, which is relatively inactive *in vitro*, is rapidly converted to the active polymyxin *in vivo*.

ADVERSE EFFECTS

Nephrotoxicity Polymyxins may cause renal tubular damage with proteinuria and acute renal failure. This has occurred most commonly when these drugs have been prescribed in normal doses to patients with renal failure.

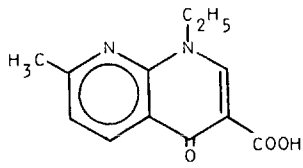
Neuromuscular blocking action Polymyxins have a neuromuscular blocking

action that is not antagonised by neostigmine. On occasions, this has precipitated respiratory failure, especially in patients with impaired renal function.

Polymyxins are capable of releasing histamine from mast cells; they are also neurotoxic and may cause a peripheral neuropathy.

CLINICAL USE In view of the severity of their adverse effects polymyxins are drugs of second choice in the treatment of serious Gram-negative infections, especially those due to *Pseudomonas* organisms, when it is administered i.m. or i.v. They should only be used when less toxic agents, such as carbenicillin and gentamicin, have failed. Topical administration to the skin, eye and in the external auditory meatus is effective in eliminating *Pseudomonas* organisms.

Nalidixic Acid



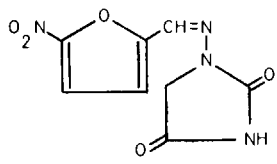
Nalidixic acid is a synthetic antibacterial agent that is bactericidal to most Gram-negative organisms but is ineffective against Gram-positive organisms and most *Pseudomonas* species. It impairs DNA synthesis without affecting RNA or protein synthesis.

Resistance develops rapidly both *in vitro* and *in vivo*.

DRUG FATE Nalidixic acid is absorbed from the gut and is over 90% protein-bound in the plasma. It is rapidly excreted, mostly as unchanged drug in the urine, the half-life varying between 2–8 hours and increasing 5–10 times in oliguric patients. The concentration of the unchanged drug in the urine is high, increasing with urine pH. There are four metabolites so far identified, one of which has some antibacterial activity.

ADVERSE EFFECTS Nalidixic acid has few side effects other than gastrointestinal symptoms. Rarely it causes a haemolytic anaemia, psychosis, raised intracranial pressure and convulsions.

CLINICAL USE Nalidixic acid is used in the treatment of urinary tract infection, especially those due to *Proteus* and *E. coli* species, and is an alternative to broad spectrum antibacterial agents. It does not reach effective concentrations in tissues other than the kidney and is not as effective as other broad-spectrum antibacterial agents in pyelonephritis or in patients with impaired renal function. It has also been used successfully in bacillary dysentery.

Nitrofurantoin 

Nitrofurantoin is a synthetic bacteriocidal compound, with quite a broad-spectrum of antibacterial activity, which includes most organisms that commonly infect the urinary tract. It is most effective in an acid urine.

SPECTRUM

Staph. aureus	*E. coli*
Strep. pyogenes	*Proteus* spp.
Strep. viridans	*Klebsiella* spp.
Strep. faecalis	*Salmonella* spp.
N. gonorrhoeae	*Shigella* spp.

Pseudomonas organisms are resistant. Nitrofurantoin antagonises nalidixic acid so that the two agents should not be used together. Resistant strains develop rapidly *in vitro* and *in vivo*.

DRUG FATE Nitrofurantoin is orally active and is rapidly metabolised, approximately one-third of an oral dose being excreted unchanged in the urine. The half-life is very short, 20 minutes, and effective antibacterial concentrations are not achieved at sites other than the urine and renal parenchyma. The concentration in the urine falls with impaired renal function and when the creatinine clearance is 60 ml/min or less, it is seldom sufficient to produce an antibacterial effect. The drug plasma concentration however only increases slightly in renal failure.

ADVERSE EFFECTS Nausea, vomiting and diarrhoea are the most common. Serious adverse effects are few but include peripheral neuropathy that occurs most frequently in patients with renal failure. Nitrofurantoin may precipitate haemolytic anaemia in glucose-6-phosphate dehydrogenase deficient patients and rarely causes megaloblastic anaemia. Other adverse effects include pulmonary interstitial fibrosis, hepatocellular damage and drug fever.

CLINICAL USE Nitrofurantoin is a useful drug in the treatment of urinary tract infections in patients with normal renal function.

Metronidazole Metronidazole is a synthetic imidazole compound that is an effective amoebicide (*see* Chapter 36) and is bactericidal to anaerobic bacteria but is ineffective against aerobic species. It is selectively concentrated in anaerobic bacteria where it impairs DNA synthesis but its mode of action is poorly understood.

SPECTRUM

Protazoa	*Trichomonas vaginalis*	Bacteria	*Bacteroides fragilis*
	Entamoeba histolytica		*Veillonella* spp.
	Giardia lamblia		*Campylobacter foetus*
			Clostridium spp.
			Treponema pallidum

FATE Metronidazole is well absorbed from the bowel and may be administered orally, rectally or i.v. It is cleared from the plasms by both hepatic metabolism and renal excretion, 60–70% of an intravenous dose being excreted as unchanged drug in the urine. The plasma $t_{\frac{1}{2}}$ in subjects with normal renal function is 8.5 hours.

ADVERSE REACTIONS These are few, nausea and vomiting being the most common. Rare serious reactions have included neutropenia, a peripheral neuropathy and a confusion state.

Interactions A disulphiram-like reaction (*see* Chapter 18) may occur if ethanol is taken by patients on the drug. Metronidazole enhances responsiveness to warfarin.

CLINICAL USE Metronidazole is the drug of choice in the treatment of infections due to the protazoa *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia* (200–800 mgs 8 hourly for 7 days). It is also most effective in the treatment of infections due to anaerobic bacteria, causing fewer serious side effects than clindamycin or lincomycin. On this account it is used in the prophylaxis and treatment of anaerobic infections following surgery to the bowel, 500 mg being given 8 hourly by continuous infusion. Metronidazole may also be of value in the treatment of Fasciola hepatica, leishmaniasis and acute ulcerative gingivitis.

Bacitracin Bacitracin, like the polymyxins, is a polypeptide. It has a relatively narrow spectrum, being effective against Gram-positive cocci, *H. influenzae*,

Preparations

Drug	*Adult dose*	*Route*	*Dose interval (h)*
Polymyxin B	6000 iu/kg	i.v.	6
	1500–2500 iu/kg	i.m.	6
	0·1–0·25%	Topical	
Colistin	6000 iu/kg	i.m.	8
Bacitracin	500 iu/g	Topical	
Nalidixic acid	500–1000 mg	Oral	6
Nitrofurantoin	50–150 mg	Oral	6
Metronidazole	150–600 mg	Oral	6

Neisseria and *T. pallidum*, but ineffective against most Gram-negative bacilli. Bacitracin acts by impairing cell wall synthesis and has the same effects on susceptible organisms as the penicillins.

Bacitracin is not absorbed from surfaces and, as it may cause nephrotoxicity within the therapeutic dose range, is not used systemically. It is commonly used as a topical antibacterial agent, often in combination with a broad-spectrum agent, and only rarely causes local hypersensitivity reactions.

ANTIFUNGAL AGENTS

Fungal infections may be due to one of three groups of fungi, the actinomyces, the dermatophytes which infect skin and nails only, and mycoses which may produce systemic infections. *Actinomyces israelii* and *Nocardia asteroides* are susceptible to antibacterial agents, the former to benzylpenicillin and the latter to sulphadiazine and minocycline, but the other fungi are not affected by antibacterial agents. Fungi have a more complex cell structure than bacteria, one of the differences being that the cell membrane of the fungi contains a sterol, ergosterol, whereas the cytoplasmic membrane of bacteria does not. This difference accounts for the fact that antifungal agents are not effective against bacteria (*see* below).

Fungal infections are not as common as bacterial or viral infections. They are most frequently encountered in debilitated patients and those with impaired defence mechanisms such as patients on immunosuppressive drugs. Infections with *Candida albicans* or with one of the dermatophytes, the two most common fungal infections encountered in the United Kingdom, are usually of nuisance value only, but systemic infections such as histoplasmosis and blastomycosis, which are more common in the United States, are frequently fatal.

The polyene antifungal agents The polyene antifungal agents, nystatin and amphotericin B, are derived from different species of streptomyces and are large cyclic lactones with a hydrophilic and hydrophobic component. Their antifungal action is due to their high affinity for the ergosterol of fungal cell membranes into which they become incorporated. Their selective toxicity for fungi is due to their greater affinity for ergosterol than for cholesterol, the principal sterol component of mammalian cell walls. They impair cell membrane function and cause a leak of intracellular contents.

Nystatin

SPECTRUM

Candida albicans
Aspergillus fumigatus
Histoplasma capsulatum
Cryptococcus neoformans
Elastomyces dermatitidis
Sporotrichum schenckii
Trichophyton spp.
Epidermophyton spp.
Microsporum audouinii

Nystatin is fungicidal at therapeutic concentrations and is most effective against

Candida albicans. It has no antibacterial effect. Resistance does not develop *in vitro* or *in vivo*.

DRUG FATE Nystatin is not absorbed from the gut or skin and is only administered orally or topically.

ADVERSE EFFECTS These are mild, gastrointestinal symptoms being the most common.

CLINICAL USE Nystatin is not available for systemic use. It is the agent of choice for Candida infections of the gut, vagina and skin and is available in tablet and pessary form as well as in creams and ointments.

Amphotericin B

SPECTRUM As for nystatin.

Amphotericin B is generally more potent than nystatin. Resistance does not emerge *in vitro* or *in vivo*. It is insoluble and is marketed as a bile salt complex. It is poorly absorbed from the gut and for systemic infections is administered i.v. It is appreciably bound to plasma proteins and to tissue sterols and does not reach therapeutic concentrations in the CSF. Less than 1% is excreted as unchanged drug in the urine and the drug does not accumulate in the plasma in the presence of renal failure.

ADVERSE EFFECTS These are common. Fever, nausea and vomiting occur during an infusion and in severe cases may be associated with rigors, confusion and hypotension. Thrombophlebitis at the site of injection is also common, as is a dose-related impairment of renal function which may be associated with hypokalaemia and renal tubular acidosis. Rarely acute tubular necrosis occurs, but some reduction in glomerular filtration rate is often irreversible on stopping therapy. Other severe adverse effects include hypersensitivity reactions of all types and hepatocellular damage. Intrathecal administration may result in lumbar nerve lesions and a chemical meningitis.

CLINICAL USE Despite its toxicity amphotericin is the drug of choice for all systemic fungal infections and has reduced considerably the very high mortality from such infections. Prolonged and recurrent courses are often necessary. It is administered as a continuous infusion in 5% dextrose, usually over 4–6 hours, repeated every 24 hours, in a dose that usually starts at 0·3 mg/kg/24 h and increases up to 0·6–1·0 mg/kg/24 h. The infusion may include hydrocortisone initially, to minimise the local and systemic reactions to the drug. The drug often comes out of solution if other drugs are added to the infusion.

5-Fluorocytosine

SPECTRUM

Candida albicans
Aspergillus fumigatus
Sporotrichum schenckii
Cryptococcus neoformans

5-Fluorocytosine is a fluorinated pyrimidine that is fungistatic to yeast-like fungi being converted in the fungus to the antimetabolite 5-fluorourocil. A number of *Candida* species are resistant to 5-fluorocytosine and resistance quite commonly develops by random mutation during a course of therapy. The value of this agent in *Aspergillus* infections is not established.

DRUG FATE 5-Fluorocytosine is orally active and diffuses readily into CSF having an apparent volume of distribution similar to that of total body water. It is mostly excreted unchanged in the urine and in subjects with normal renal function, has a plasma half-life of 3–4 hours. This varies with the creatinine clearance and is over 100 hours in oliguric patients.

ADVERSE EFFECTS Bone marrow depression is the dose-limiting effect, thrombocytopenia, anaemia and leukopenia occurring alone or together after moderate or high therapeutic doses. It is common in patients with renal failure who are treated with normal doses.

CLINICAL USE 5-Fluorocytosine is the drug of choice in *Candida* urinary tract infections as it is highly concentrated in the urine. It is less toxic at therapeutic doses than amphotericin B and is orally-active and for these reasons is often used in preference to that drug in systemic infections with sensitive fungi. It is especially useful when the meninges are involved as it diffuses readily through the blood-brain barrier in contrast to amphotericin. In severe systemic fungal infections these agents may both be administered.

5-Fluorocytosine is administered orally six hourly. It is essential to check renal function at the outset and to monitor this and bone marrow function during therapy.

Griseofulvin

SPECTRUM
Epidermophyton spp.
Trichophyton spp.
Microsporum spp.

Griseofulvin is not a polyene but is derived from a species of penicillium. It is fungistatic to the fungi that infect the hair and nails, but the mode of action is unclear. Griseofulvin is poorly absorbed from the gut, less than 50% of most oral preparations reaching the systemic circulation. Less than 1% of an oral dose is excreted unchanged in the urine, absorbed drug being metabolised, principally by demethylation and conjugation, in the liver. Griseofulvin has a predilection for precursors of keratin and becomes incorporated into newly formed keratin within 72 hours and new hair and nails become free of infection earlier than older skin appendages as a consequence.

ADVERSE EFFECTS Headaches, gastrointestinal symptoms and rashes are quite common. Serious adverse effects include drowsiness, confusion and a peripheral

neuropathy. Rarely bone marrow depression, albuminuria and hepatocellular damage occurs.

CLINICAL USE Griseofulvin is the drug of choice in fungal infections of the hair and nails. It is given orally 1–4 times/day the duration of therapy varying from three weeks for skin infections to four months for toe-nail infections.

For other topical anti-fungal agents *see* Chapter 41.

Preparations

Drug	*Adult dose*	*Route*	*Dose interval (h)*
Nystatin	0·5–1·5 Munits	Oral	8
	0·1 Munits	pessary	24
Amphotericin B	0·25–1·0 mg/kg	i.v.	24
Griseofulvin	125 mg	Oral	6
	500 mg	Oral	24
5-Fluorocytosine	10–40 mg/kg	Oral	6

Imidazoles Clotrimazole and miconazole are imidazole derivatives with a broad spectrum of antifungal and some antibacterial activity. Both may be applied topically and are as effective as nystatin in topical *Candida* infections acting by impairing fungal membrane permeability. Clotrimazole is also effective against systemic fungal infections and may be administered both orally and i.v. It has a plasma $t_{\frac{1}{2}}$ of 3–5 hours, is cleared from the plasma by metabolism and does not accumulate in renal or hepatic failure.

Local irritation occasionally occurs with both these agents. Systemic administration of clotrimazole may cause gastrointestinal symptoms, neutropenia, drowsiness and depression.

ANTIVIRAL AGENTS

Despite the plethora of viruses that are pathogenic to man, there are only four chemotherapeutic antiviral agents currently available for clinical use. The principle reasons for this paucity, relative to the number of antibacterial agents, are that viruses can only replicate inside host cells and that there are relatively few known enzyme systems necessary for virus replication that may serve as targets for antiviral agents. Furthermore, there are close similarities between the nucleic acids of viruses and those of host cell nuclei so that many antiviral agents are cytotoxic to host cells.

The major difficulty in the development of antiviral agents is that there is often a poor correlation between activity *in vitro*, e.g. against viruses in tissue culture and that *in vivo*, many agents being effective in the former circumstances but not in the latter.

Chemotherapy in virus disease is potentially a most useful form of therapy as, in contrast to immunisation, it is immediately effective and is effective during

the incubation period before there is clinical evidence of disease. Also, as virus diseases usually come in epidemics, it is useful for the treatment of contacts of established cases. Therefore, while immunisations must stand as the main bulwark of antiviral therapy, there is promise that in the future, chemotherapy may well also make a useful contribution.

Methisazone The first agent to have antiviral activity was discovered during an investigation of the antituberculous properties of certain thiosemicarbazones, when it was noticed that benzaldehyde thiosemicarbazone had antivaccinia activity. Methisazone, a congener of this compound, was developed for clinical use as it is more effective *in vivo* than other thiosemicarbazones.

ANTIVIRAL ACTIVITY Methisazone has antiviral activity *in vivo* only against pox viruses, i.e. variola, alastrim (variola minor) and vaccinia. It inhibits the assembly of viral components by inhibiting late protein synthesis.

DRUG FATE Methisazone is orally active, reaches a peak plasma concentration by 4–7 hours and is not detectable in the plasma 10–12 hours after ingestion. There is no accumulation after multiple doses.

ADVERSE EFFECTS Nausea and vomiting are the only common side-effects and occur in the majority of patients.

CLINICAL USE

Smallpox In smallpox epidemics there is a reduction in the incidence of the disease and its severity in those taking methisazone prophylactically. It is ineffective once the disease has developed. It is of use in the treatment of two complications of vaccinia, vaccinia gangrenosa and eczema vaccinatum. It reduces the incidence of alastrim in contacts of the disease.

Amantidine Amantidine, whose clinical pharmacology is considered in conjunction with its use in parkinsonism in Chapter 16, was originally introduced clinically as an antiviral agent. Although it has a fairly broad spectrum of activity against RNA viruses of the influenza type *in vitro*, it is only effective clinically against the influenza A_2 virus. Its antiviral activity is due to its ability to prevent viruses from entering host cells.

Taken prophylactically, amantidine is as effective as immunisation against A_2 influenza. It should be taken continuously during an epidemic or for ten days subsequent to contact with an infected person.

Idoxyuridine Idoxyuridine is a synthetic nucleoside and a thymine antagonist that is effective against DNA viruses, especially the herpes viruses. It inhibits several enzymes that synthesise DNA and is incorporated into DNA itself. Resistance to its antiviral effect develops quite rapidly both *in vivo* and *in vitro*.

DRUG FATE Idoxyuridine is rapidly inactivated by deaminases present in the liver and brain. It is only effective, therefore, when applied topically or by continuous infusion.

ADVERSE EFFECTS Administered systemically it has the adverse effects of other antimetabolites and may cause bone marrow depression, gastrointestinal dysfunction, hepatitis and alopecia. Applied topically to the eye it may cause inflammation of the conjunctiva and eyelids with pain and photophobia.

CLINICAL USE AND ADMINISTRATION

Herpes keratitis Application of 0·1% solution at frequent intervals (i.e. 1–2 hourly) may prevent corneal damage due to *Herpes simplex* virus. It is less effective when applied topically for herpes infections of the skin and mucous membranes.

Herpes encephalitis Initial evidence from uncontrolled clinical trials suggested that idoxyuridine is effective in lowering the mortality when given by continuous infusion (100 μg/kg/24 hours) in herpes encephalitis but this has not been substantiated by subsequent trials.

Herpes zoster Idoxuridine (40% in dimethylsulphoxide) is effective at expediting healing of zoster skin lesions when applied early in the course of the disease.

Cytarabine (cytosine arabinoside) Cytarabine is similar in its antiviral activity to idoxyuridine in that it is an antimetabolite that inhibits DNA synthesis (*see* Chapter 38) and has a similar spectrum of antiviral activity. It has the advantages that resistance develops much less readily and that it is not inactivated by brain deaminases and hence is active when given intrathecally.

Clinical evidence on the antiviral activity of this drug is sparse but suggests that it is effective in *Herpes simplex* keratitis and in systemic infections with this virus. The results in herpes encephalitis and in *Herpes zoster* infections are less encouraging.

Preparations

	Adult dose	*Route*	*Dose interval*
Methisazone	1·5 g	Oral	12 h
Amantidine	0·2 g	Oral	24 h
Idoxyuridine	0·1% solution	conjunctival sac	1–2 h
	80–100 μg/kg/24 h	i.v.	
Cytarabine	60–80 mg/24 h	i.v.	
	15–20 mg/24 h	intrathecal	

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Chapter 36

Chemotherapy of Parasitic Infections

Parasitic diseases are the commonest causes of death and chronic ill health in the world and hence the drugs used in their prophylaxis and treatment are of great importance in therapeutics. In the western world, many of these diseases are rare, so that experience of drugs used in their treatment is generally poor. In this chapter, the clinical pharmacology of drugs used in the more common parasitic diseases will be discussed. Students intending to practice in situations in which parasitic diseases are common should consult a text book on tropical diseases for more detailed discussion on drug usage.

ANTI-MALARIAL DRUGS

Malaria is the commonest chronically disabling disease in the world occurring in an area occupied by one-third of the world's population. It is caused by a protozoon, the plasmodium, of which there are four species that affect man, *P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale*. The latter two species are much less ubiquitous than *P. vivax* and *P. falciparum*, and only rarely cause clinical malaria. *P. vivax* causes benign tertian malaria and *P. falciparum* malignant tertain malaria, a more serious disease that may be complicated by cerebral malaria, haemolytic anaemia, acute renal failure, pulmonary oedema and death. In the UK there are approximately 1000 cases of malaria reported each year, of which as many as 5% are fatal, all fatal cases being due to *P. falciparum*.

Understanding of the drug treatment of malaria is based on an understanding of the life cycle of the parasite, which is summarised in Fig. 1.

The vector, the anopheline mosquito, aspirates blood from an infected subject containing the male and female gametocytes and sexual reproduction occurs in the mosquito, the oocyst developing in the gut wall. When the oocyst ruptures, sporozoites migrate to the salivary gland and are injected into the subjects from whom the mosquito sucks blood. The sporozoites free in the blood of the human are initially sequestered in the liver where the first exo-erythrocytic (or tissue schizogony) occurs. Tissue schizogony causes rupture of the infected liver cells and the sporozoites released either recolonise liver cells (secondary exo-erythrocyte or tissue schizogony) or infect RBCs where they undergo erythrocytic schizogony which terminates in rupture of the RBCs and the clinical features of an acute attack of malaria. Merozoites either reinfect RBCs and repeat the cycle of RBC-schizogony or develop into gametocytes in

RBCs. *P. falciparum* differs from the other three species in not undergoing a secondary tissue schizogony.

Public health measures against malaria are directed mostly against the anopheline mosquito using organochlorides and organophosphate insecticides and other measures. Protection of man is by means of protective clothing and nets, mosquito repellent spray and creams and by means of drug therapy.

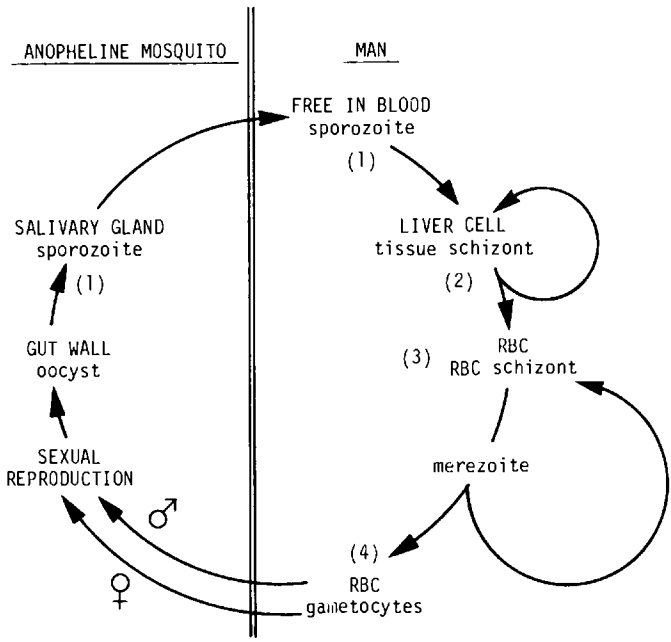
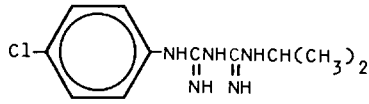


FIG. 1 Schematic representation of the life cycle of the plasmodium. The sites in the life cycle at which antimalarial agents act are:
(i) Causal prophylactics – proguanil, pyimethamine (sporontocidal drugs).
(ii) Anti-relapse drugs – primaquine.
(iii) Schizontocidal drugs – chloroquine, amodiaquine, quinine.
(iv) Gametocidal drugs – primaquine.

Drugs used in prophylaxis

There are no drugs effective against the sporozoite. Drugs used in prophylaxis (anti-folate agents, 4-aminoquinolines) are effective against the primary stage of tissue schizogony and against the RBC-schizogony. The only drugs effective against secondary tissue schizogony, the 8-aminoquinolines, are more toxic than the anti-folate agents and the 4-aminoquinolines, and hence are less suitable as prophylactic agents.

Proguanil (Chloroguanide)



This drug is a biguanide and acts by inhibiting dihydrofolate reductase so impairing nucleic acid synthesis (*see* trimethoprim, Chapter 35) having a much higher affinity for the enzyme of the plasmodium than for that of human cells. As with trimethroprim, there is synergism between proguanil and sulphonamides and sulphones.

Proguanil is effective at preventing all forms of malaria in the uninfected subject. It is toxic to the erythrocyte schizont and is effective at treating acute attacks of malaria, but has a slower onset of action than the 4-aminoquinolines. It is not effective against the tissue schizont and hence only suppresses *P. vivax*, *P. malariae* and *P. ovale* infections. It is not gametocidal, but prevents sexual reproduction in the mosquito.

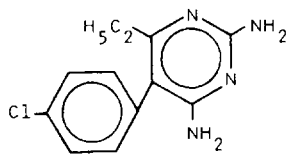
DRUG FATE Proguanil is well absorbed from the gut. In the plasma it is approximately 75% bound to plasma proteins and is concentrated in RBCs, reaching a concentration several times that in the plasma. Most of the drug is metabolised in the liver to a cyclised form, a triazine, which has anti-malarial activity and is available as a drug in its own right (cycloguanil). Both parent drug and active metabolite are rapidly cleared from the plasma, over 90% of an oral dose being eliminated in 24 hours.

ADVERSE EFFECTS Side-effects are few, nausea, vomiting and diarrhoea occurring occasionally.

Resistance In a small number of areas in Africa, resistant strains of *P. falciparum* occur, resistant organisms possessing a dihydrofolate reductase with a reduced affinity for the inhibitor. There is usually cross resistance with other anti-folate agents but not to the 4-aminoquinolines.

CLINICAL USE Proguanil is taken daily and for 24 hours before entering a malarial area. The average adult daily dose (100 mg) is continued during sojourn in a malarial area and for one month on leaving it. If the anticipated exposure to malaria is high, the daily dose may be doubled.

Pyrimethamine



Pyrimethamine is also a DHFA-reductase inhibitor, having a chemical structure very similar to cycloguanil, the triazine active metabolite of proguanil. Its

antimalarial actions are identical to those of proguanil. Pyrimethamine differs from proguanil in having a long duration of action. It is orally active; little is known of its metabolic fate in man, but small amounts of unchanged drug may be detected in the urine for weeks after a single dose.

Bone marrow depression, responsive to tetrahydrofolic acid (folinic acid), may occur after the relatively high doses used in toxoplasmosis, but are very rare at those used in malaria prophylaxis.

Pyrimethamine, 25–50 mg per week, may be used instead of proguanil in malaria prophylaxis. It may also be used in conjunction with a long-acting sulphonamide or sulphone in the treatment of chloroquine resistant malaria (*see* below).

Toxoplasmosis Pyrimethamine (25 mg/day) and sulphadizine are effective when given for up to one month in the treatment of toxoplasmosis. The blood count should be monitored during therapy with such a high dose of pyrimethamine, and prophylactic therapy with folinic acid (which does not prevent the drug's therapeutic action) should be initiated if blood count monitoring is not feasible.

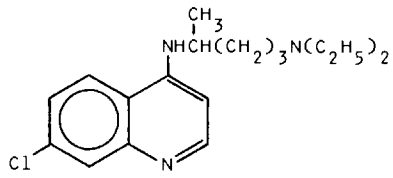
OTHER PROPHYLACTIC AGENTS Cycloguanil is as effective as proguanil and its clinical pharmacology very similar. It is available as a long-acting depot preparation, cycloguanil embonate, that has a half-life in man of six months. In semi-immune subjects, cycloguanil embonate may provide protection against malaria for several months.

Diacetyl-diaminodiphenyl sulphone (DADDS) is a sulphone and as a depot preparation has a half-life of nearly two months. This also provides long-term protection against malaria given alone or in combination with cycloguanil embonate.

Drugs used in treating acute attacks

Drugs of this group are rapidly toxic to the RBC-schizont. The 9-aminoacridine compound mepecrine (quinacrine) was the first effective erythrocyte schizonticide, but has been superceded by the 4-aminoquinolines which cause fewer adverse effects.

Chloroquine



Chloroquine is a 4-aminoquinoline and is rapidly effective at relieving the symptoms of an attack of malaria. It is lethal to the primary tissue schizont, to the erythrocyte schizont and to the gametocytes of *P. vivax*, but is ineffective against secondary tissue schizogony. In an acute attack of malaria treated with

chloroquine the temperature returns to normal in 24–48 hours and the blood is cleared of parasites in the same time.

The mode of action of chloroquine is less well understood than is that of the anti-folate agents. The drug reaches a concentration in RBCs approximately 25 times that in the plasma. It has a high affinity for nucleoproteins complexing with DNA and RNA and inhibiting DNA and RNA polymerase. It may also interfere with the digestion of haemoglobin by the plasmodium.

Chloroquine is an anti-inflammatory agent and in high doses is used for this effect in the treatment of discoid and systemic lupus erythematosus and rheumatoid arthritis (*see* Chapter 19). Its anti-inflammatory action may contribute to the rapidity with which the drug gives symptomatic relief during acute attacks.

DRUG FATE Chloroquine is orally active and is highly concentrated in the tissues achieving highest concentrations in the liver, spleen, heart and kidneys. It is also highly concentrated in melanin containing structures such as the retina, in hair and skin. It reaches the brain achieving a concentration there one-tenth that in the liver. Mepacrine is even more highly tissue bound than chloroquine, both drugs accumulating in the tissues during chronic administration. The drug plasma half-life is 8–10 hours after a single dose but increases with time as the apparent volume of distribution increases. The drug undergoes oxidative deethylation in the liver and very little unchanged drug is excreted in the urine.

ADVERSE EFFECTS Chloroquine is well tolerated at doses used in malaria, gastrointestinal symptoms and rashes being occasional side-effects. It has quinidine-like effects on the heart, but these are seldom evident during anti-malarial therapy.

Retinopathy may occur when high doses of chloroquine are used (*see* Chapter 19) in the treatment of connective tissue disorders.

Resistance Chloroquine resistant strains of *P. falciparum* are found in certain parts of South America and South East Asia, but only a few cases have been reported yet in Africa (for treatment *see* below).

CLINICAL USE

Acute attacks Chloroquine is the drug of first choice in acute attacks of malaria. An oral loading dose of 600 mg is followed by 300 mg in 6 and 12 hours and then 300 mg/day for two days. With this regime the great majority of patients are symptom-free in 24 hours. As chloroquine does not affect tissue schizonts, radical cure can only be achieved by coadministration of primaquine (*see* below).

Prophylaxis 500 mg chloroquine per week, starting 24 hours before entering a malarial area and continuing for one month on leaving, is an alternative form of prophylaxis to the antifolate agents.

Other uses Anti-inflammatory agent (*see* Chapter 19)—chloroquine may be useful in the treatment of extra-intestinal amoebiasis (*see* below).

Other 4-aminoquinolines Hydroxychloroquine and amodiaquine are very similar to chloroquine chemically and pharmacologically and there is little to choose between them in terms of their effectiveness and adverse effects.

The closely related compound mepacrine (quinacrine) causes rashes, headache and gastrointestinal symptoms more commonly than equieffective doses of the 4-aminoquinoline drugs.

Treatment of Chloroquine-resistant Malaria

P. falciparum resistant to chloroquine are prevalent in certain parts of the Far East and South America and, in some cases, the plasmodium is resistant to several anti-malarial drugs. At present, the most effective form of treatment is quinine or a combination of pyrimethamine with a long acting sulphonamide, e.g. sulphadimethoxine ($t_{\frac{1}{2}}$–35 hours), sulphalene ($t_{\frac{1}{2}}$—60 hours), sulphormethoxine ($t_{\frac{1}{2}}$—120 hours) or dapsone ($t_{\frac{1}{2}}$—25 hours) or its diformyl derivative DADDS ($t_{\frac{1}{2}}$—84 hours). Sulphonamides and sulphones are effective anti-malarial agents, having similar actions to proguanil and primethamine, but acting as competitive inhibitors of PABA incorporation into folic acid (*see* Chapter 35). The long-acting preparations have been found to be more effective than the shorter-acting sulphonamides.

Quinine Quinine is an alkaloid derived from cinchona bark, and it was first brought to Europe from South America in the 17th century. The antipyretic property of cinchona bark was soon recognised and in the 19th century quinine was isolated from the bark. It remained the only effective anti-malarial drug until the introduction of pamaquine, the forerunner of primaquine and mepacrine, in the late 1920s and early '30s.

ANTI-MALARIAL ACTION The anti-malarial actions of quinine are similar to those of chloroquine, but it is less effective at maximally tolerated doses. Quinine also has antipyretic and analgesic actions very similar to those of salicylates which may contribute to the symptomatic relief afforded by the drug.

DRUG FATE Quinine is orally active. It is highly protein-bound in the plasma, but readily diffuses across cell membranes and does not accumulate in the tissues in the same way as mepacrine and the 4-aminoquinolines. It is rapidly cleared from the plasma by metabolism, less than 10% of an oral dose being excreted in the urine, the amount varying inversely with the urine pH.

ADVERSE EFFECTS These are many and quinine has been described as a general protoplasmic poison. The symptom syndrome of overdose of quinine that may occur at therapeutic doses or even after a single dose in susceptible subjects, is known as cinchonism. Nausea, vomiting and diarrhoea, partly due to the local irritant effects of quinine and partly to a central emetic effect, may be associated with tinnitus, deafness, blurring of vision and blindness (quinine amblyopia) with spasm of retinal vessels, headaches and a confusion state which may lead to respiratory depression and death.

Hypotension due to quinidine-like actions on the heart and vasodilatation is common. Quinine has weak oxytotic actions and may induce uterine contractions and abortion in late pregnancy.

CLINICAL USE

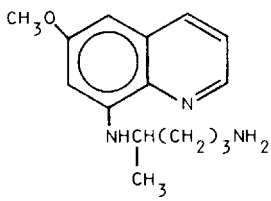
Anti-malarial The high incidence of adverse effects has resulted in quinine only being used in the treatment of attacks of chloroquine-resistant malaria. 1–2 g/day in divided doses are given per day for 5–7 days, either alone or in combination with pyrimethamine and a sulphonamide or sulphone.

Myotonia congenita This is a rare familial condition in which skeletal muscles go into spasm when voluntary movement is attempted and are then slow to relax. It is a primary disorder of muscle, but quinine, which has a curare-like action on the neuromuscular junction, in doses of 300–600 mg 6–8 hourly, is often effective at preventing muscle spasms. Procainamide is an alternative form of therapy and is generally better tolerated.

Drugs used to Prevent Relapse

None of the agents so far discussed eliminate the plasmodium during the stage of tissue schizogony such as occurs with *P. vivax* and the less common *P. malariae* and *P. ovale* infections. Cessation of therapy with anti-folate agents or the 4-aminoquinolines commonly results in a clinical relapse due to merozoites reaching the blood from the liver. The only drugs currently available that are effective against the tissue schizont are the 8-aminoquinolines of which primaquine, which causes fewer adverse effects than its cogener pamaquine, is the most widely used.

Primaquine



ANTI-MALARIAL ACTION Primaquine is a tissue schizonticide and is gametocidal. It is effective against erythrocyte schizogony of *P. vivax* but not *P. falciparum*. Primaquine is capable of eliminating infection with *P. vivax*, *P. malariae* and *P. ovale*.

The cellular effects of primaquine are different from those of the 4-aminoquinolines. It has no effect on nucleoproteins and no anti-inflammatory or analgesic actions, but it suppresses the mitochondrial function of plasmodia.

DRUG FATE Primaquine is orally-active, but is not concentrated in the tissues to the same extent as the 4-aminoquinolines. It is cleared rapidly from the plasma by two metabolic pathways, one involving hydroxylation and oxidation to the

active metabolite 5,6-quinoline-quinone and the other, N-dealkylation. Trivial amounts of unchanged drug are excreted in the urine.

ADVERSE EFFECTS The drug is generally very well tolerated, gastrointestinal symptoms being the commonest side-effect.

Haemolytic anaemia Primaquine is one of a number of drugs, including quinine and the 4-aminoquinoline group, capable of causing a self-limiting haemolysis in subjects deficient in glucose-6-phosphate dehydrogenase (*see* Chapter 5). Haemolysis occurs more commonly with primaquine than with other anti-malarials and the frequency with which it occurs increases with the dose. It is probably due to the 5,6-quinoline-quinone metabolite which is an active redox compound, oxidising the haemoglobin and other tissue constituents in RBCs with a low glutathione content.

Drug interactions Mepacrine, and to a lesser extent, proguanil, impair primaquine metabolism and cause primaquine to accumulate in the plasma. This does not occur if the drug is administered with pyrimethamine or chloroquine.

CLINICAL USE Primaquine is only used to produce radical cure in *P. vivax* infections and rarely in those due to *P. malariae* and *P. ovale*. A dose of 15 mg/day for 14 days given concomitantly with chloroquine for 72 hours (*see above*) usually produces a cure, but the dose may have to be increased with resistant organisms. Blood counts should be monitored during therapy, especially when treating subjects of races with a high incidence of glucose-6-phosphate dehydrogenase deficiency (*see* Chapter 5).

Preparations

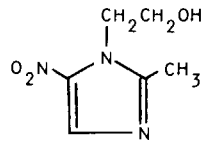
	Adult oral dose	*Dose interval*
Proguanil	100 mg	24 h
Pyrimethamine	25 mg	1 week
Chloroquine	500 mg } prophylaxis	1 week
Amodiaquine	400 mg } prophylaxis	
	(for treatment see text)	
Primaquine	15–60 mg	24 h

AMOEBICIDAL DRUGS

Entamoeba histolytica is endemic in many parts of the world, but causes disease most commonly in tropical and subtropical climates. It exists in two forms, in the colonic lumen as a trophozoite, a motile form that feeds off bacteria and cell breakdown products, and an encysted form, that is much less dependent on environmental factors and more resistant to chemotherapeutic agents. *E. histolytica* may cause acute or chronic diarrhoea (amoebic dysentery) or the trophozoite may invade the liver and cause a liver abscess and occasionally cause abscesses elsewhere. Some patients are symptomless while harbouring the amoeba in their bowel.

The treatment of amoebiasis is by means of chemotherapy. Until the advent of metronidazole, a variety of agents were used for different stages of the disease, but now metronidazole is the drug of first choice at all stages, being as effective and less toxic than older drugs such as emetine and carbarzone.

Metronidazole



ACTION Metronidazole is a highly effective amoebicide against both luminal and tissue located trophozoites. Used alone, it is capable of curing the great majority of cases of acute amoebic dysentery and amoebic abscesses and in eliminating cysts from symptomless carriers. The mechanism whereby it is toxic to amoebi is not established. It is also effective against the multiflagellate protozoon *Giadia lamblia*, which is occasionally implicated as a cause of diarrhoea and against *Trichomonas vaginalis* (*see* Chapter 35).

CLINICAL USE

Amoebiasis Metronidazole is the drug of first choice in the treatment of all forms of amoebiasis. In acute amoebic dysentery or amoebic abscess, 800 mg 8 hours given to adults for five days is usually sufficient and in symptomless carriers 400 mg 8 hours for ten days may be sufficient. If therapy is ineffective, the course can be repeated, metronidazole usually being administered with other amoebicidal drugs.

Other Amoebicides

Emetine hydrochloride Emetine is an alkaloid which was originally derived from ipecacuanha, but is now available in a synthetic form. It is highly effective against both intraluminal and tissue trophozoites and usually causes resolution of symptoms within five days. It is inactive orally and is administered i.m., but never i.v., in view of its cardiotoxic effects. Emetine is highly concentrated in the tissues, including the liver, myocardium and other muscular structures and is only very slowly excreted.

Adverse effects are common and sometimes serious. Nausea, vomiting and colicky abdominal pains occur in the majority of patients, as do T wave changes on the ECG. Cardiac dysrhythmias are the most common serious adverse effect and rarely, hepatic and renal damage occur.

Emetine, or the shorter-acting dehydroemetine, were drugs of first choice in the treatment of severe amoebiasis until the advent of metronidazole. Now it is used in conjunction with other drugs, e.g. tetracycline and diloxanide furoate in cases not responding to metronidazole. In view of the adverse effects on the heart, patients are treated in bed with 65 mg i.m. daily until symptoms subside

or for a maximum of ten days. Emetine bismuth idodide is an orally-active form of emetine, but with similar adverse effects.

Chloroquine Chloroquine (*see* above) is an effective tissue amoebicide, being concentrated in the liver, reaching a concentration there several hundred times that in the plasma, but is ineffective against the intraluminal trophozoite. In cases of amoebic liver abscess a dose of 600 mg followed by 300 mg in 6 hours and then 150 mg 12 hourly for 28 days produces cure in the majority of cases. It is usually given with an intraluminal amoebicide during acute attacks of dysentery.

Di-iodohydroxyquinoline This compound is probably the most effective intraluminal amoebicide of a number of halogenated 8-hydroxyquinolines, e.g. iodochlorhydroxyquinoline. It is not effective against the tissue located trophozoite. It is orally active, but only a small amount is absorbed, this being excreted as conjugates of the parent compound in the urine. Di-iodohydroxyquinoline causes very few adverse effects, gastrointestinal symptoms being the most common. Optic atrophy has been reported after chronic administration of large doses. There is a rise in the non-thyroxine protein-bound iodine during therapy due to the high iodide content of the drug and the protein-bound iodine may not return to normal for months (*see* Chapter 26).

The adult dose of 600 mg 8 hours for three weeks is effective in most cases of amoebic dysentery, but is much more effective when given in conjunction with other drugs, e.g. tetracycline and diloxanide furoate. Its low toxicity makes it suitable for mass therapy and it is commonly used in the symptomatic treatment of travellers' diarrhoea.

Diloxanide furoate This ester is similar in its amoebicidal activity to di-iodohydroxyquinoline, being an intraluminal amoebicide. It is orally active, is hydrolysed by colonic bacteria to furonic acid and diloxanide, the latter being partly absorbed and excreted as metabolites of the parent compound in the urine. Adverse reactions are few and not severe, and the drug is given with other amoebicides, e.g. tetracycline and chloroquine in acute attacks of dysentery, the adult dose being 500 mg 8 hours for ten days.

Carbarsone Carbarsone is an organic arsenical compound effective against intraluminal but not tissue amoebi. It is much less toxic than other arsenicals and until recently was very widely used in mild and chronic cases of amoebic dysentery. It is orally active and well tolerated generally, but serious adverse effects include skin lesions, such as exfoliative dermatitis, hepatitis, peripheral neuropathy and encephalopathy. It is seldom used nowadays as the intraluminal amoebicides described above cause fewer serious adverse effects.

Antibiotics

Antibiotics, of which the tetracyclines have proved the most effective, are not amoebicidal, but are helpful in the treatment of amoebic dysentery and in the

elimination of amoebae and cysts from the stools, as they prevent secondary bacterial infection of the bowel already damaged by amoebae. The combination of tetracycline with an intraluminal amoebicide and a tissue amoebicide is highly effective at curing acute amoebic dysentery and may be used in cases failing to respond to metronidazole.

DRUGS USED IN OTHER PROTOZOAL DISEASES

Suramin

Trypanosoma brucei gambiense
Trypanosoma brucei rhodesiense

Suramin is a trypanocide effective against the African forms of trypanosomiasis (sleeping sickness) caused by *T. brucei gambiense* and *T. brucei rhodesiense*. There is no effective drug against South American trypanosomiasis (Chaga's disease) caused by *T. cruzi*. *T. Brucei* is a flagellate protozoa that is transmitted to man by the tsetse fly. Early in the course of the disease there is fever and lymphadenopathy, but the meninges are rapidly involved and the clinical features are principally determined by the meningo-encephalitis that develops. Untreated, the disease is fatal in nearly all cases. Suramin is highly effective against the systemic but not against the meningo-encephalitic form of the disease.

Suramin is a tissue irritant and must be given i.v. It is very highly-bound to serum albumin and as a consequence does not reach the CSF in effective concentrations. If there is meningeal involvement, an organic arsenical or nitrofurazone should be administered concurrently. It is excreted very slowly, mostly as unchanged drug by glomerular filtration.

Adverse reactions are common and may be serious. Nausea and vomiting and hypotension may occur shortly after injection and an initial dose of 200 mg i.v. is usually given to see if the patient is excessively sensitive to the drug. Later reactions include albuminura, skin rashes, parasthesiae and bone marrow depression.

Suramin is the drug of choice in the treatment of *T. brucei* infections. 1 g is given twice weekly for two weeks to adults and is followed by 1 g weekly for up to six weeks. A single dose of 1 g i.v. is usually effective prophylactically for up to six months.

Organoarsenicals

T. brucei gambinese
T. brucei rhodesiense

Melarsoprol, melarsonyl (Mel-W) and tryparsamide are all effective trypanosides against *T. brucei* and unlike suramin, readily cross the blood-brain barrier, being effective against the meningo-encephalitic form of the disease.

Tryparsamide and melarsoprol are given i.v. being tissue irritants, but melarsonyl may be given i.m. They are agents with a short duration of action

and are unsuitable for prophylaxis. They are more toxic than suramin, the principle adverse effect of melarsoprol and melarsonyl being an encephalopathy and that for tryparsamide an optic neuritis that may result in blindness. However, the organoarsenicals are less toxic than the only other trypanocidal drugs that cross the blood-brain barrier, nitrofurazone and furaltadone, which may cause a peripheral neuropathy and a haemolytic anaemia.

Pentamidine

T. brucei gambiense
T. brucei rhodesiense

Pentamidine is effective against a number of protozoa and fungi. In *T. brucei* infections it is similar to suramin, being effective against the systemic protozoan but not penetrating the blood-brain barrier and so not being effective once the meninges is involved. It is highly bound to tissues and a single injection is effective prophylactically for months against *T. brucei gambiense* infections.

Pentamidine is an effective alternative to antimonials in systemic Leishmoniasis and may be used in patients not responding to those agents or who are allergic to them. It is also effective in the treatment of systemic blastomycosis and in pneumonia caused by the protozoan *Pneumocystis carinii*, although co-trimoxazole is the drug of choice in this condition.

The usual therapeutic dose of pentamidine for adults and children is 4 mg/kg every 24–48 hours for up to 15 doses, a single dose being effective for up to six months prophylactically against *T. brucei gambiense*. The principle adverse effects are hypotension, which may be severe, and hyperglycaemia, the latter seldom being severe and responding to insulin.

Antimonials

Leishmania donvani
Leishmania tropica

Antimonials have been used in therapeutics since the earliest times, but are now used only in the treatment of Leishmaniasis. Tartar emetic, a trivalent antimonial, was the most commonly used form of antimony until recent times and now the less toxic pentavalent forms only are used, of which sodium stibogluconate is the most popular.

Leishmaniasis is due to the protozoan *Leishmania* which is transmitted by the bite of sandflies. There are four species, *L. donovani* causing kala-azar, *L. tropica* causing oriental sore and *L. mexicana* and *L. brasiliensis* causing American cutaneous Leishmaniasis. Antimonials are effective against the first two, but not the second two species. Kala-azar (systemic Leishmoniasis) is a chronic wasting disorder, characterised by a swinging fever, lymphadenopathy, hepatosplenomegaly, anaemia and oedema, which often ends fatally. Sodium stibogluconate cures over 90% of cases, but is less effective in treating oriental sore.

Sodium stibogluconate is given i.v. or i.m. in doses of 0·6–2·0 g i.v. or i.m. to adults daily for ten days, a course being repeated as necessary, at 10–14 day intervals. It is concentrated in the tissues, including the liver and spleen and excreted very slowly as unchanged drug in the urine. Adverse effects are common and often severe. Hypotension may occur shortly after injection as may nausea and headaches. ECG changes are common and rashes, abdominal colic, bradycardia, hepatitis, convulsions and anaphylactic reactions have all been attributed to the drug.

Sodium stibogluconate is the drug of choice in kala-azar. Pentamidine is a suitable alternative in patients with hepatic or cardiac disease.

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Chapter 37

Anthelmintic Drugs

The helminths are the commonest parasites of man. Many occur in temperate as well as tropical climates, such as *Enterobius vermicularis* (thread worm), while others, such as schistosomes, occur only in tropical or subtropical climates. Most helminitic infections cause minor symptoms or debility, but others such as the *Schistosoma* species may cause a serious degree of morbidity. Although the worms often have quite complex life cycles, in most cases drug therapy is directed against the adult worm located in the human bowel or extraluminal tissues.

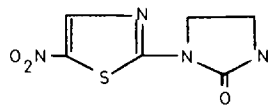
There are a large number of drugs used as anthelmintics, often several being recommended against the same worm. There is a dearth of clinical trial data in this area of therapeutics and there is seldom a concensus as to which is the drug of choice in a given condition. In this section, the anthelmintic drugs, other than those active against liver flukes, are dealt with briefly in Table 1, the order of preference being based on current fashion. All drugs shown are effective at curing 80% or more cases of the particular worm infection for which they are prescribed in the doses set out. Purging, except where stated, is no longer required as the modern drugs are much less toxic to the host than agents such as aspidium (male fern) that were used previously.

Antischistosomal Drugs

Schistosomiasis is the commonest of a number of diseases due to nematode blood flukes. There are three forms of schistoma that cause disease in man, *S. mansoni*, *S. haematobium* and *S. japonicum*, the latter being the least common and most resistant to therapy. Schistosomiasis affects between 200–300 million people located in tropical and subtropical areas and is second only to malaria in the numbers of people afflicted by the disease.

Drug therapy is directed against the adult worms located in the submucosal vessels of the bowel (*S. mansoni* and *S. japonicum*) or the bladder and pelvic organs (*S. haematobium*) from which sites the adults lay eggs that appear in the faeces or urine. As yet there is no reliable prophylactic agent active against the cercaria, in which form the parasite enters man and gains access to the blood stream. All antischistosomal drugs cause potentially dangerous adverse effects so that treatment of this common disease is far from satisfactory.

Niridazole



Niridazole is the most widely used antischistosomal drug. It is toxic to the adult worms and their eggs, being concentrated in both after therapeutic doses. It produces cure, resolution of symptoms and death of all worms in over 90% of *S. haematobium* infestations, the response rate of *S. mansoni* and *S. japonicum* being less satisfactory (40–80%). In cases in which the adult worms are not killed their genital organs are damaged and they are not able to reproduce for a period of weeks, but after this, live ova again appear in excreta and symptoms return.

DRUG FATE Niridazole is slowly absorbed, reaching a peak plasma concentration by 6 hours. It is metabolised in the liver, the half-life of the parent compound being 12–15 hours and the metabolites, which have much longer half-lives (40 hours) are excreted in the urine and are responsible for the brown discolouration of the urine that may occur. Metabolism of niridazole is delayed in patients with hepatocellular failure who have an appreciable porto-systemic shunt.

ADVERSE EFFECTS Minor side-effects, nausea, diarrhoea, abdominal pains and headache occur in 10–15% of patients. A tachycardia with T wave changes on the ECG is also common.

CNS effects Confusion, psychotic episodes and convulsions are serious side-effects that occur most commonly in patients with impaired hepatic function, resulting in higher concentrations of unchanged drug in the plasma and CNS.

CLINICAL USE Niridazole 25 mg/kg/day orally in 2 daily doses for up to seven days is the drug of choice in all schistosomal infestations. The effectiveness of therapy is determined by monitoring symptoms and the number of live ova excreted in the faeces in *S. mansoni* and *S. japonicum* infestations and in the urine in those due to *S. haematobium*. A lower dose should be used in patients with hepatocellular disease such as is common in the South American forms of *S. mansoni* infestations.

Stibocaptate This drug is a trivalent antimonial, but is better tolerated than other trivalent antimonials such as tartar emetic. Its effectiveness is similar to that of niridazole, being most effective against *S. haematobium*. It is inactive orally, being given i.m. or i.v. 5–10 mg/kg twice weekly for five doses. Nausea, vomiting and rashes are the most common adverse effects, the incidence and nature of serious adverse effects being similar to that of sodium stibogluconate (*see* Chapter 36).

OTHER FLUKE INFESTATIONS *Fasciola hepatica* and *Paragonimus westermani* infestations respond to bithionol 30–50 mg/kg every two days for 10–15 doses, gastrointestinal symptoms being the commonest side effects. There is no generally accepted treatment for *Clonorchis sinensis* infestation, chloroquine being used most commonly, although the newer compound niclofolan, which is as yet relatively untried clinically, is probably more effective.

Table 1

Drug	*Indications*	*Preference*	*Adult dose*	*Absorption & elimination*	*Adverse effects*
Mebendazole	Broad spectrum Suitable for mixed bowel infections	1	100 mg oral single dose adults and children	Less than 10% absorbed. Excreted as metabolites in urine by 24 h.	Minor gastro-intestinal symptoms
	Enterobius vermicularis *Ascaris lumbricoides* *Ancylostoma duodenale* *Necator Americanus*	1 or 2	repeat weekly as required		
	Trichuris trichuria (whip worm)	1			
Piperazine (citrate phosphate adipate)	*Lumbricoides* (round worm)	2	150 mg/kg oral single dose	Well absorbed. 5–30% unchanged drug in urine by 24 h.	5% nausea and vomiting. CNS effects—confusion, ataxia, convulsions, EEG changes, especially in patients with CNS disorders or renal failure.
	Vermicularis (thread worm, pin worm)	2	75 mg/kg/d oral 7 days	Rapid excretion	
Viprynium embonate	*E. vermicularis*	1	7·5 mg/kg oral single dose. Repeat weekly as required	Poorly absorbed	red staining of stools, nausea, diarrhoea

*Levamisole (L-isomer of tetramisole)	*A. lumbricoides*	1	2·5 mg/kg oral single dose	Poorly absorbed	Not established
Thiabendazole	Broad spectrum All types of worm other than tapeworms.		25 mg/kg ×2/d oral 1–3 days	Well absorbed 85% excreted in urine as metabolites	Nausea, vomiting, diarrhoea, CNS effects—confusion psychotic reactions
	Strongyloides stercoralis	1			
	Trichinella spiralis (only affects intestinal parasites)	1			
	Toxocara larva migrans–visceral	1	Continue for 7 days		
Tetrachloroethylene	*A. duodenale*	2	0·1 ml/kg oral single dose (5 ml max)	Moderate absorption	Nausea, vomiting, headache, ataxia, confusion 10–30 mins. Increased activity of *A. lumbricoides*, therefore, in mixed infections, give levamisole or piperazine initially.
	N. Americanus	1			
Pyrantelemboate	*A. lumbricoides*	2	10 mg/kg oral	Poorly absorbed	Vomiting, diarrhoea, colic.
	A. duodenale	2			
	N. Americanus	2			
Bephenium hydroxynaphthoate	*A. duodenale* (hook worms)	1	5 g oral single dose repeat 2–4 as required	Poorly absorbed	Nausea, vomiting, colic
	N. Americanus	2			
	A. lumbricoides	2			

(*contd*, see next page)

Table 1 (*contd*)

Drug	*Indications*	*Preference*	*Adult dose*	*Absorption & elimination*	*Adverse effects*
Niclosamide	*Taenia saginata* (tapeworms)	1	2 g in 2 doses oral on empty stomach	Poorly absorbed	Nausea, diarrhoea
	T. solium (does not kill ova, therefore give saline purge after 2 h)	1	+ saline purge after 2 h		
	Diphyllobothrium latum (fish tapeworm)	1	(as for *T. sagitum*)		
	Hymenolepis nana	1	2 g in 2 doses oral 1 g/day × 6		
Diethylcarbamazine	*Wuchereria bancrofti*	1	6–8 mg/kg/d oral 21 days	Well absorbed	Drug well tolerated. Reaction to dead worms and micro-filariae include lymphadenitis, abscess formation, soft tissue swelling, iritis (loa loa)
	Brugia malayi	1			
	Loa loa	1			
	Onchocerca volvulus (kills only micro-filariae. For adults use suramin therapy)	1			

* Levamisole stimulates cell mediated immune mechanisms. In rheumatoid arthritis it causes a reduction in joint pain and inflammation. It has a slow onset of action, as with colloidal gold and penicillamine, and symptomatic relief is associated with a fall in ESR and rheumatoid factor in the blood. It is currently under investigation as a therapeutic agent in rheumatoid arthritis and a variety of other diseases, but as yet its only established place in therapeutics is in the treatment of *A. lumbricoides*.

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Chapter 38

Cytotoxic Drugs

Cytotoxic drugs are drugs whose therapeutic effect is determined by their ability to cause cell death and they are used most commonly in the chemotherapy of malignant disease. They are also used to depress immune mechanisms in organ transplantation and occasionally in diseases in which an abnormal immune response is thought to be important in pathogenesis, e.g. rheumatoid arthritis and the nephrotic syndrome. In this chapter some general principles of cytotoxic drug therapy will first be considered before the individual drug groups. As there are a large number of cytotoxic agents, only a short summary of the clinical pharmacology of each will be given without reference to practical details. In view of the many dangers in administering these drugs and the rapid development to the field of chemotherapy, their use is best left to oncologists who specialise in the treatment of malignant disease as a whole.

Cytotoxic actions Cytotoxic agents cause cell death by interfering with cellular mechanisms essential for cell life and the molecular sites of action will be discussed under the individual agents. Nearly all cytotoxic drugs act by interfering with cell replication. The cycle of normal cell mitosis and cell death is shown in Fig. 1.

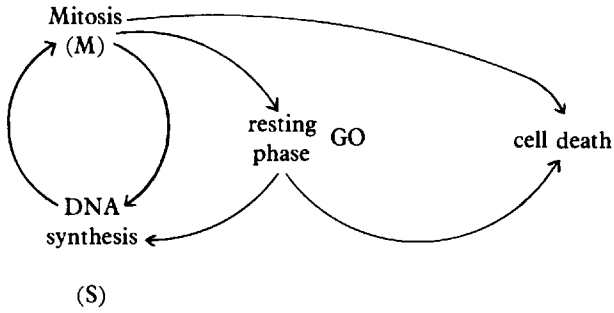


FIG. 1 Cell mitosis and cell death

DNA synthesis (stage S) occurs before mitosis (stage M) after which a proportion of cells go into a resting phase, some die and the rest go immediately into stage S. Most cytotoxic drugs, e.g. alkylating agents, antimetabolites, antibiotics and procarbazine, impair DNA synthesis (stage S). Others, e.g. the vinca alkaloids, act at stage M arresting mitosis at metaphase. They are called

metaphase inhibitors or spindle poisons as they prevent chromosome migration by altering spindle function. All cytotoxic drugs are most effective against cells that are rapidly synthesising DNA (cycling cells) but only a few are active against cells in the resting phase (GO) or non-cycling cells, e.g. alkylating agents, antibiotics and procarbazine. Those acting only on cycling cells are described as being 'phase dependent', while those acting at any stage in the cell cycle, are 'phase independent'.

Basis of Selectivity

Qualitative differences between normal and neoplastic cells The objective of cytotoxic therapy is to kill all neoplastic cells while leaving sufficient host cells to sustain the life of the patient. This is analogous to the objectives of antibacterial therapy, but the bases of the selectivity of antibacterial agents are the major structural and biochemical differences between mammalian cells and bacteria (Chapter 35). No such major differences exist between neoplastic and normal cells. Indeed, at the present time only one qualitative difference has been demonstrated and this only in certain types of leukaemia and lymphoma. These cells, unlike normal cells, cannot synthesise the essential amino acid L-asparagine which they therefore obtain by diffusion from the extracellular space. The selective toxicity of the enzyme asparaginase for these cells is based on this difference (*see* page 528).

Quantitative differences Differences in the concentration of various enzymes have been found between some tumour cells and normal tissues and attempts have been made to use these as a means of concentrating cytotoxic drugs selectively in tumour cells, e.g. neoplastic cells have a higher concentration of phosphoramidases than normal cells. Knowledge of this was the basis for the development of the nitrogen mustard cyclophosphamide. This agent is inactive itself as the active alkylating compound is linked to a cyclic phosphoramide side chain (Fig. 2). It was hoped that cleavage of the side-chain would occur selectively in tumour cells but in practice it was found that the side-chain was removed very rapidly by liver enzymes. Tumour cells are also rich in sulphydryl groups. Azathioprine is an inactive precursor of 6-mercaptopurine (6-MP), in which the active compound, 6-MP, is linked to an imidazole side-chain by a disulphide bond. It is approximately twice as potent as 6-MP and this may in part be explained by reduction of the disulphide bond by sulphydryl groups in tumour cells selectively concentrating 6-MP at the tumour site.

Cell culture studies have been most useful in relating susceptibility to cytotoxic drugs to rates of cell replication. Cytotoxic drugs cause an exponential fall with time in the number of viable cells in a colony and the percentage killed by a given drug concentration is constant, varying with the rate of cell replication, i.e. the faster the cells replicate, the more susceptible they are to cytotoxic drugs. Thus, if a given concentration of a cytotoxic agent eliminates a colony of cells with a doubling time of 24 hours in 35 days, it will take 1750 days to eliminate one whose cells have a doubling time of 50 days.

In general, the same relationship holds *in vivo*, so that the faster the rate of cell replication the greater the susceptibility to cytotoxic drugs. Thus normoblasts, with a doubling time of 15–18 hours, and colonic mucosal cells, with a doubling time of 25 hours, are highly susceptible to these agents, whereas tissues with a much slower turnover rate, e.g. muscles, skin and neuronal tissue, are much less susceptible. The doubling times of neoplastic tissues, like those of normal tissues, vary enormously, e.g. that for Burkit's tumour is 24 hours, while that for carcinoma of the breast is 90 days. The range of doubling times for neoplastic cells, in fact, is little different from that of normal tissues, the abnormality in the former being a failure to regulate cell division rather than an increase in cell replication.

Differences in rates of cell replication, therefore, are not a basis for the selective toxicity of cytotoxic drugs for neoplastic cells but they are a useful means of predicting the susceptibility of both normal and neoplastic tissues to these agents. The proportion of cells in a resting stage is variable for both normal and neoplastic tissues and this is another important determinant of tissue responsiveness. Some tumours with very high cell doubling rates are resistant to a wide range of cytotoxic drugs, so that cell doubling time is not the only determinant of tissue responsiveness to these drugs.

Response to cytotoxic drugs *in vivo* The absence of major biochemical and structural differences between neoplastic and normal cells has resulted in the clinical use in malignant disease of drugs that are invariably harmful to some normal tissues within the therapeutic dose range. In general, lymphomas and acute leukaemias are more susceptible than other tumours. Solid tumours respond poorly on the whole and this is partly due to the relatively sparse vasculature of such tumours, which results in a slow rate of drug diffusion into tumour cells.

In practice, an empirical approach is adopted in the testing of new drugs and new drug combinations. In preliminary studies in man, the adverse effects on the bone marrow and other tissues are evaluated in the dose range to be used therapeutically. In the first studies in patients, the response of the tumour cells is compared to that of the bone marrow and other normal tissues. If the preliminary studies indicate that the new drug or new drug combination promises to improve on existing therapeutic regimes, it is essential that it is then compared with the best alternative form of therapy in a controlled clinical trial. The need for good clinical trials in the evaluation of new therapeutic regimes for malignant disease is crucial, as the emotive response to this disease amongst both patients and doctors introduces a pronounced bias in favour of new forms of therapy. Notwithstanding this, only a minority of drug trials in malignant disease are adequately designed, controlled trials.

Adverse Effects of Cytotoxic Drugs

All cytotoxic drugs are dangerous drugs capable of killing patients at therapeutic

doses. There are many adverse effects that are common to most cytotoxic agents, although the probability of their occurring at therapeutic doses varies considerably between agents. In general, tissues with a high rate of cell division are most susceptible to their cytotoxic effects.

Bone marrow Only the steroid hormones do not cause bone marrow depression at therapeutic doses. Of the rest, bleomycin and vincristine are the least bone marrow depressant when given alone. Usually all formed elements are depressed but there are some differences between agents in their effects on the various cell types, e.g. vinca alkaloids depress platelet formation less than that of red and white cell series. Busulphan depresses RBCs less than white cells and platelets.

Reticular endothelial tissue (RE) Cells of the RE system are highly susceptible to cytotoxic agents, administration of these drugs causing atrophy of lymphatic tissue, a fall in blood lymphocyte count and prolonged therapy may cause an impairment of antibody production. These changes, the fall in granulocyte count and possibly the direct anti-inflammatory effect of these agents, predisposes patients to infection. Fungal infections are common and Gram-negative septicaemias and other severe infections are occasional fatal complications of therapy.

Anti-inflammatory effect Cytotoxic agents have an anti-inflammatory effect independent of the effect on the RE system which may delay healing as well as predisposing to infection. This action may account for part of the success of these agents when used in immunosuppressive therapy.

Gastrointestinal tract The mucosal cells of the gastrointestinal tract are highly susceptible to cytotoxic drugs and gastrointestinal symptoms, epigastric pain, diarrhoea, cheilosis and glossitis commonly accompany their use. Nausea and vomiting are also common and this is partly due to a central emetic action of the drugs themselves and partly to that of circulating cell breakdown products. In cases of severe overdose, mouth ulceration and bloody diarrhoea can occur.

Gonads Cytotoxic drugs may induce anovular amenorrhoea and aspermia. Their high toxicity precludes their use as anti-fertility drugs.

Fetal tissues Cytotoxic drugs interfere with the functions of DNA and this may give rise to changes in cell function (mutagenesis) without the changes being sufficient to cause cell death. If they are administered to pregnant women during the first trimester when organogenesis is occurring, they may cause fetal death and spontaneous abortion, or teratogenic changes in the fetus.

Carcinogenes Paradoxically, there is an increase in the incidence of malignant disease in patients on long-term treatment with cytotoxic drugs, whether it be for malignant disease itself or for immunosuppression, e.g. following renal transplantation. This may be a mutagenic effect, causing impairment of cell

growth control, or elimination of the immune mechanisms suppressing tumour growth.

Gout Cytotoxic drugs increase the rate of nucleic acid catabolism, raise the plasma uric acid concentration and increase the amount of uric acid excreted in the urine. Their use is quite often accompanied by clinical attacks of gout which can be prevented by the prophylactic administration of the xanthine oxidase inhibitor allopurinol, but this drug must not be administered with 6-mercaptopurine or azathioprine (*see* page 526).

RESISTANCE Resistance to cytotoxic drugs may be primary or acquired. Acquired resistance is commonplace clinically when a malignant process that has remained in remission and responsive to chemotherapy suddenly flares up. The molecular mechanisms involved in resistance of malignant cells in man have seldom been elucidated.

THE ALKYLATING AGENTS

Drugs of this group owe their cytotoxic action to their ability to add an alkyl group to nucleophilic constituents of the tissues (amino, sulphydryl, phosphate, imidazole, hydroxyl, and carboxyl groups). The alkyl groups are covalently bound to receptor molecules so that the cellular effects of these drugs are irreversible. Those agents with a bifunctional alkyl group, i.e. in which both ends of an alkyl group can bind to nucleophilic groups, are most effective. The principal site of action of these drugs is DNA and one of their most important binding sites is the 7 position on the imidazole ring of guanine, causing cross linking of guanine molecules on adjacent strands of DNA so preventing DNA function and replication. They effect non-cycling cells as well as cycling cells and impair many aspects of cell function such as protein synthesis and respiration.

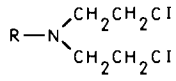
Nitrogen mustards

Nitrogen mustards were used for their irritant properties in mustard gas during the 1914–1918 war. Their cytotoxic effects were noticed at the time and neutropenia was a common feature in fatal cases of gassing. There are many nitrogen mustards but only four are commonly used (*see* Fig. 2).

Mustine (mechlorethamine) is the parent compound of the nitrogen mustards. It forms the highly reactive, unstable carbonium ion in aqueous solution and the carbonium ion alkylates nucleophilic groups in the tissues (Fig. 3). It is itself rapidly hydrolysed to an inactive compound so that a solution of mustine must be freshly made up before administration.

Mustine causes irreversible changes in tissues but is only active for a period of minutes after administration. It is a very irritant substance and can only be administered i.v. It quite commonly causes a thrombophlebitis at the site of

General formula



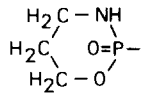
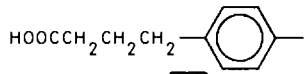
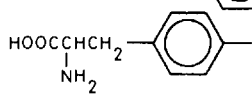
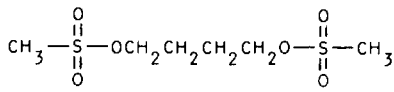
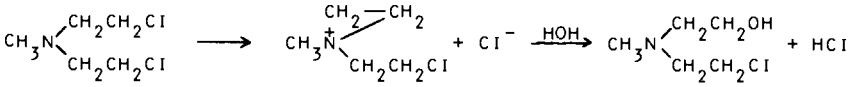
NAME	R-
MUSTINE	$-CH_3$
CYCLOPHOSPHAMIDE	
CHLORAMBUCIL	
MELPHALAN	
SULPHUR MUSTARD	
BUSULPHAN	

FIG. 2 Nitrogen mustards

injection and a leak into subcutaneous tissues causes tissue necrosis. It has been used in many types of malignant disease but is most commonly used in Hodgkin's disease in combination with other drugs. Nausea and vomiting occur very rapidly after an injection and bone marrow depression is the dose limiting adverse effect.

CLINICAL USES Hodgkin's disease.

ADVERSE EFFECTS Myelosuppression
local irritant.



MUSTINE CYCLISATION IN WATER

FIG. 3 Mustine in aqueous solution

Cyclophosphamide In this drug, the active alkylating group is linked to a cyclic phosphoramide side-chain. The parent drug is inactive itself but is converted by liver microsomal enzymes to an active alkylating metabolite, or probably metabolites. It is much more stable than mustine, is active orally, has a slower onset of action and does not have irritant properties. Most of an oral dose of cyclophosphamide is excreted in the faeces, partly as unchanged drug. The active metabolites are inactivated by liver enzymes and only a small proportion of the drug is excreted unchanged in the urine.

Cyclophosphamide is effective in Hodgkin's disease, myelomatosis and chronic lymphatic leukaemia. It occasionally causes regression in carcinomas, but the response is usually poor and of short duration. It is the best single agent for the treatment of a small cell carcinoma of the lung.

Alopecia occurs in a majority of patients, but is usually reversible. Haemorrhagic cystitis is an occasional adverse effect. Depression of the bone marrow is less frequent than with mustine but is the dose-limiting effect. Hyponatraemia and water intoxication occur occasionally due to inappropriate ADH secretion.

CLINICAL USES

Hodgkin's Disease	carcinomas – breast	immunosuppresion
myelomatosis	ovary	
chronic lymphatic	lung	
leukaemia	reticulum cell	
	sarcoma	

ADVERSE EFFECTS

Alopecia
cystitis
myelosuppression

Chlorambucil This agent has an aromatic side-chain, is orally active and has a slower onset of action than other nitrogen mustards. In clinical practice it is useful in maintenance therapy, especially of chronic lymphatic leukaemia, as there is an impression that it is less myelosuppressive than other nitrogen mustards.

CLINICAL USES

Chronic lymphatic leukaemia	Waldenstrom's macroglobulinaemia
Hodgkin's disease	seminoma
lymphosarcoma	carcinoma—ovary

ADVERSE EFFECTS Myelosuppression.

Melphalan This phenylalanine mustard is orally active and has similar properties to chlorambucil but is more myelosuppressive. It has been used most frequently as maintenance therapy in myelomatosis. Although melanin is derived from phenylalanine, melphalan is not selectively toxic for malignant melanoma cells, although it is a useful drug in local perfusion therapy in this condition.

CLINICAL USES
Myeloma
seminoma
melanoma (local perfusion)

ADVERSE EFFECTS
Myelosuppression

Sulphur Mustard

Busulphan This drug is the only sulphur mustard in use. It is an alkylating agent acting in a similar way to the nitrogen mustards, causing cross linkage of opposing guanine bases of DNA. It is more toxic to cells of the bone marrow than to other tissues, affecting the granulocyte series and platelets at lower doses than the red cell series.

Busulphan is orally active and is only used in maintenance therapy in chronic myeloid leukaemia, being of little value in the acute phase. Its toxicity is almost exclusively to the bone marrow, although it rarely causes interstitial pulmonary fibrosis and gastrointestinal symptoms.

CLINICAL USES
Chronic myeloid leukaemia
polycythaemia rubra vera

ADVERSE EFFECTS
Myelosuppression
interstitial pulmonary fibrosis

Other Alkylating Agents

Ethylene imines, e.g. thiotepa, differ little from the nitrogen mustards and have no clear cut advantages over them.

Diepoxides, e.g. ethoglucid, also have no advantages over nitrogen mustards and are seldom used.

Carmustine is an orally active alkylating agent which diffuses readily into CSF and is hence useful in the treatment and prophylaxis of cerebral spread of susceptible tumours such as Hodgkin's disease or acute leukaemias.

ANTIMETABOLITES

Antimetabolites are chemical analogues of various endogenous compounds (Fig. 4), and compete with these compounds for active sites on enzymes involved in cellular metabolism. They either block a synthetic pathway by inhibiting an enzyme or, like the sulphonamides, become incorporated into the molecule being synthesised, whose biological function then becomes grossly impaired. Antimetabolites are active at the S-phase in mitosis and are inactive against non-cycling cells.

Folic acid analogues

Methotrexate is the most widely used of this class of drugs. It is structurally similar to folic acid (*see* Fig. 4), but has a much higher affinity for dihydrofolic acid (DHFA) reductase than DHFA itself. It is water soluble and is transported by an active carrier mechanism into cells where it inhibits DHFA reductase and hence stops the synthesis of the active compound tetrahydrofolic acid (THFA or folinic acid). The fall in THFA impairs the demethylation of deoxyuridilic acid to thymidilic acid and hence a reduction in DNA synthesis. Methotrexate has a much higher affinity for mammalian DHFA than does the antibacterial agent trimethoprim (*see* Chapter 35).

Resistance to methotrexate may occur during therapy or be a characteristic of certain types of tumour. Possible mechanisms of resistance are the production of more DHFA reductase by tumour cells, or a reduction in its affinity for methotrexate, or in the affinity of the active carrier mechanism that transports the drug into cells. In some cases resistance can be overcome by the administration of very large doses of methotrexate (3–7·5 g/m^2) given over 6 hours by continuous infusion, followed by large doses of folinic acid (15 mg/3–6 hours) over 48 hours. In this way, some tumours (e.g. osteogenic sarcoma) that are resistant to conventional doses of the drug respond to therapy and the folinic acid prevents most of the serious adverse effects. Responsiveness to methotrexate can be further increased by prior administration of the metaphase inhibitor vincistine. This interaction is due to vincistine causing partial synchronisation of cells, so that on stopping therapy there is a larger proportion of tumour cells entering the stage of DNA synthesis when methotrexate is most effective.

Methotrexate is orally active. After i.v. administration, elimination from the plasma occurs in a triphasic fashion, the terminal phase having a $t_{\frac{1}{2}}$ of 25–30 hours. Most of the drug is excreted unchanged in the urine and it accumulates in renal failure. The maintenance dose requirement therefore is reduced when renal function is impaired. It is a highly polar compound and does not cross the blood-brain barrier in significant amounts when given systemically. Administered intrathecally, it is effective in treating or preventing meningeal and CNS metastases in leukaemia and other malignancies. Neurotoxicity with meningeal irritation, transient or permanent paraparesis and encephalopathy only occur after intrathecal administration and are related to the CSF-methotrexate concentration.

In chorioncarcinoma, methotrexate alone has produced cures but now this condition is usually treated by combination chemotherapy. It is most commonly used in combination with other agents in acute lymphatic leukaemia and has proved useful in the treatment of severe psoriasis, a disorder in which there is an increase in the turnover of epithelial cells (*see* Chapter 41).

Myelosuppression is the main adverse effect. Diarrhoea usually indicates gut mucosal damage and is a late sign of overdosage, severe overdosage causing bloody diarrhoea. Folinic acid given gefore cell damage develops, may prevent

cell damage, but is of no value once it has occurred. L-asparginase, given after methotrexate, limits the myelosuppressive effects of methotrexate as it prevents bone marrow cells entering the stage of DNA synthesis, when they are most susceptible to methotrexate.

Hepatic cirrhosis develops quite commonly after chronic administration of methotrexate to psoriatic patients. A granulomatous pneumonitis is an occasional adverse effect. After high dose regimes, such as are used against resistant tumours, a cutaneous vasculitis and renal impairment may develop, the latter being due to a direct effect on renal tubules.

CLINICAL USES

Chorioncarcinoma
acute lymphatic leukaemia
psoriasis

ADVERSE EFFECTS

Myelosuppression
gut mucosal damage
neurotoxicity (intrathecal administration)
hepatocellular damage.

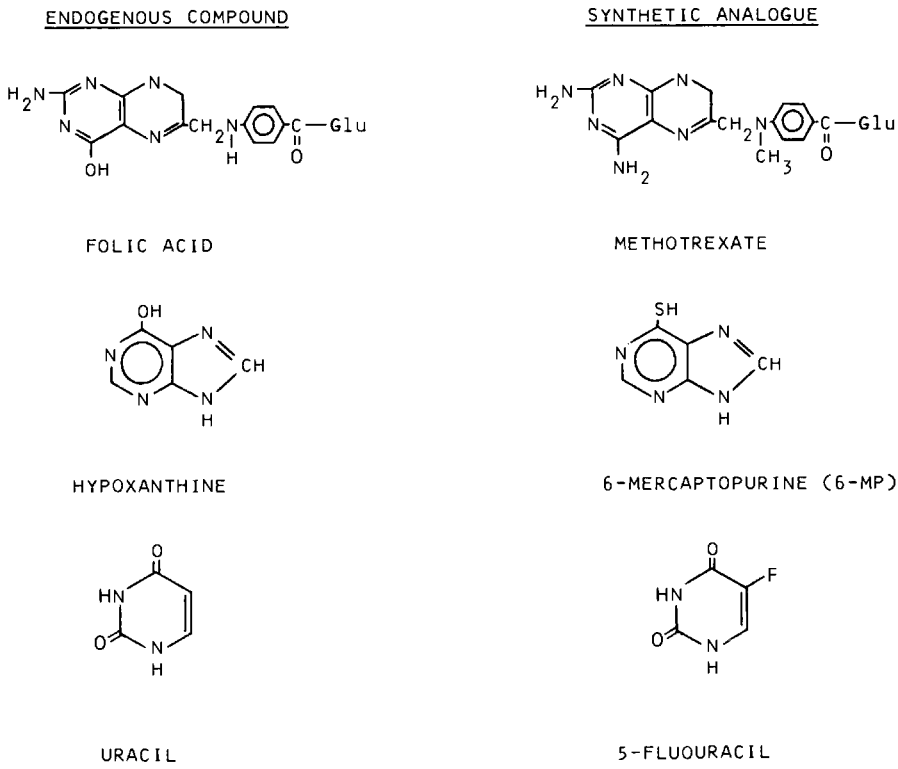


FIG. 4 Antimetabolites

Purine analogues

6-Mercaptopurine (6-MP) is the most widely-used of the purine analogues (Fig. 4). It is a hypoxanthine analogue and is converted to its ribonucleotide *in vivo*. This abnormal synthetic compound then inhibits several steps in DNA synthesis. 6-Mercaptopurine is orally-active but has a plasma half-life of less than one hour. It is mostly inactivated by metabolism, only 20% of an i.v. dose being excreted unchanged in the urine. Xanthine oxidase participates in 6-MP metabolism and coadministration of the xanthine oxidase inhibitor allopurinol causes an accumulation of 6-MP in the plasma and an increased incidence of myelosuppression.

The most common use for 6-MP is in maintenance therapy for patients in remission with acute leukaemias. Bone marrow depression and gastrointestinal dysfunction are dose limiting adverse effects.

CLINICAL USES

Acute leukaemias (maintenance)

ADVERSE EFFECTS

Myelosuppression
gastrointestinal damage
hepatocellular jaundice

Azathioprine This agent is converted to 6-MP by sulphydryl groups in the tissues which reduce the disulphide link between 6-MP and an imidazole side chain. Its cytotoxic and toxic effects are similar to 6-MP but it is a more effective immunosuppressive agent. It is well absorbed from the bowel, but has a slower onset of action than 6-MP and is rapidly metabolised to inactive metabolites. It is used most widely as an immunosuppressive agent, although much of its effectiveness may be due to an anti-inflammatory action.

6-thioguanine The only important advantage that this agent has over 6-MP is that it is not metabolised by xanthine oxidase and can therefore be administered safely with allopurinol.

Pyrimidine analogues

5-Fluoruracil (Fig. 4) This drug is converted to its deoxynucleotide and as such, inhibits thymidylate synthesis. It thus has a similar action to methotrexate, impairing DNA synthesis. It causes tumour regression in carcinomas of the gut, ovary, breast and skin. Its principle adverse effects are myelosuppression and gastrointestinal dysfunction. It causes cerebellar dysfunction after intrathecal administration due to the formation of a neurotoxic metabolite.

Cytarabine (cystosine arabinoside). This pyridine nucleoside analogue is converted to the active metabolite arabinoside cytidine triphosphate, which is a competitive inhibitor of DNA polymerase. The drug is rapidly deaminated to the inactive metabolite, uracil arabinoside, and as a consequence, less than 20% of an oral dose reaches the systemic circulation. Very little unchanged drug is

excreted in the urine. After i.v. administration the half-life of the terminal phase of the elimination curve is 2–3 hours.

Cytarabine is a drug of first choice in the treatment of acute myeloid leukaemia in combination with daunorubicin. Myelosuppression is its principle adverse effect.

VINCA ALKALOIDS

Vincristine and vinblastine are derived from the West Indian periwinkle and are closely related chemically. Both are metaphase inhibitors, causing microtubule disruption and fatty spindle formation during mitosis. Vinblastine also impairs the function of transfer-RNA. They have a similar spectrum of activity against neoplastic cells. Both are effective in Hodgkin's disease, but vinblastine is more effective in choriocarcinoma and vincristine in acute lymphatic leukaemia. There is no information regarding their fate in the body but they are very rapidly inactivated.

Both are more toxic to the granulocyte series than to reticulocytes or megakaryocytes and with vinblastine, this is the dose limiting effect. By contrast, vincristine has little effect on the bone marrow at therapeutic doses but may cause peripheral and autonomic neuropathies and cranial nerve palsies that are dose related, symetrical and usually reversible. It may also cause convulsions and inappropriate ADH secretion. Vinblastine is also neurotoxic but usually only at doses that cause severe bone marrow depression.

Vinca alkaloids decrease the number of tumour cells in the stage of DNA synthesis and hence it is possible that they may reduce the effectiveness of drugs active at this stage, if these are given concurrently. Doses that do not kill cells cause partial synchronisation of cells and increase the number entering stage S. Thus it is possible that prior administration of vincristine will increase the effectiveness of cytotoxic drugs acting at stage S, e.g. methotrexate, cytosine arabinoside and bleomycin.

Vinblastine

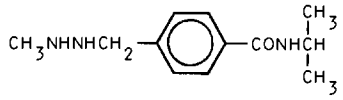
CLINICAL USES
- Hodgkin's disease
- choriocarcinoma

ADVERSE EFFECTS
- Granulocytopenia

Vincristine

CLINICAL USES
- Acute lymphatic leukaemia
- Hodgkin's disease

ADVERSE EFFECTS
- Neurotoxicity
- granulocytopenia
- ADH-secretion

Procarbazine 

Procarbazine is a methylhydrazine. Its cytotoxic effect is related to its ability to undergo auto-oxidation *in vivo*, forming hydrogen peroxide and hydroxyl radicals which react with DNA, altering its physicochemical properties. Apart from a direct effect on DNA, it causes arrest of mitosis at interphase and chromatid breaks and is therefore effective against cycling and non-cycling cells. Procarbazine has very similar effects to those of ionising radiation.

The drug is orally active being well absorbed from the gut, but may also be given by injection. It is rapidly metabolised and most of an oral dose is excreted in the urine as metabolites over 24 hours, negligible amounts being excreted as unchanged drug.

Procarbazine is effective in Hodgkin's disease when it is used in combination with other agents. Myelosuppression is the dose limiting adverse effect but nausea and vomiting, drowsiness, ataxia and confusion are not uncommon. It is a weak monoamine oxidase inhibitor and causes hypomania in a small percentage of patients. Very occasionally it may interact with amines in foods and with drugs as do other MAOIs (*see* Chapter 15). Procarbazine is one of the most carcinogenic of all cytotoxic drugs.

CLINICAL USES

Hodgkin's disease
reticulosarcoma
lymphosarcoma

ADVERSE EFFECTS

Myelosuppression
gastrointestinal dysfunction
drowsiness, ataxia, confusion
hypomania
drug interactions

L-Asparaginase This enzyme catalyses the hydrolysis of L-asparaginine to aspartic acic and ammonia. It is derived commercially from various micro-organisms, including *E. coli* and has a molecular weight of 139 000. It is administered i.v. and 70–80% of the dose remains in the plasma, the concentration in the extracellular space being 10–20% that in the plasma. Asparaginase depletes the plasma and extracellular space of the essential amino acid L-asparagine and cells incapable of synthesising adequate quantities of the amino acid themselves, such as certain leukaemic cells and some lymphoma cells, are killed as a consequence.

After i.v. administration, asparaginase has a half-life of 8–30 hours. No enzyme is excreted in the urine or reaches the CSF and the mechanism of its removal from the plasma has not been established but is independent of both hepatic and renal function.

L-asparaginase is only useful clinically in acute lymphatic leukaemia, the poor response of other cells probably being due to their ability to synthesize L-asparagine. Adverse effects are common, notably anorexia, weight loss, hepatocellular damage, clotting disorders, pancreatitis, hyperglycaemia and myelosuppression. Confusion and drowsiness are very common and reversible, and are associated with an increase in plasma ammonia concentration. Sensitivity reactions such as urticaria and anaphylaxis also occur.

CLINICAL USES

Acute lymphatic leukaemia

ADVERSE EFFECTS

Myelosuppresion
gastrointestinal dysfunction
encephalopathy
hepatocellular damage
clotting disorders
pancreatitis
sensitivity reactions

ANTIBIOTICS

This group is comprised of a number of agents derived from various species of streptomyces. They are cytotoxic to mammalian cells and bacteria, but are not used as antibacterial agents. They act by binding directly with DNA and impair DNA replication. The number of antibiotics used as cytotoxic drugs is growing rapidly and only the fairly well established agents will be discussed. They are all large, complex molecules that appear to be removed from the plasma principally by biliary excretion.

Actinomycin D This was the first antibiotic to be used in malignant disease. Its cytotoxic effect is due to its ability to complex with DNA and to inhibit RNA polymerase.

It is a tissue irritant and is administered i.v. as a bolus or by continuous infusion. It causes thrombophlebitis and ulceration at the site of injection leaks. It is very rapidly removed from the blood stream.

Actinomycin D may cause tumour regression in sarcomas affecting children, including Wilm's tumour, Ewing's tumour and rhabdomyosarcoma and is effective in choriocarcinoma. It is highly toxic, causing myelosuppression, thrombocytopenia and most commonly, nausea and vomiting.

Daunorubicin This agent combines with DNA impairing DNA and RNA synthesis. It is given i.v. and is rapidly cleared from the plasma, mostly by metabolism, 15% of an oral dose being excreted unchanged in the urine and 20% in the faeces. The urine may turn red shortly after drug administration.

Daunorubicin is a drug of first choice in acute myeloid leukaemia and is usually administered with cytosine arabinoside. It causes myelosuppression and in high doses is toxic to the myocardium causing ECG changes, tachycardia and cardiac failure, the latter occurring at any age.

Doxorubicin This is a hydroxylated derivative of daunorubicin which has a broad spectrum of antitumour activity, and is the most effective agent known against soft tissue sarcomas, and thyroid tumours. It is also active against a number of cancers and lymphomas. It inhibits both DNA polymerase and DNA dependent RNA polymerase. It is most active in the S phase but is also active against non-cycling cells.

The drug is rapidly taken up by the heart, lungs and kidneys and is removed from the body by biliary excretion, the terminal plasma $t_{\frac{1}{2}}$ being 17 hours. Trivial amounts of unchanged drug are excreted in the urine. Myelosuppression, alopecia and stomatitis are the principle adverse effects, and, like daunorubicin, it is cardiotoxic, causing left ventricular failure, etc.

Bleomycin Bleomycin is moderately effective against squamous cell carcinoma of the head and neck and elsewhere, causing tumour regression in a proportion of cases. It is no more effective than cyclophosphamide in carcinoma of the lung. It is effective alone or in combination with other agents in lymphomas. It is concentrated in the lungs and skin and may cause a pneumonitis that can be fatal. Common adverse effects are erythema of the skin, glossitis, and alopecia, pigmentation over pressure areas and swelling and pain of the hands. It is less myelosuppressive than other cytotoxic drugs except for the steroid hormones.

Mithramycin Mithramycin is highly effective in embryonal cell carcinoma of the testis in which it may cause complete regression. It has been used in cases of hypercalcaemia due to bony secondaries and in Paget's disease of bone, in which it may cause a fall in alkaline phosphatase and in urinary hydroxyproline. It is highly toxic, causing haemorrhagic disorders and hepatic, renal and neurological dysfunction.

HORMONES

Certain steroid hormones have an important place in chemotherapy of malignant disease. The clinical pharmacology of these agents has been dealt with elsewhere and only those aspects relevant to their use in malignant disease will be considered.

Corticosteroids Glucocorticoids, e.g. prednisolone and dexamethazone, cause lymphopenia in normal subjects, principally due to redistribution of lymphocytes to sites other than the blood. They are cytotoxic to acute lymphatic leukaemia cells and to malignant lymphomas, especially Hodgkin's disease, affecting both resting and proliferating cells. They have the advantage over

other cytotoxic agents in that they do not depress the bone marrow even in very high doses and in short course, do not cause many adverse effects.

They are effective in the treatment and prophylaxis of haemolytic anaemia and occasionally in thrombocytopenia which may be complications of lymphatic leukaemia or a malignant lymphoma. Their ability to impair cerebral oedema formation is also useful in the management of primary or secondary cerebral tumours (*see* Chapter 27).

Oestrogens

Carcinoma of the prostate Oestrogens, alone, or in conjunction with orchidectomy, cause remission of up to two years in a high proportion of patients with carcinoma of the prostate with metastases. The doses necessary, 3–6 mg/24 hours, are sufficient to suppress testosterone secretion by the testes, and cause gynaecomastia and testicular atrophy. There is an increase in incidence of fatal complications of cardiovascular disease in patients treated with long-term oestrogen therapy. The tumour inevitably develops resistance to oestrogens.

Carcinoma of the breast In women who are five years or more postmenopausal oestrogens induce remission in disseminated carcinoma of the breast in 20–30% of cases. Remission may last for a period of months to years.

Androgens In carcinoma of the breast occurring during or shortly after the menopause, androgens (e.g. methyltestosterone) induce remission in a small percentage of patients, but they are usually of short duration and are inevitably accompanied by virilising side effects.

Progestogens Progestogens (e.g. norethynodrel) like androgens, may induce remissions in disseminated carcinoma of the breast and sometimes cause regression in carcinomas of the uterus.

COMBINATION THERAPY

In almost all malignant diseases that are responsive to cytotoxic drugs, the response is enhanced by administering two or more cytotoxic drugs at the same time. In Hodgkin's disease a complete remission is induced in 70–80% of patients using a combination of four drugs and this is two or three times higher than the incidence of remission induced by the single most effective drug (vincristine) given alone. Combination chemotherapy along with radiotherapeutic advances have revolutionised the treatment of this disease so that approximately 70% of treated patients have a normal life span. In acute leukaemia, a combination of cytotoxic agents can induce remissions in 80–95% of cases in acute lymphatic leukaemia and 50–60% of cases in acute myeloid leukaemia.

In acute lymphatic leukaemia, combination chemotherapy is highly effective, approximately 80% of patients surviving 5 years. This is largely due to the fact that the drugs used to induce a remission, prednisone and vincristine, are much

more toxic to the lymphatic leukaemic cells than to the bone marrow and other normal tissues. Chemotherapy in acute myeloid leukaemia is much less successful, as the best combinations of drugs (*see* Table 1) are toxic to normal cells at similar concentrations to those that kill tumour cells.

Possible reasons for the success of combination therapy are two-fold:

1. At any one time, tumours contain some cells that are undergoing replication and some that are in the resting phase. It is possible, therefore, that administration of a combination of two drugs, one active against replicating and the other against resting cells, is more effective than either drug alone. It is also possible that a combination of drugs with different mechanisms of action is more effective than a combination with the same mechanism. Neither of these theoretical points however have yet been substantiated in man.

2. The spectrum of adverse effects of different classes of cytotoxic drug are not the same. When drugs of different classes are prescribed together, their cytotoxic effect is usually additive but their adverse effects may not be. The effect of such a combination is therefore, that at equieffective therapeutic doses, the adverse effects with the drug combination are less than those with a single drug. For example, most cytotoxic drugs cause myelosuppression, but prednisone does not and vincristine and bleomycin seldom do at therapeutic doses. Including these drugs in combinations of cytotoxic drugs, therefore, increases the anti-tumour effect without increasing myelosuppression. Examples of some commonly used drug combinations are shown in Table 1.

Table 1
Commonly used drug combinations

Hodgkin's disease	Mustine Vincristine Procarbazine Prednisone
Acute lymphatic leukaemia (induction phase)	Prednisone Vincristine
Acute myelogenous leukaemia (induction phase)	Daunorubicin Cytosine arabinoside

DRUG ADMINISTRATION The size of the dose of a cytotoxic drug is determined empirically and is usually limited by myelosuppressive and other adverse effects. The effects these drugs produce on cells are usually irreversible and far outlast the presence of the drug in the plasma, so that dosage schedules are not aimed at maintaining a concentration of drugs in the plasma above a certain value. In general, the larger the tumour the less responsive it is to cytotoxic drugs, so therapy is often initiated (induction phase) with relatively larger doses of two or more drugs. The objective of this induction phase is to reduce very substantially the number of tumour cells in the body. This has the effect of

increasing the proportion of cells undergoing replication, as the smaller the number of tumour cells the greater the proportion at this stage. Thus, a successful induction phase increases the susceptibility of tumour cells to phase-dependent agents and maintenance therapy can often then be carried out by a single agent of this type.

The dose interval is theoretically determined by a comparison of the replication rate of normal cells (especially those of the bone marrow and gastrointestinal tract) with that of malignant cells. In general, the replication rate of the former is greater than that of the latter, e.g. the doubling time of normal white cells is one-half to one-third that of leukaemia white cells, so that normal cells of the bone marrow recover from the effects of cytotoxic drugs more rapidly than do malignant cells. By allowing a long dose interval, e.g. 5–7 days, it is possible to maintain a tumour in remission while allowing partial or full recovery of the bone marrow between doses. A therapeutic regime for Hodgkin's disease is an example of intermittent (or pulsed) combination chemotherapy and is shown in Table 2. The treatment is given for at least six

Table 2

Intermittent combination chemotherapy for Hodgkin's disease

Drug	*Route*	*Dose*	*Day of course*
Mustine	i.v.	6 mg/m^2	1,8
Vincristine	i.v.	1·4 mg/m^2	1,8
Prednisone	Oral	40 mg/m^2	1–15
Procarbazine	Oral	100 mg/m^2	1–15

courses with a two-week gap between them. The need for further therapy is then determined by the course of the disease.

Many of the cytotoxic agents used in the treatment of acute leukaemias do not diffuse readily across the blood-brain barrier and cerebral metastases occur commonly if these agents are only given systemically. Thus therapy in acute leukaemias must include the prophylactic administration of intrathecal chemotherapy with, for example, methotrexate and irradiation of the brain.

MONITORING THERAPY Cytotoxic therapy is monitored by observation of the patient's symptoms and where possible, by the size of the tumour or by white cell count, e.g. in leukaemias. In choriocarcinoma the size of the tumour is related to the amount of human chorionic-gonadotrophin excreted in the urine and measurement of this is a useful means of monitoring response to therapy. As the principal and dose-limiting adverse effect of most cytotoxic drugs is myelosuppression, it is necessary to monitor all formed elements of the blood throughout a course of therapy.

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Chapter 39

Drugs used in Allergic Disorders

Allergic reactions are an essential component of the body's defence mechanisms against disease. In certain conditions, however, such reactions contribute to the pathogenesis of the disease and hence to its symptomatology. Of the four types of allergic reactions (*see* Chapter 8), the type-1 reaction (anaphylactic, reagin-dependent) is most commonly implicated as a contributor to the pathogenesis of disease in man, e.g. in anaphylaxis, urticaria, hayfever and asthma. The type 4 reaction (delayed or cell mediated allergy), in which tissue located allergens react with lymphocytes containing receptors specific for such allergens, is responsible for homograft rejection and contact dermatitis, and plays an essential role in the pathogenesis of 'auto immune disease'.

Therapy in allergic disorders is directed towards:

1. Identification and avoidance of the responsible allergen or allergens. If it is not possible to avoid the allergen, desensitisation may be feasible.
2. The administration of drugs that impair the synthesis or the release of chemical mediators by mast cells (e.g. disodium chromoglycate, beta-adrenergic agonists).
3. Antagonising the actions of chemical mediators by (a) competitive antagonists, e.g. antihistamines, (b), non-competitive antagonists that act on different receptors on effector-cells to those used by the chemical mediators and have opposite effects, e.g. adrenaline.
4. Anti-inflammatory agents, e.g. glucocorticoids and cytotoxic agents, that modify the inflammatory response to allergic reactions and alter lymphocyte distribution and function.

In this chapter, only the antihistamines, theophylline and disodium chromoglycate will be discussed as the other drugs used in allergic disorders are discussed elsewhere, e.g. adrenergic agonists in Chapter 11, glucocorticoids in Chapter 27, and cytotoxic drugs in Chapter 38.

ANTIHISTAMINES

The actions of histamines are summarised in Table 1.

The physiological role of histamine has not been clearly established but histamine has been implicated as a chemical mediator in type 1 allergic reactions and in the pathogenesis of some diseases (*see* below).

Antihistamine drugs compete with histamine for histamine receptors and

Table 1

Action	*Receptor type*
1. constriction of bronchial and gastrointestinal smooth muscle	H_1
2. dilatation of vascular smooth muscle	↓
3. increased capillary permeability and oedema formation	↓
4. increased nasal, lacrimal and bronchial secretions	↓
5. stimulation of gastric secretion	H_2
6. positive chronotropic effect	↓

antagonise its actions. There are two types of histamine receptors, H_1-receptors, responsible for actions 1–4 in Table 1 and H_2-receptors responsible for actions 5–6. Only H_1-receptor antagonists are used in the treatment of allergic disorders. The H_2-receptor antagonists are considered in Chapter 30.

H_1-receptor antagonists

All the antihistamines in general use are H_1-receptor antagonists and will therefore be referred to in this text as 'antihistamines'. There are a large number of such drugs in clinical use, most being available over the counter without prescription. They have been classified on chemical grounds into five categories (Table 2). Although there are a number of antihistamines that cannot be classified into these groups, all antihistamines, in common with histamine,

Table 2
H_1 receptor antagonists

Chemical family	*Examples*	*Adult dose*	*Adverse effects*
Ethylenediamine lene	triprolidine	2·5 mg	Gastrointestinal symptoms common Sedation uncommon
	methaprylene	25–50	
Alkylamine	chlorpheniramine	4–8	Sedation uncommon
Ethanolamine	diphenhydramine	25–50	Antimuscarinic symptoms and sedation common
	dimenhydrinate	50	
	orphenadrine		
Piperazine	cyclizine	50	Sedation uncommon
	meclizine	50	
Phenothiazine	promethazine	25	Sedation common
	ethopropazine	50–100	

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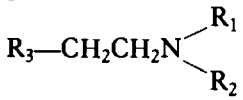


which presumably accounts for their high affinity for H_1-receptors.

Despite the large number of agents, the clinical pharmacology is similar for all antihistamines, the principle differences being in the frequency and severity of adverse effects.

ACTIONS

Antihistamine The antihistamines antagonise all the actions of histamine injected systemically or applied locally, other than those mediated by H_2-receptors. They prevent histamine-induced bronchospasm, oedema formation, increased salivation and increased bronchial and lacrimal secretions. They modify, but do not prevent completely, the vasodilatation induced by histamine. Antihistamines also antagonise histamine-induced pain and itch.

The contribution of the type 1 allergic reaction and of histamine in particular to the pathogenesis of disease cannot be established with confidence from clinical data but is usually suspected when the symptoms and signs of disease are similar to those produced by the local or systemic administration of histamine. The therapeutic efficacy of antihistamine drugs therefore is established empirically and when the response is poor, as in bronchial asthma, the assumption is made that autocoids other than histamine contribute to the pathogenesis of the disease.

Antimuscarinic Many antihistamines have antimuscarinic activity, especially the ethanolamine, piperazine and phenothiazine derivatives. This action accounts for the dry mouth and other antimuscarinic side effects and probably for their anti-emetic and anti-parkinsonian actions. Some antihistamines also antagonise the actions of 5-hydroxytryptamine, e.g. cyproheptadine, but the contributioon of this action to their clinical effectiveness is not established.

Anti-emetic Antihistamines are effective at preventing motion sickness, the piperazine group being as effective in this regard as scopolamine (*see* Chapter 30).

Anti-parkinsonism The effectiveness of these agents in Parkinson's disease is usually related to their antimuscarinic activity. Orphenadrine and ethopropazine are commonly used for this purpose (see Chapter 16).

Hypnotic The phenothiazine antihistamine promethazine is used as a hypnotic and has been shown to be superior to placebo for this purpose. Although other agents often cause drowsiness during the day, in very few cases have hypnotic qualities been demonstrated in controlled clinical trials.

Menière's disease Certain antihistamines, e.g. cinnarazine and betahistine, have been shown to be superior to a placebo in ameliorating vertigo in Menière's syndrome and other disorders of vestibular function.

Appetite stimulant The antihistamine cyproheptadine, which also antagon-

ises 5-hydroxytryptamine and the muscarinic effects of acetylcholine, stimulates the appetite and has been shown to be superior to a placebo increasing the weight of subjects who are underweight.

Antihistamines have local anaesthetic actions and, in doses larger than those used clinically, have quinidine-like actions on the heart.

DRUG FATE Antihistamines are orally active. Little is known of their disposition and metabolic fate in the body. The time of onset of action after therapeutic doses is 30–60 minutes and the duration of action of single doses is 4–6 hours, although the effect of some agents (e.g. meclezine) may last 12–24 hours. The drugs are quite rapidly metabolised, as little unchanged drug is excreted in the urine, but routes of metabolism and pharmacokinetic parameters have not been established for most agents.

ADVERSE EFFECTS

Drowsiness is the most common and most troublesome side-effect. There is considerable interindividual variation in susceptibility to this effect which occurs most commonly with the phenothiazine antihistamines and to a lesser extent with those of the ethanolamine group.

Dry mouth, anorexia, nausea, colicky abdominal pains, diarrhoea and constipation are also common and have been attributed to a weak spasmogenic activity of these drugs on the gastrointestinal tract.

Sensitivity reactions Paradoxically, contact dermatitis may be caused by topical application of antihistamines. Rarely parenteral administration may cause an anaphylactic like reaction as these drugs may release histamine from mast cells.

Serious adverse effects, e.g. neutropenia, have only rarely been attributed to antihistamines and a teratogenic effect has not been established.

Overdose of antihistamine is similar to that of atropine, excitement, a fluctuating level of consciousness, delirium, psychoses and convulsions being common symptoms. The margin of safety is greater than for barbiturates, but not as great as for the benzodiazepines and overdosage has proved fatal, especially in children.

CLINICAL USES The broad spectrum of action of the antihistamines results in their having a number of clinical uses.

1. In the treatment of *allergic disorders*.

   (a) The response to antihistamines in treatment and prophylaxis is usually good in urticaria and angio-neurotic oedema. In anaphylaxis, the response is much less rapid than to adrenaline and glucorticoids which are the drugs of choice in this condition.

   (b) The response is moderate in hayfever and vasomotor rhinitis, some patients responding well, others poorly, at doses causing pronounced side-effects. Rashes due to allergic reactions other than urticaria, may also benefit from antihistamines and these drugs may relieve 'itch' due to any cause, probably through a central as much as through a peripheral effect.

Topical application of antihistamines are seldom of therapeutic benefit and may themselves cause a contact dermatitis.

(c) *Asthma* As only very few patients derive benefit from these drugs, antihistamines have no established place in the treatment of asthma.

2. *Motion sickness* Antihistamines (e.g. dimenhydrinate, cyclizine, meclizine) are the drugs most commonly used in the prophylaxis of motion sickness.

3. *Parkinsonism* Antihistamines with pronounced antimuscarinic activity, e.g. orphenadrine, ethopropazine, are commonly used as anti-parkinsonian drugs.

4. *Miscellaneous* Promethazine is used as a hypnotic, but as it does not have the wide therapeutic index of the benzodiazepines, is not a hypnotic of first choice. Certain antihistamines are of some value in the treatment of Menière's disease and as a means of stimulating appetite (*see* above).

CHOICE OF AGENT Certain antihistamines have become established agents in the treatment of various disorders (*see* clinical uses) but the relative value of one agent *vis à vis* another is seldom established on the basis of clinical trial data. As there are quite wide interindividual differences in the response to the therapeutic effects of these drugs and in the frequency and severity of adverse effects, it is best to adopt an empirical approach in establishing the most suitable agent for a given patient, perhaps starting with the agent most commonly found to be of benefit in the condition in question.

DRUGS IN THE TREATMENT AND PROPHYLAXIS OF ASTHMA

Asthma is a condition characterised by recurrent episodes of shortness of breath. During these episodes there is an increase in the resistance to air flow in the small airways due to contraction of bronchial smooth muscle and to the accumulation of viscid bronchial secretions.

Although it is a very common disorder with an appreciable morbidity and mortality, the pathogenesis of asthma is not well understood. Allergic asthma has been most intensively studied and the model showing how bronchoconstriction can be initiated by an allergen is shown in Fig. 1. Mast cells which are present in high concentrations in the lungs, contain granuoles filled with a number of substances that constrict bronchial smooth muscle, including histamine, 5-hydroxytryptamine, slow reacting substances and possibly prostaglandins. Degranulation of mast cells is modulated, at least in part, by the ratio of cyclic AMP/cyclic GMP and is impaired by a rise in this ratio and facilitated by a fall. Thus, beta$_2$-adrenergic receptor agonists and theophylline prevent mast cell degranulation by causing a rise in cyclic AMP and the antimuscarinic agents, e.g. ipratropium (*see* Chapter 10) by causing a fall in cyclic GMP. Disodium chromoglycate, however, stabilises mast cell granuole membranes by a mechanism independent of cyclic nucleotides.

A precipitating allergen can only be identified in a minority of asthmatic patients and most of these are children. Clinical evidence suggests that respiratory tract infections, emotional factors and exercise are often as impor-

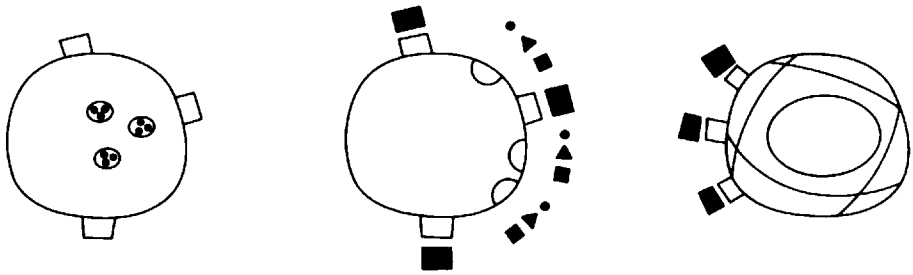


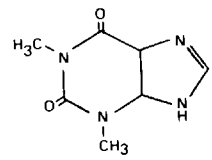
FIG. 1 Bronchoconstriction initiated by an allergen

tant as allergens in precipitating attacks in many asthmatic patients and in the majority at least two of these seem to be operative.

Of the physiological factors modulating airway patency, the autonomic nervous system and circulating catecholamines are best understood. Bronchial smooth muscle contains beta$_2$-receptors and beta-agonists interact with these to cause bronchodilatation. Alpha-agonists cause bronchoconstriction but only at concentrations at least ten-times that at which beta-agonists are effective. Acetylcholine causes bronchoconstriction and an increase in bronchial secretions due to interaction with muscarinic receptors. Thus asthma may be precipitated by beta$_2$-receptor blockers and by cholinergic agents, and be relieved by beta$_2$-receptor agonists and antimuscarinic agents.

The drugs that are used most widely in asthma are the bronchodilator drugs beta$_2$-agonists (Chapter 11) and theophylline, and disodium chromoglycate and glycocorticoids (Chapter 27). The use of antimuscarinic agents is considered in Chapter 10. Mucolytic agents are drugs that purport to facilitate the expectoration of viscid bronchial secretions but as none have shown to be of therapeutic benefit in asthma, they will not be considered.

Theophylline (1,3 Dimethylaxanthine)



Theophylline, unlike caffeine and theobromine (1,7 dimethylxanthine), is a commonly-used drug in therapeutics. Although theophylline has some stimulant effect on the central nervous system, this is less than that produced by an

equivalent dose by weight of caffeine, and it is not used for this effect clinically, but rather for its bronchodilator and positive inotropic effects.

Theophylline is available for use clinically either as the free base or in the form of double salts, e.g. theophylline ethylenediamine (aminophylline), choline theophylline, theophylline sodium glycinate.

ACTIONS

Smooth muscle relaxation Theophylline causes relaxation of bronchial smooth muscle and of vascular smooth muscle at all sites other than the CNS. It causes relief from breathlessness within 2–3 minutes in most asthmatic patients when given as a bolus i.v., often being effective when beta-receptor agonists such as adrenaline, isoprenaline, salbutamol, etc. have failed to give symptomatic relief. The bronchodilator effect of theophylline is directly related to its plasma concentration, the optimal therapeutic range being 5–15 μg/ml.

Theophylline causes vasodilatation but this is antagonised by its stimulant effect on the cardiovascular centre in the medulla which causes vasoconstriction and by a direct positive inotropic effect. It does not cause clinically important changes in blood pressure at therapeutic doses. Dilatation of the pulmonary vasculature in asthmatic patients often exacerbates the ventilation-perfusion defect and results in a slight fall in pO_2. Theophylline is of no established value as a vasodilator drug in the treatment of angina pectoris.

Positive inotropic effect Theophylline has a positive inotropic and positive chronotropic effect that comes on as rapidly as the bronchodilator effect and lasts as long. It is used on account of this effect in the symptomatic relief of acute left ventricular failure.

Diuretic effect Theophylline causes a diuresis by a direct effect on the renal tubule and, in patients with impaired left ventricular function, by its positive inotropic effect which increases cardiac output and hence glomerular filtration rate.

BIOCHEMICAL BASIS Theophylline and the other methylxanthines inhibit phosphodiesterase and retard the hydrolysis of cyclic 3,5-AMP to 5-AMP, hence allowing the concentration of cyclic AMP to accumulate inside cells. The methylxanthines thus cause an increase in intracellular cyclic AMP as does adrenaline but the two drugs act at different cellular sites. It is not established whether all the clinical effects of theophylline are the consequence of phosphodiesterase inhibition.

DRUG FATE Approximately 90% of an oral dose of theophylline, taken as aminophylline or choline theophylline, is absorbed from the bowel, absorption being delayed by food. Peak plasma concentration is obtained 1–3 hours after ingestion and is delayed in sustained release preparations. Absorption from the rectum is similar to but more variable than after oral administration.

Theophylline is usually administered i.v. as aminophylline and is cleared from the plasma by metabolism with a mean half-life of 4·5 hours, the range being 3–9 hours, the $t_{\frac{1}{2}}$ being appreciably shorter in smokers than non-smokers. It has an apparent volume of distribution of 0·35–0·5 l/kg. Like caffeine, theophylline is both oxidised and demethylated and is excreted as 1-methyl-uric acid, 3-methyl-xanthine and 1,3-dimethyl-uric acid. Very little theophylline is excreted unchanged in the urine.

ADVERSE EFFECTS

Nausea and vomiting occur commonly when theophylline is administered orally and has been attributed to its local irritant effect. Nausea also occurs when high plasma concentrations are achieved after parenteral administration which implies that theophylline also has a central emetic effect. The irritant effect of theophylline causes tissue damage and ulceration if the drug is given subcutaneously.

Cardiac dysrhythmias Theophylline may cause tachydysrhythmic and ectopic beats, especially when given by bolus injection.

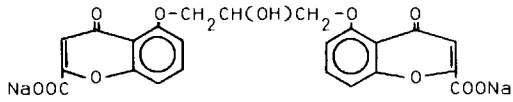
Convulsions are rare but may occur after high doses.

CLINICAL USE

Asthma In status asthmaticus, aminophylline i.v. is the bronchodilator of choice when beta adrenergic agonists, e.g. *salbutamol* by inhalation or orally have failed to give symptomatic relief. An initial bolus of 2·8 mg/kg or 250 mg is give over 5 minutes in a volume of 10 ml or greater, the patient's pulse rate being monitored if a cardiac monitor is not available. The dose is repeated after 30 minutes. If the response is unfavourable, a continuous infusion is set up at a rate of 0·9 mg/kg/h. Failure to respond to aminophylline given as one or two bolus injections is usually accepted as an indication for glucocorticosteroids, and commonly hydrocortisone in high doses is administered concurrently. Because of the wide interindividual differences in the rates of theophylline metabolism, the maintenance therapy should be carefully monitored for its effect on airways resistance, e.g. using a peak flow meter, and on the cardiac rate and rhythm.

Acute left ventricular failure Aminophylline is commonly given as an i.v. bolus injection alone or more frequently with a diuretic for the symptomatic relief of acute pulmonary oedema due to left ventricular failure. The same precautions should be used as for its use in asthma, especially as many such patients are predisposed to its dysrhythmic effects on account of hypoxaemia or a precedent myocardial infarct.

Disodium Chromoglycate



ACTION Disodium chromoglycate (DSCG) is a synthetic biscromone capable of inhibiting type-1 sensitivity reactions. It prevents passive cutaneous anaphylaxis

in animals sensitised with human reaginic serum, and in man it prevents asthma induced by inhaled allergens. In asthmatic patients, the prophylactic administration of DSCG reduces the incidence and severity of asthmatic attacks and the need for bronchodilators and glucocorticoids. It is most effective in children and in patients with 'extrinsic' asthma (i.e. who give a positive response to topical or subcutaneous administration of one or more identified allergens) but may also be of value in adults and in patients with 'intrinsic' asthma. It is effective against exercise-induced asthma, and when applied topically to the nasal mucosa may be of value in preventing attacks of allergic rhinitis.

Disodium chromoglycate acts by preventing the degranulation of mast cells sensitised by reaginic antibodies when challenged by allergen. Hence it prevents the release into the extracellular space of histamine and other biologically-active compounds located in mast cell granuoles. It has no bronchodilator or antihistaminic activity and it does not prevent the interaction of allergen with reaginic cytophilic antibodies.

ABSORPTION AND DISPOSITION For clinical purposes, DSCG is a powder and is inhaled into the lungs (or sniffed into the nose). Most of an inhaled dose remains in the upper airways, only a small proportion reaching the small airways. As with other drugs taken by inhalation, the majority of a dose is eventually swallowed. The drug is very poorly absorbed however, as most of it remains in solid form in the gut lumen and 85% or more of a dose is excreted in the faeces. No metabolites have yet been identified. The small proportion of the dose that is absorbed reaches a peak plasma concentration 15 minutes after inhalation and is cleared from the plasma with a half-life of 80 minutes.

ADVERSE EFFECTS Inhalation of the powdered DSCG may cause a cough and rarely may exacerbate bronchospasm in asthmatic subjects. To overcome this effect, some preparations include small amounts (100 μg/puff) of isoprenaline.

No other adverse systemic effects have been reported.

CLINICAL USE

Asthma DSCG is taken prophylactically, initially one inhalation 8 hourly, by means of a spin inhaler, each capsule containing 20 mg $\pm$ 100 μg isoprenaline. The dose and dose frequency are then adjusted according to the response, the factor limiting the size of the dose/24 hours not being toxicity, but the high cost of the compound. DSCG is of no value in the therapy of an acute attack of asthma.

The majority of children with asthma benefit from the drug and in some it prevents attacks altogether. Only a minority of adult asthmatics benefit and often symptomatic benefit is obtained when no effect is evident on respiratory function tests. It is frequently of value in subjects in whom an asthmatic attack is initiated by exercise. As it is difficult to predict the response to DSCG in the individual patient a trial of therapy is always worthwhile.

Hay fever Most patients with hay fever obtain appreciable symptomatic relief with the much cheaper antihistamines so that DSCG is never the drug

of first choice in this condition. Moreover, not all patients with hayfever derive benefit from the drug, but in those with severe symptoms not benefiting from other measures, DSCG taken as a nasal insufflation may give symptomatic relief. Similarly, in vasomotor rhinitis nasal insufflation of DSCG is only tried when other cheaper measures have proved ineffective.

Preparations

Disodium chromoglycate	20–40 mg	inhalation	8
Aminophylline	250–500 mg	i.v. (Bolus)	
Aminophylline	0·9 mg/kg hour	infusion	
Cholinetheophylline	360 mg	per rectum	8
Cholinetheophylline	200–300 mg	oral	8
Theophylline sodium glycinate	400–1200 mg	oral	8

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Chapter 40

Drug Overdose and Self-poisoning

Drug overdose is a state in which a drug is present in the body in sufficient concentration to impair organ function, to cause damage to tissues or to cause death. Drug overdosage occurring within the accepted therapeutic dose range is considered in Chapter 8. Overdose after ingestion of a dose above the therapeutic dose range may occur as a voluntary act of self-poisoning, as the result of an accidental poisoning, e.g. in most cases of poisoning in children, or, very rarely, in attempted homicide.

Although deaths from suicide by all methods including drugs, have declined since 1965, the prevalence of self-poisoning has steadily increased and is now the commonest cause of admission to acute medical wards in the UK, accounting for approximately 15% of all such admissions. In contrast to suicide by self-poisoning which is most frequently in elderly men, attempted self-poisoning occurs mostly in young adults and there is a preponderance of females over males. The motivation is only rarely interpreted as a serious attempt at self-destruction but is frequently an expression of psychiatric illness or inadequacy.

Drugs used in self-poisoning The drugs used in self-poisoning reflect the prescribing fashions of the time, especially the drugs used in psychiatry. In the 1960s, the barbiturates were the most commonly-prescribed seditive and they were also the most commonly-used drugs in self-poisoning. In the 1970s, the benzodiazepines superseded the barbiturates in both these respects. Similarly, the increased use of paracetamol, the mixture of methaqualone and diphenhydramine and tricyclic antidepressants, has lead to an increase in the frequency with which these drugs are used in self-poisoning. The drugs most commonly used in self-poisonings in 1973–74 are shown in Table 1.

Other drugs commonly ingested include other hypnotics and sedatives, other analgesics, drugs of dependence such as heroin, amphetamine, LSD and monoamine oxidase inhibitors and methanol. The drugs most commonly-ingested by children in accidental poisoning are iron tablets, oral contraceptives and salicylates.

The use of more than one drug, often including ethanol, is very common and is increasing in frequency, sometimes as many as five drugs being taken at one time. Drugs are usually taken orally but the intravenous route is commonly used by narcotic and barbiturate addicts.

Table 1

Drug	*% of total admissions*
Mixtures Benzodiazepines	30–40
Barbiturates Tricyclic antidepressants Salicylates	15–20
Ethanol Paracetamol	5–10

Diagnosis of drug ingestion Most patients admitted to hospital after self-poisoning are unconscious or have impaired consciousness, notable exceptions being those who have taken salicylate or paracetamol overdoses. There is often circumstantial evidence that the patient has taken an overdose so the clinical diagnosis is seldom difficult. If the nature of the drug ingested is not known, its identification from clinical signs and symptoms is not often possible as mixtures are commonly used and as the signs of acute toxicity are similar for a wide range of drugs. Furthermore, supportive measures are the mainstay of most therapeutic regimes so the identification of the ingested drug or drugs is seldom of therapeutic importance. Exceptions to this rule are the narcotic analgesics for which there is an effective competitive antagonist, salicylates whose excretion may be expedited by forced alkaline diuresis and paracetamol whose toxic effects may be reduced by cysteamine or methionine therapy.

Clinical signs of drug overdose The clinical signs of acute poisoning of the drugs most commonly-used in self-poisoning are as follows:

Benzodiazepines The patient is unconscious but moves spontaneously, seldom suffers from pressure sores or a serious depression of respiration or blood pressure.

Barbiturates The patient is deeply comatose, has no elicitable reflexes but may have bilateral extensor plantar responses. Pupils may be dilated and not react to light, respirations slow and shallow and cyanosis may be evident. The blood pressure is often low. As spontaneous movements are depressed, pressure sores are common.

Other hypnotics Chloral, mixtures containing methaqualone, glutethimide, methyprylon, ethclorvynol, mebrobamate and ethanol all cause signs similar to acute barbiturate overdose. Papilloedema may occur with glutethimide and methaqualone and both drugs may cause pulmonary oedema and convulsions. A fluctuating level of consciousness may occur after large doses of glutethimide and hypotension is common.

Tricyclic antidepressants The patient is unconscious and initially may be

areflexic. With recovery, the reflexes become exaggerated, the plantars extensor and myoclonic seizures may occur. Pupils are often dilated and unreactive to light when the patient is not deeply comatose, the pulse is rapid and dystrhythmias are common. Pyrexia may occur and be severe. Urinary retention may occur and bowel sounds are often absent, which are the clinical consequences of the anti-muscarinic effects of these drugs.

Monoamine oxidase inhibitors Clinical features of overdose are similar to those of the tricyclic antidepressants but hypertension and hyperpyrexia are often prominant features. Quite commonly drugs are taken with tricyclic antidepressants.

Salicylates The patient is conscious and complains of tinnitus and nausea. Over-breathing is the most prominent clinical sign which causes a respiratory alkalosis. In severely ill patients and commonly in children, a metabolic acidosis and fluid depletion develop and these may be associated with clouding of consciousness and carry a grave prognosis.

Paracetamol The patient is conscious and is often nauseated but initially has no abnormal physical signs. In the majority of patients who have ingested 7·5 g or more, hepatocellular damage develops within 3–5 days and is fatal in 10–30% of cases. If the prothrombin ratio is 2·2 or less or the bilirubin 70 μM or less by the fourth day then the prognosis is good.

Narcotic analgesics The patient is unconscious, has depressed or absent reflexes, pinpoint pupils, slow and shallow respirations and cyanosis. Arterial gas analysis shows a low pO_2 and a raised pCO_2. Heroin, morphine and methadone are the narcotic analgesics most commonly used in self-poisoning but cogeners such as codeine, dihydrocodeine, dextropropoxyphene and diphenoxylate will all produce similar clinical signs in large doses.

Phenothiazines Unconsciousness and respiratory depression only develop after large doses. Reflexes are usually brisk and there may be cogwheel rigidity. A large overdose may cause opisthotonus, convulsions, hypothermia and cardiac dysrhythmias.

Drug estimations Qualitative estimations of drug in gastric aspirate, plasma and urine may be useful in identification of drug or drugs ingested if this is not evident clinically. For the reasons mentioned above, this is seldom necessary therapeutically but is often necessary for forensic purposes.

Quantitative estimations of drug concentrations in the plasma are widely used in the management of salicylate and barbiturate overdoses but there is normally a poor correlation between plasma concentration of these drugs and their clinical effect when a single plasma concentration is determined. The reasons for this are that:

1. It is usually impossible to know which point on the plasma concentration-

time curve the sample is located. It may represent the peak plasma concentration or any point before or after the peak.

2. There are large interindividual differences in the responsiveness of patients to large doses of drugs and the susceptability of a given patient cannot be predicted.

3. Tolerance to barbiturates develops rapidly and if multiple plasma concentrations are determined, it is quite commonly found that patients recover consciousness at concentrations higher than those causing unconsciousness initially (Fig. 1).

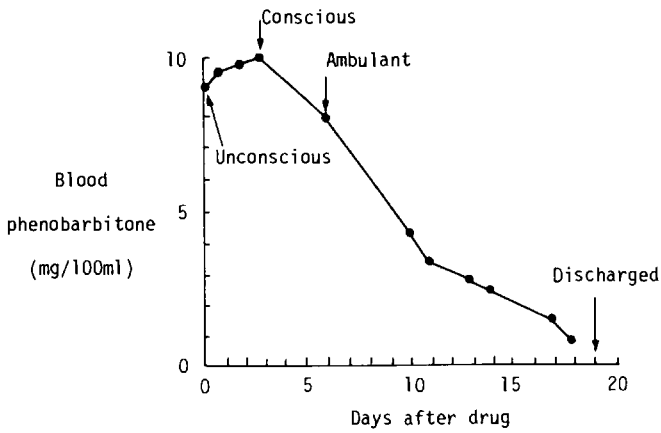

FIG. 1 Blood phenobarbitone concentration in 25-year-old woman after taking 8000 mg (From Harder and Oswald, 1970).

Notwithstanding these points, plasma concentrations of salicylates and barbiturates in particular have been used to determine the severity of poisoning and the response to therapy.

In paracetamol poisoning, the degree of hepatocellular damage likely to occur can be predicted from the plasma half-life of the drug and to a lesser degree from the initial plasma concentration. Patients can be selected for cysteamine therapy on the basis of these values (*see* below).

Clinical course The great majority of self-poisonings recover without treatment and leave hospital within three days. Morbidity in survivors is usually related to the depth and duration of unconsciousness. The common morbid consequences of self-poisoning are pressure sores to skin and soft tissues, e.g. pressure neuropathies, pneumonia (often due to aspiration) and in severe cases dementia. The overall mortality is around 1% of all cases admitted to hospital. The incidence of morbidity and mortality while increasing with the dose of any

drug ingested, varies with the nature of the drug and the susceptability of the patient to the drug.

1. The drug Self-poisoning with barbiturates, tricyclic antidepressants, MAOIs, all hypnotics other than the benzodiazepines, ethanol and narcotic analgesics, may cause death, usually due to respiratory depression. Self-poisoning with paracetamol causes appreciable mortality due to hepatocellular damage but salicylates, although they are occasionally fatal when taken in the accidental poisoning of children, are very rarely so when taken by adults.

Benzodiazepines have rarely, if ever, been the sole agents responsible for deaths after overdosage and deaths after overdosage of phenothiazines are also rare in adults.

2. The patient Infants and young children are especially at risk and deaths through accidental poisoning with salicylates and iron tablets are quite common. Even drugs that are safe to adults, e.g. phenothiazines, have occasionally caused deaths in children. Old people are also more susceptible to most drug effects than are young adults and this may contribute to the much higher rate of suicide due to drugs in elderly people. Drug-dependent patients can usually tolerate higher doses of the drugs on which they are dependent, e.g. barbiturates, narcotic analgesics, than non-dependent patients.

Principles of treatment Measures taken in the treatment of drug overdose are designed to:

1. counteract the harmful effects of the drug.
2. antagonise the drug effects.
3. prevent ingested drug from reaching sites of action.
4. expedite the excretion of the drug.

1. The harmful effects of the drugs commonly taken in self-poisoning vary between groups of drugs and in only a small percentage of patients are active measures to counteract these effects necessary. Life-threatening harmful effects that require treatment are:

Respiratory failure Airway patency should be maintained in unconscious patients. If the patient is cyanosed or the pO_2 is 60 mmHg or less and the pCO_2 is raised, high-concentration oxygen therapy is indicated, which should be monitored by means of arterial blood gas values. If the pCO_2 continues to rise tracheal intubation and positive pressure respiration should be initiated. Respiration stimulants, e.g. doxapam (Chapter 17) have no place in the routine management of respiratory failure but may be of value in places where no facilities for ventilating patients exist.

Hypotension Inadequate tissue perfusion may result from drug induced depression of the vasomotor centre, myocardium or vascular smooth muscle or a combination of two or more of these effects. Hypotensive patients should be catheterised and tissue perfusion is best aided by administration of a plasma-

expander such as low molecular weight dextran. Before administering the plasma expander, the adequacy of renal function should be assessed by administration of frusemide 40–80 mg i.v. If the response is adequate a central venous cannular should be inserted and the central venous pressure (CVP) monitored during administration of the plasma expander to avoid overloading the heart and causing pulmonary oedema. If the CVP rises and the blood pressure and urine output does not, a positive inotropic agent is indicated. Dopamine, given by continuous infusion, has a positive inotropic effect and dilates renal vessels so increasing renal blood flow and is probably the drug of choice. Agents that only cause vasoconstriction, e.g. noradrenaline and methoxamine, are of less value in this situation as they usually cause a fall in renal perfusion.

Acute renal failure This may develop as a complication of hypotension. Patients admitted with hypotension who do not respond to i.v. frusemide should be managed with fluid restriction. Frequently under these circumstances haemodialysis is required.

Other measures The usual measures in the treatment of the unconscious patient are undertaken. Pneumonia, which is a common complication of drug overdosage either due to aspiration or to pooling of secretions after prolonged unconsciousness, is treated with postural draining, aspiration of secretions and a broad-spectrum antibiotic. A fever associated with a raised white count and raised plasma enzyme concentrations commonly occurs in patients who are unconscious for longer than 24 hours, due to pressure damage to soft tissues and this may make the diagnosis of pneumonia and infections elsewhere difficult. Fluid depletion and electrolyte abnormalities and pressure injuries are treated in the usual way.

In paracetamol poisoning in animals, there is convincing evidence that the hepatotoxic effects are due to sulphydryl-group-binding metabolites of paracetamol and that hepatotoxicity can be prevented by cysteamine. This is a lipid-soluble aminoacid containing two sulphydryl groups and it is thought that these react with the reactive metabolites of paracetamol preventing their hepatptoxic effects. Initial clinical trials indicate that intravenous cysteamine i.v. or oral methionine if given within 10 hours of paracetamol ingestion can ameliorate or prevent liver cell damage. Cysteamine is given as a bolus 1–2 g over 10 minutes and then 400 mg 8 hourly for 24 hours. Adverse effects are very common and include nausea and vomiting, drowsiness and flushing. Methionine is taken orally, 2·0 g 4 hourly to 10 g, the major adverse effects being visual hallucinations, ataxia, delirium, increased salivation and hyperhydrosis.

2. Of the drugs commonly taken in self-poisoning, the only group whose actions can be effectively antagonised are the narcotic analgesics. Naloxone is an antagonist of morphine and competatively antagonises the central effects of all narcotic analgesics. If given intravenously to patients unconscious after a

narcotic analgesic overdose, naloxone (0·4–1·2 mg) increases the level of consciousness and the rate and depth of respirations within 2 minutes of administration. Repeated injections may be required after long-acting agents, such as methadone, until the effect of the narcotic has worn off. Naloxone may cause withdrawal effects in narcotic-dependent patients.

Analeptics Analeptics such as amphetamine, nikethimide, bemigride and doxapam have been widely used to counteract the respiratory depressant effects of drugs such as barbiturates and other hypnotics after attempted self-poisoning. However, unlike naloxone, they are not competitive antagonists of any of these drugs, they have a narrow therapeutic index and cause convulsions in high doses. They have to be given i.v. and have a short duration of action so that repeated bolus injections or a continuous infusion is necessary. Their use in the therapy of barbiturate overdose probably increased the overall mortality and when facilities for positive pressure ventilation are available, these drugs have no place in therapy of drug overdose.

3. Ingested drug may take some time to be absorbed and to reach its site of action. It may be removed from the stomach before absorption or be inactivated in the gut or blood stream so preventing it reaching sites of action. Measures concerned with preventing drug absorption after overdosage are time-honoured as therapeutic procedures. However, like most long practised first-aid measures, there is no clinical trial evidence that such measures decrease mortality or morbidity. As the two standard methods (*see* below) have potentially serious side-effects, they should be carried out with the utmost caution, under close supervision and only when the available evidence suggests a serious overdose.

(a) *Gastric aspiration and lavage.* In this procedure a tube is passed into the stomach, the contents aspirated and the stomach repeatedly washed out with warm water. With barbiturate overdose and probably with most other drugs only very small amounts of drug can be aspirated 4 hours or more after drug ingestion, but after salicylate overdose large amounts may be obtained up to 9 hours after ingestion. The most serious side-effect of this unpleasant procedure is inhalation of gastric contents and the development of an aspiration pneumonia. This occurs most commonly in unconscious patients with a depressed gag reflex and in such patients tracheal intubation is mandatory before gastric intubation.

(b) *Emetics* Ipecacuanha syrup 15–20 ml followed by 200 ml of water causes vomiting in 15–30 minutes in the majority of patients and is suitable for the treatment of accidental poisoning in children. Apomorphine i.m. is probably as effective at inducing vomiting but the response may be excessive and result in fluid depletion and hypovolaemia.

Inhalation pneumonia is also the most serious side effect of emetic drugs and these should not be administered if consciousness is impaired. Salt and water are

recommended as emetic in some first-aid and nursing texts. This is a highly dangerous form of therapy as excessive salt intake causes hypernatraemia and may be rapidly fatal. It should *never* be used.

(c) *Chelating agents* After accidental poisoning with iron tablets in children, desferrioxamine administered by gastric tube or i.v., forms a stable, inactive and excretable chelate with ionised iron and reduces the amount of iron reaching the tissues.

Although activated charcoal given within 30 minutes of a dose of salicylates reduces the amount of drug absorbed, the place of this substance in the therapy of drug overdose has not been established as most patients are admitted many hours after drug ingestion.

4. Much therapeutic activity in the treatment of self-poisoning has been concerned with measures that increase the rate of excretion of drugs but it is still not clear whether such measures increase patient survival.

Measures that expedite drug excretion seldom affect peak plasma or tissue drug concentrations as they are usually started after the peak plasma concentration has been achieved but they do decrease the area under the plasma concentration-time curve. The therapeutic benefits of such measures have not been evaluated in man but they continue to be used in cases of salicylate poisoning and in severe poisoning with other dialysable drugs.

Measures to expedite excretion of unchanged drug from the plasma are only effective when the amount of drug removed by renal excretion appreciably increases the rate at which the drug is removed from the plasma and tissues, i.e. decreases appreciably the area under the plasma concentration-time curve. This is not the case if (1) the drug is highly protein-bound and hence not accessible from plasma water (e.g. phenothazines and benzodiazepines) (2) if the drug has a large apparent volume of distribution (e.g. a phenothiazine or digoxin) as the drug in the plasma represetns only a small fraction of the drug in the body (3) if drug metabolism is very much more rapid than renal excretion of unchanged drug (e.g. barbiturates other than phenobarbitone and barbitone).

There are three means of increasing the rate at which a drug is excreted:

1. Forced diuresis with ion trapping.
2. Peritoneal dialysis.
3. Haemodialysis.

Forced diuresis The rate at which unchanged drug is excreted in the urine increases with the urine volume and with the extent to which the drug is ionised in the renal tubule. Thus, for weak bases such as narcotic analgesics and amphetamines, the rate of excretion is increased if the urine is made more acid and for weak acids such as salicylates and barbiturates, if it is made more alkaline. As there is no safe and readily available method of acidifying the urine only forced alkaline diuresis is undertaken routinely and this is most commonly used in salicylate poisoning.

The renal clearance of salicylate (pK 2·9) increases over tenfold if the urine pH is increased from 5·0 to 8·0 and above pH 7·4 it exceeds that of creatinine. Moreover, an alkalinising regime by raising the plasma pH also decreases the intracellular concentration of salicylate and may, as a consequence, decrease the effects of the drug on the central nervous system. A typical alkalinising regime is one litre containing 75 mmol NaCl, 75 mmol $NaHCO_3$ and 42 mmol KCl and one litre of 5% dextrose per hour. This regime appreciably increases the rate at which salicylates are excreted in the urine and is usually only maintained while the plasma salicylate concentration is 500 mg/l or greater. Such a regime also increases the rate at which phenobarbitone, barbitone, meprobamate and ethchlorvynol are excreted unchanged in the urine.

Precautions Acute renal failure must be ruled out before initiating a forced diuresis. As the amount of sodium administered is high, forced alkaline diuresis is not suitable in patients with impaired ability to excrete sodium ions, e.g. with congestive cardiac failure or chronic renal failure. Potassium loss in the urine is high during such a regime so that plasma potassium must be monitored closely and replacement must be adequate.

Dialysis

1. Peritoneal dialysis This is more effective at removing unchanged drug than forced diuresis and can be undertaken without special facilities. The drug in the plasma diffuses down a concentration gradient across the semi-permeable peritoneal membrane and the rate of drug dialysance is usually several times that of renal clearance achieved with a forced diuresis.
2. Haemodialysis The drug in the plasma is removed principally by ultra filtration across a synthetic semi-permeable membrane and the dialysance produced is usually several times that achieved with peritoneal dialysis.

In most studies of the therapeutic benefit of dialysis in the treatment of drug poisoning, the mortality in patients treated with dialysis has not been significantly better than other forms of therapy. However, as there have been no prospective randomised controlled trials, the results may reflect a bias minimising the effectiveness of dialysis as it is usually only the more severely affected patients that are treated in this way.

Haemodialysis is indicated when acute renal failure occurs as a consequence of drug overdose, or in methanol poisoning, in which toxicity is related to the accumulation of the principal metabolite, formaldehyde. Methanol can be removed rapidly by haemodialysis, and as its metabolism to formaldehyde is delayed by ethanol, an ethanol infusion should be initiated while the patient waits for haemodialysis.

Prophylactic measures

Psychiatric The deliberate taking of an overdose of a drug is commonly a manifestation of either psychiatric illness or a personality disorder. It is essential to find out in each case the nature of the precipitating event and the

factors causing such a potentially dangerous course of action. Psychiatric help is now made available to all cases of self-poisoning admitted to UK hospitals in the hope that treatment of, e.g., a depressive illness, will prevent further self-poisonings. Unfortunately, as yet, there is only scant evidence to suggest that this form of prophylactic psychiatry is effective.

Pharmaceutical The pharmaceutical industry can contribute to reducing the severity of drug overdoses by the provision of drugs, especially analgesics and drugs used in psychiatry that have a high therapeutic index. A good example of this is the replacement of barbiturates by the benzodiazepines and phenothiazines. The industry can also help by packaging drugs in such a way to make them less accessible or less attractive to children. This has lowered the incidence of self-poisoning in children with iron tablets and salicylates.

Prescribing The medical practitioner can help to lower the morbidity and mortality from drug overdosage by reducing the frequency with which drugs such as hypnotics and sedatives are prescribed; by limiting the number of drugs prescribed in any instance and by choosing drugs with a high therapeutic index when there is a choice between drugs of similar efficacy that differ in their therapeutic index.

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Chapter 41

Miscellaneous Drugs

CHELATING AGENTS

Chelating agents form stable complexes (chelates) with heavy metals and are used in the treatment of heavy metal poisoning or in the treatment of conditions due to excess deposition of heavy metal in the tissues, e.g. Wilson's disease. Heavy metals themselves have a high affinity for chemical groups in the tissues with two free electrons, e.g. sulphydryl, amino, carboxyl, hydroxyl, acid phosphate and imidazole groups. The formation of stable complexes between heavy metals and such electron-donating groups in macromolecules, e.g. enzymes and membranes, results in dysfunction of the macromolecules and eventually clinical evidence of disease.

Chelating agents possess two or more electron donor groups capable of forming two or more co-ordinate bonds with a heavy metal ion. Chelating agents thus compete with tissue binding sites for the metal ion to form relatively stable, non-toxic complexes, that are readily excreted in the urine.

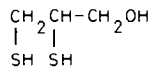
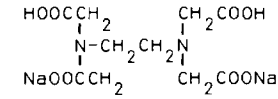
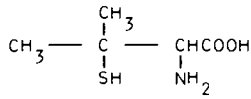
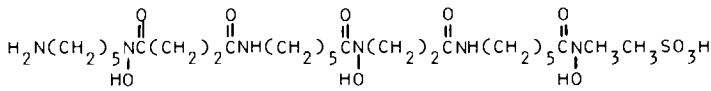
There are only four chelating agents available for clinical use and the indications for use of these compounds is summarised in Table 1. There is no established chelating agent in the treatment of poisoning with manganese, cadmium, thallium and berillium.

Dimercaprol (British Anti-lewisite, BAL) This agent was designed to antagonise the toxic effects of arsenical gases, such as lewisite, that were used extensively in the First World War. Dimercaprol had a high affinity for arsenic and is effective in the treatment of all forms of arsenic poisoning other than that due to arsine gas. It is also effective in the treatment of gold poisoning such as may occur with sodium thioauromaleate treatment in rheumatoid arthritis (*see* Chapter 19) and in mercury poisoning.

Dimercaprol is administered i.m. It is widely distributed in the tissues and is rapidly metabolised, the metabolic products being excreted in the urine. The incidence of adverse effects is dose-related and the most common of these are nausea, vomiting, colic, salivation, a burning sensation in the mouth, sweating and paraesthesia.

Dimercaprol is given by deep i.m. injection, 3–5 mg/kg being given in cases of severe poisoning. The injections are painful and may be followed by a rise in blood pressure and a tachycardia. The dose may be repeated 4 hourly without the drug accumulating. Injections are usually given 4 hourly over 48 hours in severe poisoning, the dose interval decreased then to twice daily for up to 10 days, depending on the clinical response.

Table 1
Indications for chelating agents

Drug	*Structure*	*Indication*
DIMERCAPROL (BAL)		INDICATIONS: ARSENIC, GOLD, MERCURY OR LEAD POISONING.
ETHYLENE DIAMINE TETRA ACETIC ACID (EDTA)		INDICATIONS: LEAD POISONING.
PENICILLAMINE		INDICATIONS: WILSON'S DISEASE, LEAD OR MERCURY POISONING.
DESFERRIOXAMINE		INDICATIONS: IRON POISONING.

Ethylenediaminetetra-acetic acid (EDTA) This agent has a high affinity for lead and is useful in the treatment of severe lead poisoning. Lead induced encephalopathy is the usual indication as this condition has a high mortality. Disodium EDTA binds plasma calcium causing hypocalcaemia, but this adverse effect does not occur when the calcium disodium salt ($CaNa_2EDTA$) is used.

EDTA is a highly polar compound and is poorly absorbed from the gut. It is administered i.m. or i.v. and is distributed in total body water, very little reaching the cerebrospinal fluid and it is very rapidly excreted unchanged in the urine by glomerular filtration and tubular secretion. It has a plasma half-life of 1 hour. Hypocalcaemia does not occur with $CaNa_2EDTA$. EDTA is nephropathic both as $CaNa_2EDTA$ and Na_2EDTA and may cause acute renal failure and the nephrotic syndrome, premonitory signs being the appearance of albumin and

casts in the urine. Concentration of 1% or greater may cause thrombophlebitis when given i.v. and other adverse effects include fever, muscle and joint pains, hypotension and urticaria.

Calcium disodium EDTA is given by constant infusion or by deep i.m. injection with procaine in a dose up to 75 mg/kg. In severe lead poisoning the earlier therapy is initiated the better the response, and results may be improved by the administration of another chelating agent as well, e.g. dimercaprol or diethylene triamine penta-acetic acid, which has similar chelating properties to EDTA.

Penicillamine Penicillamine has a high affinity for copper, mercury and lead. It is used as an anti-inflammatory agent in rheumatoid arthritis (*see* Chapter 19) but other than this, it is used most frequently in the treatment of Wilson's disease. In Wilson's disease there is a deficiency of the copper binding plasma protein caeruloplasmin and, as a consequence, excess deposition of copper in the tissues occurs. The defect is transmitted by an autosomal recessive gene and hepatocellular failure and parkinsonism are the most common clinical consequences. Penicillamine forms a stable complex with copper and greatly increases its urinary excretion with a resultant amelioration of symptoms. Penicillamine is also as effective as $CaNa_2EDTA$ in the treatment of severe lead poisoning and is effective in mercury poisoning.

In contrast with the other clinically used chelating agents, penicillamine is well absorbed from the gut and hence is orally active. Little is known of its metabolism in man, but most of an oral dose is eliminated in the urine in 24 hours. It is better tolerated than most chelating agents, but may occasionally cause bone marrow depression with thrombocytopenia and neutropenia and the nephrotic syndrome. Some patients are sensitive to low doses (250 mg/day) which causes fever, skin rash, nausea and bone marrow depression.

In Wilson's disease penicillamine is given orally 1·5–3·0 g/24 hours and is capable of increasing the urinary excretion of copper 100-fold. The drug is continued indefinitely and if administered prophylactically to homozygotes may delay or prevent the onset of hepatic failure and parkinsonism. It may also be useful in the treatment of milder cases of lead poisoning and in the treatment of mercury poisoning.

Desferrioxamine Desferrioxamine is elaborated by *Streptomyces pilosus*. It is highly specific for iron, binding free trivalent iron. It does not bind iron already complexed with porphyrins or protein bound iron. It removes iron from iron stores and is most useful in the treatment of acute iron poisoning. Desferrioxamine is of some value in transfusion haemosiderosis but in haemochromatosis is of little value as it causes only a slight increase in urinary excretion of iron.

Desferrioxamine is very poorly absorbed from the bowel. It is metabolised by many tissues and partly excreted unchanged in the urine. Iron is not released from the chelating agent as a consequence of its metabolism. Intramuscular injections of desferrioxamine are painful and the unchanged drug may cause an

orange discolouration of the urine. The drug is well tolerated but may cause hypotension if infused rapidly and occasionally sensitivity reactions.

Desferrioxamine mesylate is the preparation most frequently used in acute iron poisoning, which is a potentially fatal condition, occurring almost exclusively in children (*see* Chapter 32). Diethylenetriamine tetra-acetic acid is also effective in this condition but has not been so widely used as desferrioxamine. In mild cases, 1 g of desferrioxamine is given by nasogastric tube after gastric lavage and 1 g is given i.m. In more severe cases the drug is given by constant infusion after an initial dose of 1–2 g i.m. at a rate not exceeding 15 mg/kg/24 hours, to a total dose of 1–2 g/24 hours.

In the haemolytic anaemia beta thalassaemia major frequent blood transfusions prevent the serious consequences of prolonged anaemia and enable patients to survive till the second and third decade, but they then die of transfusion haemosiderosis. Desferrioxamine can reduce the iron overload that such patients receive if 2–4 g are administered i/v with each transfused pint of blood and then 1 g/24 h s.c. in between transfusions. Such a regime can cause excretion in the urine of up to a third of the iron load of a transfusion. Furthermore, there are preliminary studies showing that if desferrioxamine can be administered by a continuous s.c. infusion indefinitely, that iron balance can be achieved and hence transfusion haemosiderosis prevented. The clinical benefits of such therapy are under evaluation.

DRUGS IN THE TREATMENT OF OBESITY

Obesity is a condition in which the patient's weight for height is above the 'ideal', taking account of sex. The 'ideal' weight is calculated from life assurance data and is that weight for height with the best life expectancy in otherwise healthy subjects. Life expectancy falls progressively with an increase in weight above that ideal for any height. The principal morbid consequences of obesity are coronary artery disease, cerebrovascular disease, diabetes mellitus and hypertension and there are many other less serious diseases associated with obesity.

Obesity is very common in developed communities. Of the adult population in the USA and UK 20–30% are 10% or more above the ideal weight for height. There is evidence to suggest that lowering the weight of obese subjects causes an improvement in glucose tolerance and a fall in blood pressure and in plasma lipoproteins and an overall improvement in life expectancy.

Despite the prevalence of the disorders and the apparent benefits of successful treatment, the therapy for obesity is unsuccessful in the majority of patients. Of the measures available diet is by far the most important and other measures should only be used as an adjunct to dieting or when this has failed. Various types of drug have been used to treat obesity but only those that reduce appetite (anoretic agents) have been shown to be of any value.

Amphetamine, dexamphetamine These agents were the first to be used to reduce appetite. In controlled clinical trials they caused significantly greater

weight loss than a placebo. Weight loss is greatest during the first six weeks of therapy and is seldom greater than 5–10 kg if the drug is continued over a six month period. Side effects are common and the high abuse liability of the amphetamines and closely related anorectic compounds phenmetrazine and chlorphentermine make them unsuitable for the treatment of obesity.

There are three groups of drug currently available for the treatment of obesity, all being similar to amphetamine in that they act by reducing appetite, but have a lower abuse liability.

1. **Fluorinated amphetamines.** *Fenfluramine* This agent is as effective as D-amphetamine at inducing weight loss and most of this represents a loss of adipose tissue. It causes less CNS stimulation than amphetamines, the principle adverse effects being drowsiness and diarrhoea, and depression on withdrawal of the drug. Fenfluramine does not potentiate the effects of catecholamines or antagonise the actions of methyldopa or the guanidinium hypotensive agents. It has a very low abuse liability. The features of an overdose are similar to those of D-amphetamine.

2. **Non-fluorinated amphetamines,** e.g. *phentermine, diethylpropion*. These agents are as effective as D-amphetamine and fenfluramine. Adverse effects due to CNS stimulation are fewer than with an equiactive dose of D-amphetamine and they both have a low abuse liability. They enhance the effect of catecholamines, may cause depression on stopping therapy and antagonise the effects of methyldopa and the guanidinium hypotensive agents.

3. **Imadazo-isoindole compounds,** e.g. *mazindol*. Though differing chemically from amphetamine, these drugs have pharmacological and clinical effects similar to the drugs of group 2. The effectiveness in obese patients is no greater than with the other agents and abuse liability is probably low.

DRUGS IN THE TREATMENT OF SKIN DISEASES

The singular features concerning drug usage in dermatology are:

1. Many diseases are specific to the skin and do not affect other organs, e.g. psoriasis, acne, eczema. The actions of drugs should therefore be interpreted in terms of what is known concerning pathogenesis of the various skin diseases.

2. Very commonly, drugs are applied topically direct onto the lesion, whereas in most other areas of medicine they are given systemically. Disorders of the skin arise commonly as a consequence of adverse drug effects. This subject has already been considered in Chapter 8.

The topical application of drugs to the skin The principles to be considered are firstly the physical and biological properties of the vehicles in which the drugs are applied to the skin, and secondly the pharmacokinetic consequences for the drugs so applied. The forms in which drugs may be applied to the skin are shown in Table 2. They may contribute to the therapeutic effect of the drug,

Table 2
Forms in which drugs may be applied to the skin

Form of application	*Physical properties*	*Biological properties*
Powders	High surface area, absorbant or water repellant	Drying, lubricant, cooling.
Lotions	True solutions	Cooling.
Suspensions	Insoluble particles in suspension in aqueous medium	Cooling.
Creams	Emulsions of oil in water or water in oil	Mix with exudates; cooling. Do not mix with exudates; cooling.
Ointments	Water-free fats and greases	Adhere to surfaces; prevent evaporations; barrier to diffusion of chemicals; removed only with organic solvents.
Pastes	Ointment containing solids	As for ointments; absorbant.
Dressings	Various	Physical barriers.
Occlusive dressing	Polythene	Prevent evaporation.

e.g. the cooling action of an application has an analgesic effect on an area of inflammation.

The pharmacokinetics of drugs applied to the skin The skin consists of two layers, the epidermis, comprising cells that mature, keratinise and eventually die forming the horny layer and deep to this, the dermis, which consists mainly of connective tissue fibres embedded in a matrix of ground substance and small blood vessels. Some drugs act on the skin surface and horny layer, e.g. cooling agents, keratolytics, irritant agents and barrier preparations, while others affect deeper structures and thus have to penetrate the horny layer.

The steps in the diffusion of a drug from the surface to the dermis are shown in Fig. 1.

The drug must first diffuse out of the vehicle in which it is applied to the surface of the horny layer. The rate at which this occurs depends on the solubility of the drug in the vehicle, the more soluble it is, the more slowly will it diffuse across the horny layer. The horny layer covers 99·8% of the surface of the epidermis, the remaining 0·2% being accounted for by sweat gland and hair follicle orifices. In most instances, diffusion across the horny layer is the rate

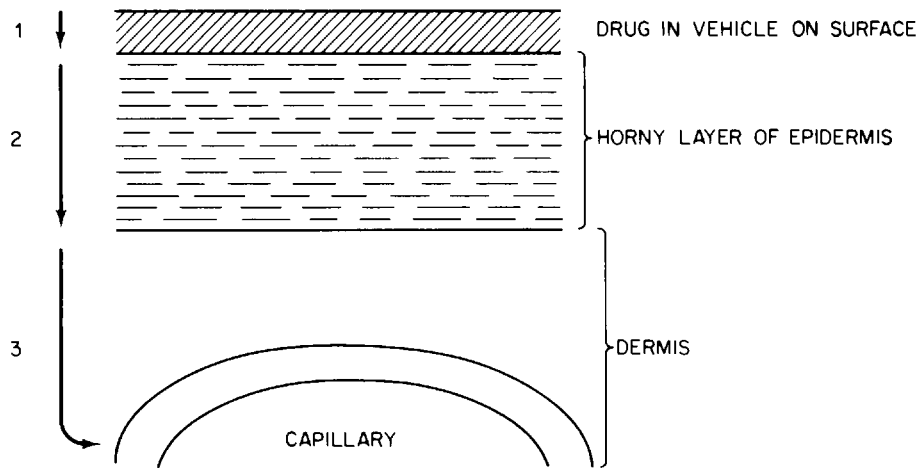


FIG. 1 Steps in drug diffusion from surface to dermis

limiting step in the passage of a drug from the skin surface to the dermis and systemic circulation. The horny layer has the characteristics of a lipid membrane as far as drug diffusion is concerned, in that the more lipid-soluble the drug, the more rapid is its passage across the horny layer. For example, if testosterone, progesterone and hydrocortisone are applied in equal concentrations to the skin, the peak plasma concentrations of the lipid-soluble testosterone and progesterone are 3–4 times that of the more water-soluble hydrocortisone. After topical application, the rates of absorption of even highly lipid-soluble drugs are slower than their rates of elimination from the plasma so that the rates of absorption determine their duration of action. The time taken for elimination of half a dose of hydrocortisone administered intradermally is 4·5 hours while that for the topically applied drug is 20 hours. Similarly, the half-life of topical testosterone and progesterone (19 hours) is very much longer than after intradermal or i.m. administration. The prolonged action of drugs applied topically means that the interval between doses can be increased. Only a small part of a topically applied drug is absorbed. This can be greatly increased by covering the drugs by occlusive dressings such as polythene. These prevent evaporation of sweat and cause 100% hydration of the horny layer which greatly increases its permeability. Indeed, hydration of the horny layer may increase permeability of the skin to some drugs as much as one hundred-fold. Water-soluble drugs applied to the skin diffuse to the dermis via the sweat glands and hair follicles. This is a slow process, but when covered by an occlusive dressing, even such drugs as the water-soluble ephedrine and norephedrine are 40–60% absorbed, albeit more slowly than after oral administration. Increasing the temperature of the skin and damaging the epidermis also augment skin

permeability, as do agents such as dimethylsulphoxide (DMSO) which may be incorporated into dressings.

Drug actions in skin disease

Some drugs are exclusively used in dermatology, e.g. keratolytics, irritants, insecticides, etc., and the actions of these drugs will be described briefly. Others have effects on the skin similar to those on other tissues, e.g. steroids, cytotoxic agents and anti-bacterial agents. Such drugs will be discussed in terms of their effects on a few of the more common skin diseases.

Anti-inflammatory agents Inflammation plays an important role in the pathogenesis of many skin diseases. In some, the cause may be known as in pyodermas or contact dermatitis, when therapy is also directed against provoking factors. Anti-inflammatory agents are often useful in the symptomatic treatment of these conditions and in those where no cause is evident, e.g. eczema or pemphigus.

In dermatology, glucocorticosteroids are the most commonly used anti-inflammatory agents and approximately 50% of all dermatological prescriptions are for these agents. Steroids are usually applied topically, the fluorinated derivatives of prednisone, e.g. betamethazone 17-valerate and the more recently introduced beclomethazone dipropionate and clobetasol propionate being the most potent topical anti-inflammatory agents. These seldom produce systemic effects, e.g. depress the hypothalamic-pituitary-adrenal axis when applied topically in adults, but if more than 50 g of clobetasol propionate is applied to the skin per week, there may be marked evidence of hypothalamic-pituitary-adrenal axis depression.

In children and infants steroids are more readily absorbed and the potent preparations should only be applied for short periods. Steroids are administered systemically only when lesions are widespread and especially in life threatening situations, e.g. pemphigus, exfoliative dermatitis and severe cases of eczema. They only suppress symptoms and the dose requirement in each case is established empirically and may be high.

Adverse systemic reactions are described in Chapter 27. Prolonged topical application of potent steroids, particularly at sites where the skin is thin, such as the face, produces side effects of atrophy and telangiectasia and sometimes hyperaemia and striae.

Cytotoxic drugs These are used for primary and secondary malignancies of the skin and also as immunosuppressive anti-inflammatory agents in severe cases of pemphigus, pemphigoid and in psoriasis.

Topically applied cytotoxic agents such as 5-fluorouricil, are effective at curing 95–99% of solar keratomas and some basal cell epitheliomas (rodent ulcers) and squamous cell carcinomas of the skin. The lymphoma, mycosis fungoides, also responds to topically applied cytotoxic agents, at least as long as it is localised to the skin.

Psoriasis is a skin disease characterised by a greatly increased rate of epithelial cell replication. In its milder forms, local treatment of lesions with emollients, antipruritics and keratolytic agents only is required. But when the disease is severe, cytotoxic drugs taken systemically are effective at decreasing the extent and severity of the skin lesions, acting by decreasing the rate of epithelial cell replication. Methotrexate and azathioprine in particular have been used for this purpose, both acting by impairing nucleic acid synthesis (*see* Chapter 38) and both may be effective in quite small doses (e.g. 50 mg methotrexate 12 hourly times 3 and repeated weekly). Adverse effects are dose related and similar to those recorded in Chapter 38.

Analgesia The pain from skin lesions may be relieved by systemic analgesics as in other painful disorders or by topical therapy. The pain and itch induced by inflammatory lesions is eased by topical anti-inflammatory applications. Local anaesthetics included in dermatological preparations, relieve pain by anaesthetising pain fibres in the skin. The protein-denaturing agents phenol and resorcinol also have a local anaesthetic action in low concentrations, but may cause irreversible damage to nerves in high concentrations.

Irritant drugs are agents capable of inducing an inflammatory response and when applied to the skin, cause hyperaemia and a sensation of warmth. Camphor, methylsalicylate, eucalyptus oil, mustard and cantharides are examples of irritant substances which may be used on the skin over painful lesions affecting underlying tissues, bones, joints, and soft tissues. The 'counter-irritant' effect of these drugs often has an analgesic effect, but in high concentrations irritants can cause skin damage, with vesicle formation and local exfoliation.

Keratolytics Drugs of this group soften keratin and may cause tissue damage and an inflammatory reaction. They are used in dermatology to facilitate the removal of excess keratin. They are used in warts and ichthyosis, in which there is failure of epidermal cells to shed keratin, in seborrhoeic dermatitis, chronic eczematous lesions, psoriasis and in fungal infections of the skin. Agents used as keratolytics include resorcinol, phenol, salicylic and benzoic acid, trichloracetic acid, podophyllin and coal tar. Coal tar contains a number of compounds including benzene, phenol and naphthalene and has antipruritic as well as keratolytic activity.

In acne, there is reduced shedding of keratin from the neck of hair follicles and this leads to the formation of a keratinous impaction or comedo. Sebum accumulates in hair follicles and the triglycerides in sebum are partly broken down to irritant fatty acids by the skin commensal *Corynebacterium acnes*. Keratolytics and selenium sulphide are often helpful in this condition when applied topically, presumably acting by removing the keratinous plug. *C. acnes* is susceptible to broad-spectrum antibacterial agents and this may account for the beneficial effect of small doses of these drugs in acne, e.g. 250 mg tetracycline/24 hours.

Barriers Skin lesions are particularly prone to physical, chemical and radiation damage. Dressings, including polythene dressings, are an obvious means of protecting lesions, but pharmaceutical preparations are also available in the form of inert viscous fluids such as collodion and the silicone oil dimethicone, which act as occlusive dressings protecting against chemical injury.

Photosensitivity reactions, or adverse skin reactions to sunlight, are common. In disorders of melanin formation, such as albinism and vitiligo, the protective effect of melanin is absent, but photosensitivity may also result from the presence of photosensitisers, i.e. substances that absorb sunlight and hence facilitate the adverse effects of sunlight on the skin. Porphyrins are endogenous photosensitisers and account for the cutaneous manifestations of porphyria cutanea tarda. Exogenous sensitisers may be present in cosmetics, deodorants and topical antibacterial and antifungal preparations, such as those containing halogenated salicylanilide. Drugs taken systemically may also cause photosensitivity reactions. Those most commonly implicated include phenothiazines, sulphonamides, thiazide diuretics, hypoglycaemic agents and tetracyclines. Isoniazid, which impairs the phosphorylation of pyridoxine, may cause a pellagra-like syndrome with photosensitive skin lesions due to the dependence of the metabolic function of nicotinic acid on pyridoxal phosphate.

Treatment of photosensitivity reactions consists of protecting the skin against actinic light and identifying and removing exogenous photosensitisers. The application of creams and ointments that decrease the amount of radiation absorbed by the skin also plays a part in the management of such conditions.

Powders These are made of relatively inert solids such as magnesium trisilicate (talc), zinc oxide, starch, bismuth salts, etc. By providing a large surface area, they absorb moisture and by facilitating evaporation from its surface they cool the skin. They also lessen friction between skin surfaces.

Antibacterial and antifungal agents Bacterial infections of the skin are common, *Strep. pyogenes* and *Staph. aureus* being the most frequent pathogens. Antibacterial agents may be applied topically or given systemically. There is no good clinical evidence that topical administration is more effective or causes fewer adverse effects than systemic administration. The use of antibacterial agents in dermatology follows the principles laid down in Chapter 35.

Fungal infections of skin and skin appendages are also common and often respond to topical therapy. Fungal infections of the hair and nails are best treated by systemic griseofulvin (*see* Chapter 35) but skin infections with *Trichophyton*, *Microsporum* and *Epidermophyton* are best treated by topical antifungal agents. There are a large number of these including nystatin, amphoteracin B, clotrimazole and miconazole, potassium permanganate, undecylenic acid, phenylbenzoic and salicyclic acids. If such topical preparations are ineffective, systemic therapy with griseofulvin may be more successful.

Insecticides Skin insect and mite parasites, *Acarus scabiei* (scabies) and

Pediculosis (lice) are treated with topical insecticide compounds. Benzylbenzoate applied as a lotion or powder is widely used for this purpose, being relatively harmless to the skin and highly toxic to *Acarus scabiei* and *pediculosis*. Alternative preparations include gammabenzenehexachloride, malathione and monosulfiram.

DRUGS USED IN MIGRAINE

Migraine is a syndrome characterised by recurrent headaches, usually unilateral and often severe, associated with prodromal visual symptoms and with photophobia, nausea and vomiting. In severe cases, there may be a localised neurological deficit such as a partial visual field defect or hemiplegia that may persist for a variable time after cessation of the headache.

The initiating event in migraine is a localised arterial vasoconstriction of vessels in the distribution of the internal carotid artery on one side, and in severe cases this may be demonstrable on carotid angiography. The headache occurs after the arterial spasm and is caused by dilatation of extra-cranial blood vessels. Much attention has been directed towards establishing the chemical mediators responsible for these changes in vascular smooth muscle tone, but no single agent has been implicated. 5-hydroxytryptamine has been most clearly implicated as the 5-hydroxytryptamine antagonist methysergide is effective at preventing attacks of migraine. As the exact pathogenesis of migraine attacks has yet to be established, treatment and prophylaxis remain empirical.

Treatment of attacks of migraine

Ergotamine is the most effective vasoconstrictor of the ergot alkaloids. It also causes constriction of smooth muscle at other sites, notably the gastrointestinal tract and uterus and is an alpha-adrenoreceptor blocking agent.

If taken early in an attack of migraine, ergotamine prevents or modifies the development of the headache and associated symptoms in the majority of patients, but is of little benefit once the headache has developed. This therapeutic effect is attributed to its vasoconstrictor action in preventing the extra-cranial vasodilatation and associated headache.

DRUG FATE Little is known of the fate of ergotamine in the body. An oral dose of ergotamine is 4–5 times larger than the parenteral dose that achieves a similar therapeutic effect implying either poor absorption or very rapid metabolism of the drug during its first passage through the liver. When given parenterally, it has a slower onset of action on uterine and vascular smooth muscle than does ergometrine.

ADVERSE EFFECTS Nausea and vomiting are quite common and are due to a central emetic effect. Abdominal cramps and diarrhoea occur as a result of the constrictor effect of ergotamine on gastrointestinal smooth muscle. The most serious adverse effect is prolonged vasoconstriction causing ischaemic necrosis of the fingers and toes due to overdosage. This may also occur after doses only

2–3 times that recommended for therapeutic purposes, especially in patients with impaired hepatic function. Coronary vasoconstriction may occur at therapeutic doses and cause angina or myocardial infarction in patients with coronary artery disease. Ergotamine also causes an increase in venous tone and hence, venous return to the heart and may precipitate pulmonary oedema in patients with impaired cardiac function.

CLINICAL USE Ergotamine tartrate is the drug of choice in the treatment of attacks of migraine and caffeine is said to enhance its effectiveness. It is usually taken orally or sublingually, but it may also be taken as an aerosol or as a suppository. If it is not effective orally, it may be given s.c. or i.m., especially in patients who have gastrointestinal symptoms during an attack in whom there is some evidence that drug absorption from the gut is reduced. An initial dose 2–4 mg orally (0·5–1·0 mg s.c.) is best taken immediately prodromal symptoms occur and if the headache progresses may be repeated twice at 30 minute intervals to a maximum dose of 8 mg orally or 2 mg parenterally in 24 hours. Ergotamine is often given in combination with caffeine and an antiemetic (e.g. cyclizine) to counteract its central emetic effect.

Prevention of attacks The first successful agent at preventing attacks of migraine was the 5-hydroxytryptamine antagonist methysergide. This drug, when taken prophylactically, 2–6 mg/day, prevents or ameliorates migraine attacks in the majority of patients. Adverse effects, however, are common and include nausea and vomiting, vertigo, weight gain and psychotic reactions. If given in high doses or for longer than three months, retroperitoneal and pleuropulmonary fibrosis may occur.

Clonidine This drug is a partial agonist of alpha-adrenoceptors and an effective hypotensive agent (*see* Chapter 23). In small doses (150 μg/24 hours or less) it decreases the frequency and severity of migrainous attacks in the majority of patients. At the low doses necessary for this effect, it does not cause hypotension, drowsiness, a dry mouth or nasal stuffiness. Rebound hypertension does not occur on stopping such doses. The mechanism whereby clonidine prevents migraine is not established but at the doses used clinically, it decreases vascular responsiveness to a number of vasoactive substances and this may contribute to its therapeutic effect. In patients not benefiting from ergotamine preparations, clonidine in an initial dose of 25 μg 8 hourly is often effective, while causing very few adverse effects.

DRUGS IN THE TREATMENT OF GALL STONES

The three main constituents of bile are cholesterol, the phospholipid lecithin and bile salts, the latter being derived from cholesterol. Cholesterol is poorly soluble in aqueous solution and is held in solution in bile by lecithin and bile salts. An increase in cholesterol concentration relative to the other two components of bile, causes bile to become supersaturated with cholesterol and,

as a consequence, cholesterol comes out of solution and cholesterol gall stones are formed.

Gall stones are common in western communities and it is estimated that 15–16 million subjects in the USA have gall stones and that 90% of gall stones are cholesterol stones. A prerequisite for the formation of cholesterol gall stones is that the bile is saturated with cholesterol and contains too little bile salts and lecithin for the concentration of cholesterol.

The established method of treating gall stones is by surgery. However, there is evidence that the creation of unsaturated bile, by decreasing the concentration of cholesterol relative to that of bile salts and lecithin, may cause cholesterol stones to dissolve and prevent further stone formation. The most effective way of bringing about such a change has been through the use of the naturally occurring bile salt, chenodeoxycholic acid.

Chenodeoxycholic acid (3,7-hydroxycholic acid) This causes a decrease in size of the majority of radiolucent cholesterol gall stones and, over a period of 6–12 months, may cause complete dissolution of such stones. It is only effective against cholesterol stones in patients with a patent cystic duct and hence a functioning gall bladder. Administration of the drug is not associated with a change in plasma cholesterol but there may be a fall in fasting triglycerides. The principal effect of the drug is a reduction in cholesterol synthesis and its secretion into bile and an increase in the bile acid pool.

Chenodeoxycholic acid is taken orally in a dose of 0·75–1·5 g/day. It may cause hepatocellular damage and a rise in serum aspartate transferase and alkaline phosphatase, but this is rare when the daily dose is 1·5 g or less. It will probably be of value to patients who have cholesterol gall stones and a functioning gall bladder and such patients constitute 20% of patients waiting for cholecystectomy.

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Chapter 42

Drug Usage in Paediatrics and Geriatrics

Throughout this book, with very few exceptions, no mention has been made of the patient's age as a factor to be considered in drug administration, and all dosage schedules have been those suitable for adults. Indifference to the age of the patient is justifiable between the ages of 15–65 years in that age itself is much less important as a determinant of responsiveness to drugs than a number of other factors, e.g. weight, the disease being treated, renal and hepatic function etc. But at the extremes of age, especially during the neonatal period, age is an important consideration.

In the very young and the very old and infirm there are major *practical* problems affecting drug administration in view of the limited extent to which patients in these age groups can co-operate in drug taking. Such practical therapeutic problems will only briefly be discussed in this chapter.

The Influence of Age on Drug Absorption, Disposition, Metabolism and Excretion

Despite the fact that children and the 15% of the population of the UK aged 65 or over, use a great deal of the nation's health resources, including drugs, there is very little evidence on alterations in drug pharmacokinetics with age.

ABSORPTION There is little to suggest that drug absorption is affected by age. In the neonate however, gastric acid production, which in the first 24 hours of life is similar to that of adults, falls to negligible proportions by 9–10 days and then slowly climbs to adult values over the next 3 years, During the period of relative achlorhydria drugs susceptible to acid hydrolysis (e.g. benzylpenicillin, ampicillin and nafcillin) are more readily absorbed than in adults and achieve higher peak plasma concentrations. In the first year of life and in the elderly there is commonly a decrease in bowel-transit time and if this is associated with a delay in gastric emptying, the rate of absorption of drugs from the small bowel is reduced.

DISPOSITION Plasma albumin falls slightly with age which would tend to increase the amount of unbound drug present in the plasma but there is little evidence that such small changes are of clinical importance.

The major factor determining drug disposition that varies with age is the size of the various fluid compartments. These changes are summarised in Table 1.

Table 1

Changes in total body water, extracellular water, intracellular water and plasma water with age

% body weight	*Newborn*	*1 year*	*30 years*
Total body water	78	60	58
Extracellular water	45	27	17
Intracellular water	34	35	40
Plasma water	4 – 5	4 – 5	4 – 5

It will be seen that during the first year of life there is a rapid fall in total body water and in extracellular water as a proportion of body weight, and that the size of the intracellular space increases slightly. The changes in the body spaces in old people are less well documented than those in children and in geriatric patients the situation is often complicated by heart failure and impaired renal functions. In one study of 80-year-olds with congestive cardiac failure, total body water was found to be only 48% of body weight and the extracellular water, both before and after effective therapy, accounted for a greater proportion of the total body water than did the intracellular water.

Changes in the size of body compartments will result in an alteration of the volume of distribution of drugs. Drugs distributed in the extracellular water, e.g. salicylates and highly-ionised species such as quaternary compounds, will have a higher apparent volume of distribution in neonates than adults, and as the size of the extracellular space varies with body surface area, in children under 3, the doses of such drugs are best calculated on the basis of the body surface area rather than weight. For drugs distributed in plasma water or total body water, or concentrated in the tissues, the dose is best calculated on the basis of body weight regardless of the age of the patient.

DRUG METABOLISM The major change in rates of drug metabolism with age occurs in the neonatal period. At birth the hepatic enzyme systems for both phase 1 and phase 2 reactions (*see* Chapter 3) are underdeveloped and as a consequence, the rate at which many drugs are metabolised is decreased and their half-lives correspondingly increased. This has been demonstrated for pethidine, barbiturates and other anticonvulsants, promazine, bupivacaine and for chloramphenicol and can be anticipated for all drugs that require biotransformation before excretion. The drug-metabolising enzyme systems develop rapidly after birth and reach maturity by about three months.

Children metabolise some drugs more rapidly than adults, e.g. phenobarbitone, theophylline, ethosuximide, diazoxide and 6-mercaptopurine and young adults metabolise some drugs, e.g. phenylbutazone and antipyrine more rapidly

than do old adults. Although there have been few studies on the effect of age on drug metabolism it appears probable that there is a gradual fall in the capacity of the liver to metabolise foreign compounds starting in childhood and continuing throughout adult life. There is also a fall in the hepatic blood-flow as a proportion of cardiac output with age.

DRUG EXCRETION In the fetus, glomeruli appear fully developed by 36 weeks but the glomerular filtration rate at birth is usually less than 10 ml/min and takes one year to reach adult values. Renal tubules are immature at birth and their active secretory capacity is very limited. The clearance of para-aminohippuric acid, which is actively secreted by the renal tubules at such a rate that, in the adult, its clearance rate of 650 ml/min approximates to that of renal plasma flow, is only 10–20 ml in the neonate and takes approximately 30 weeks to reach adult values.

As a consequence of the poor secretory capacity of the renal tubules in the neonate, the half-lives of drugs and their metabolites, e.g. acid conjugates, cleared from the plasma by this process, are increased. The half-lives of all the aminoglycoside antibiotics and of the penicillins are higher in neonates than in adults. For instance, the $t_{\frac{1}{2}}$ for kanamycin in adults is approximately 2·0 hours but in infants of less than one week, it is 18 hours. The $t_{\frac{1}{2}}$ for ampicillin is four hours at birth and falls to 1·7 hours by 30 days. The glucuronic acid conjugate of chloramphenicol accumulates in premature infants and may contribute to the adverse effect that this drug causes if given in high doses to premature infants (*see* Chapter 35).

In the elderly, the creatinine clearance is usually 50–60% of peak values, reflecting a fall in glomerular filtration rate, presumably the consequence of atherosclerosis. This results in an increase in the half-lives of drugs excreted unchanged in the urine, e.g. the $t_{\frac{1}{2}}$ of benzylpenicillin varies inversely with the creatinine clearance and in the elderly is usually 1·5–2·0 times that in early adult life. The same relationship is well established for digoxin and, as the therapeutic index for this drug is narrow, maintenance doses in the elderly should be reduced in accordance with the fall in the creatinine clearance.

The Influence of Age on Responsiveness to Drugs

The variability in responsiveness to the pharmacodynamic effects of drugs can only be evaluated when variability in pharmacokinetics has been determined. There have been very few pharmacokinetic studies in the elderly and so there is little reliable data on changes in the pharmacodynamic effects of drugs.

The paediatric dose of a drug is usually calculated by a variety of means from the adult dose using either the child's weight or surface area. As implied above, the surface area is the best guide to the dose of a drug distributed in the extracellular space but for the rest, the weight is the best guide. Reliance on an 'ideal dose' for any drug is as hazardous in children, as in adults, as there is considerable interindividual variation in the pharmacokinetics of drugs in

children, so that the most reliable means of establishing the correct dose is to monitor closely the drug's effects.

In the elderly, degenerative disorders commonly affect many organs and this may alter or enhance drug effects. There may be an enhanced response to CNS depressants in elderly subjects with cerebrovascular disease who may become ataxic or even unconscious on doses of barbiturates or benzodiazepines that for younger adults would have only mild sedative effects. The negative inotropic effect of beta-adrenergic blocking agents and anti-dysrhythmic drugs other than digoxin, may precipitate left ventricular failure in elderly patients with no signs of impaired cardiac function. In treating the elderly patient, therefore, it is advisable to start with a lower dose than with younger adults and to monitor drug effects carefully before increasing the dose.

Drug Administration in the Elderly

Elderly patients often have failing intellectual powers which sometimes prevent them understanding instructions concerning drug taking. Poor eyesight also limits their ability to read instructions and impairment of memory results in their forgetting to take drugs at appropriate times. They usually suffer from two or more disorders at the same time, all of which may require drug therapy. As a consequence, they often end up being treated with a number of drugs but failing to comply with drug taking instructions. Drug regimes for elderly patients should therefore be simple, carefully explained to them and clearly written down. Where possible these instructions should also be given to a relative or friend.

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