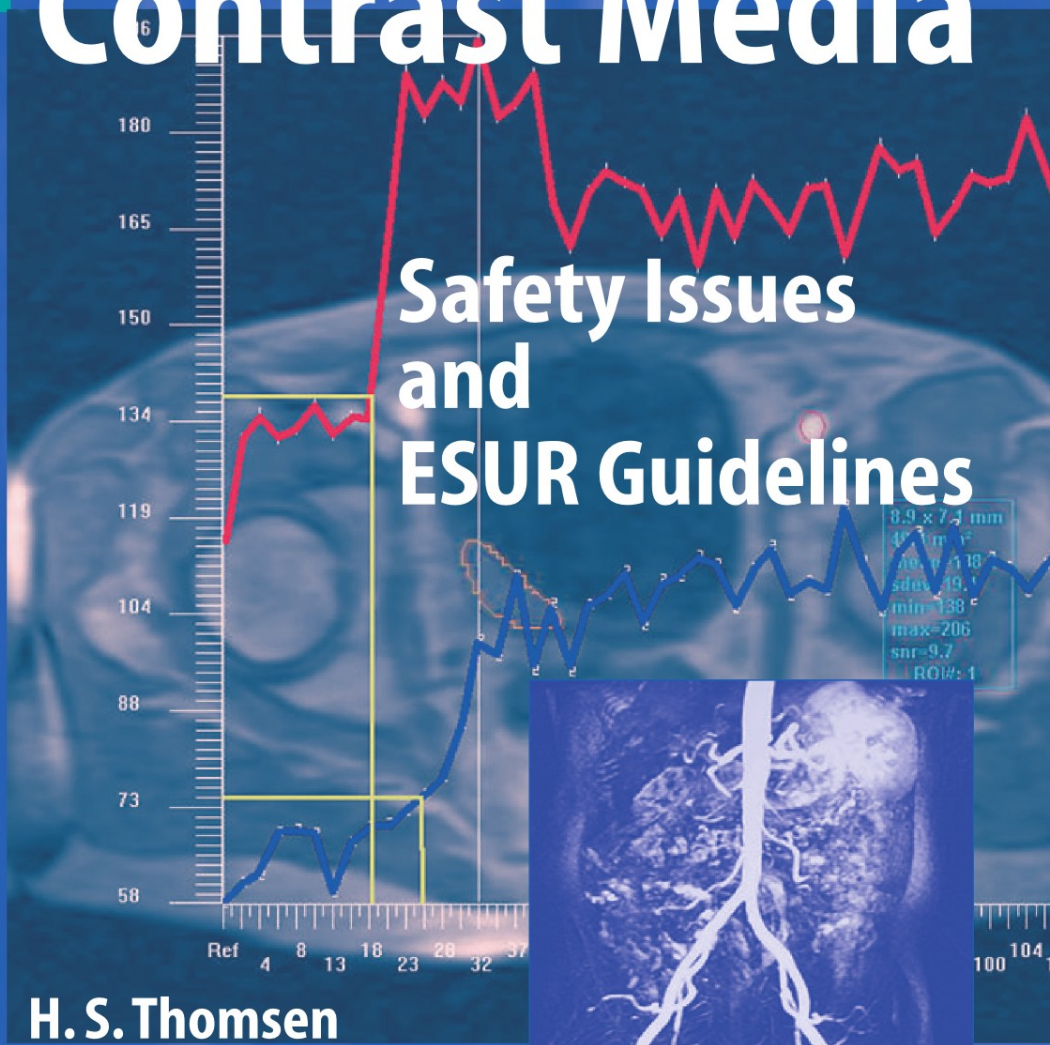
MEDICAL RADIOLOGY

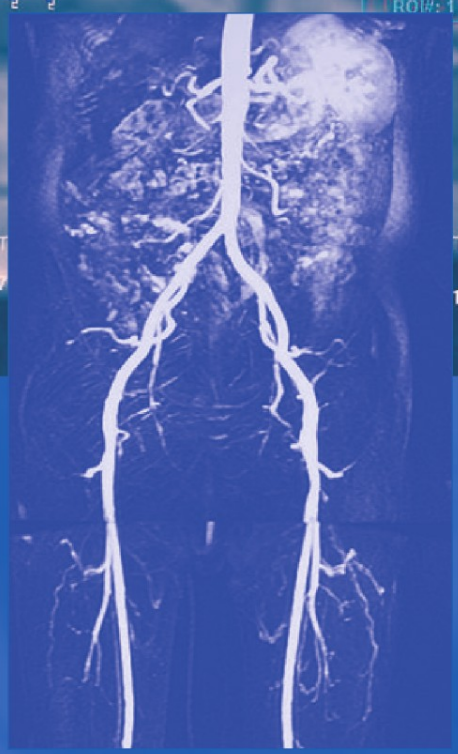
Diagnostic Imaging

A. L. Baert
K. Sartor

Contrast Media

Safety Issues and ESUR Guidelines





H. S. Thomsen

Editor

Springer

MEDICAL RADIOLOGY
Diagnostic Imaging

H. S. Thomsen (Ed.)

Contrast Media

Safety Issues and ESUR Guidelines

With Contributions by

P. Aspelin · M.-F. Bellin · R. W. F. Geenen · J. Å. Jakobsen · G. P. Krestin · S. K. Morcos · R. Oyen
J. M. Raine · F. Stacul · H. S. Thomsen · A. J. van der Molen · J. A. W. Webb

Foreword by
A. L. Baert

With 2 Figures and 27 Tables

Springer

Henrik S. Thomsen, MD
Professor, Department of Diagnostic Radiology 54E2
Copenhagen University Hospital at Herlev
Herlev Ringvej 75
DK-2730 Herlev
Denmark

Medical Radiology · Diagnostic Imaging and Radiation Oncology
Series Editors: A. L. Baert · L. W. Brady · H.-P. Heilmann · M. Molls · K. Sartor

Continuation of Handbuch der medizinischen Radiologie
Encyclopedia of Medical Radiology

Library of Congress Control Number: 2005925776

ISBN 3-540-20448-2 Springer Berlin Heidelberg New York
ISBN 978-3-540-20448-0 Springer Berlin Heidelberg New York

Medical Editor: Dr. Ute Heilmann, Heidelberg
Desk Editor: Ursula N. Davis, Heidelberg
Production Editor: Kurt Teichmann, Mauer
Cover-Design and Typesetting: Verlagsservice Teichmann, Mauer

Printed on acid-free paper – 21/3151xq – 5 4 3 2 1 0

Foreword

For more than 10 years the ESUR contrast media safety committee has been providing radiologists with the latest information and updates on the adverse effects and risks of contrast media. The recommendations and guidelines from this committee have generated great interest and are now universally recognized for their high scientific value. They are based on solid scientific research, objective data and comprehensive, independent literature analysis. The long-standing and extensive personal clinical expertise of each of the committee members constitute the base for authoritative statements on many controversial issues regarding the correct use of contrast agents in clinical radiology.

As a comprehensive work, this book covers not only the classic iodinated contrast media and barium preparations, but also the more recent MR and US contrast agents. Indeed, this work brings together an immense volume of data and invaluable specific information, originally scattered throughout the literature but now available in one publication.

I most sincerely congratulate H. S. Thomsen and all contributing authors for this outstanding volume, which deserves to become the standard reference in the field.

I am confident that it will be of great interest for radiologists and referring physicians in their daily practice.

Leuven

Albert L. Baert

Preface

The European Society of Urogenital Radiology established its Contrast Media Safety Committee in 1994. Over the years it has consisted of between 12 and 14 members, the majority of whom are experts in the field of contrast media research. There is currently one member from the scientific section of each of the pharmaceutical companies producing contrast agents (Bracco, Italy; GE Healthcare Diagnostics, USA; Guerbet, France; Schering, Germany). Although the members of the committee have diverse views the Contrast Media Safety Committee works as one group for the good of patients. The committee benefits from the wealth of knowledge on contrast agents brought to it by the representatives of the pharmaceutical companies. However, the rules of the Contrast Media Safety Committee forbid any commercial promotion and the committee deals with all types of contrast agents based purely on objective analysis, sound scientific data, well documented clinical experience and clinical common sense. Disagreement within the committee is discussed rationally and without commercial influence. All contrast media are referred to by their generic names, except when the generic name is confusing (e.g. ultrasound contrast agents). After 11 years of work the committee has covered all the topics of clinical importance regarding the safe use of contrast media. The current book is mainly a collection of this work together with a few new chapters. The chapters have been prepared by the individual authors based on their original papers (see Appendix) when applicable and an up to date review of the literature. Some chapters are new and have never been published as papers by the committee. The chapters have not been circulated among or discussed by the members of the committee and have been edited by myself. In the appendix the latest version of the ESUR guidelines agreed at the meeting of the committee in Copenhagen, February 2005, is presented.

The ESUR guidelines have been well received by the radiological community. They are frequently cited in the literature. They have been incorporated into the protocols of many departments all over the world. They are also used by the health authorities in many countries as a reference for good radiological practice. Several of the guidelines have been translated into languages other than English, for example Spanish, Russian and Japanese.

I am sure the readers will agree that this book offers an invaluable, unique, practical and unparalleled resource dealing with safety issues related to radiographic, MR and ultrasound contrast media, and that it will ultimately benefit patients.

It has been a great honor for me to serve as chairman of this prestigious committee for 9 years. Special mention goes to the secretary of committee, Dr. Sameh Morcos, whose close cooperation has always been highly productive and inspirational. Without his energy and enthusiasm we would never have accomplished what we have. Also, the past and current members of the committee deserve sincere thanks for their continu-

ing involvement and for the outstanding discussions at the annual committee meeting. Despite disagreements we have always reached a consensus. A special thank you goes to Dr. Judith Webb, who has not only participated actively in our work but has also ensured that our manuscripts were published in correct English. Dr. Webb has revised the English throughout this book and I am most grateful for her outstanding and continuous support. We also thank Professor Albert L. Baert, Editor-in-Chief of European Radiology and Editor-in-Chief of this book series, as well as Springer-Verlag for their immediate endorsement and support of the book.

Finally, I wish to thank my family, especially my wife Pia, for allowing me to invest so many hours of family time in this project.

Herlev, Denmark — Henrik S. Thomsen

Contents

1 Classification and Terminology

Peter Aspelin, Marie-France Bellin, Jarl Å. Jakobsen, and Judith A. W. Webb

CONTENTS

1.1 Introduction

Current radiological imaging uses either electromagnetic radiation (X-rays or radiowaves) or ultrasound. X-rays have a frequency and photon energy several powers higher than visible light and can penetrate the body. The radiation which emerges from the body is detected either by analogue radiological film or by a variety of digital media. The radiowaves used in magnetic resonance imaging have a frequency and photon energy several powers lower than visible light. The radiowaves cause deflection of protons in the body which have aligned in the magnetic field in the scanner and as the protons relax back to their resting position, they emit radiowaves which are used to generate the image. Ultrasound imaging uses sound (pressure) waves several powers higher than audible sound which are reflected back from tissue interfaces in the body to generate the image.

Contrast media may be used with all of these imaging techniques to enhance the differences seen between the body tissues on the images. Contrast media alter the response of the tissues to the applied electromagnetic or ultrasound energy by a variety of mechanisms. The ideal contrast medium would achieve a very high concentration in the tissues without producing any adverse effects. Unfortunately, so far this has not been possible and all contrast media have adverse effects.

This chapter deals with the classification of contrast agents and the terminology used to describe them.

1.2 Radiographic Contrast Media

Radiographic contrast media are divided into positive and negative contrast agents. The positive contrast media attenuate X-rays more than do the body soft tissues and can be divided into water soluble iodine agents and non water soluble barium agents. Negative contrast media attenuate X-rays less than do the body soft tissues. No negative contrast media are commercially available.

1.2.1 Iodine Agents

Water soluble iodinated contrast agents which diffuse throughout the extracellular space are principally used for angiography, during computed tomography (CT) and conventional radiography. They can also be administered directly into the body cavities, for example the gastrointestinal tract and urinary tract.

P. Aspelin, MD
Department of Radiology, Karolinska University Hospital, 14186 Stockholm, Sweden
M.-F. Bellin, MD
Department of Radiology, University Paris-Sud 11, Paul Brousse Hospital, AP-HP, 12–14 avenue. Paul Vaillant Couturier, 94804 Villejuif Cedex, France
J. Å. Jakobsen, MD
Department of Diagnostic Radiology, Rikshospitalet, 0017 Oslo, Norway
J. A. W. Webb, MD
Department of Diagnostic Imaging, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK

All of these contrast media are based on a benzene ring to which three iodine atoms are attached. A monomer contains one tri-iodinated benzene ring and a dimer contains two tri-iodinated benzene rings.

Iodinated contrast media can be divided into two groups, ionic and nonionic based on their water solubility. The water in the body is polarised unevenly with positive poles around the hydrogen atoms and negative poles around oxygen atoms. Ionic contrast media are water soluble because they dissociate into negative and positive ions which attract the negative and positive poles of the water molecules. Nonionic contrast media do not dissociate and are rendered water soluble by their polar OH groups. Electrical poles in the contrast medium OH groups are attracted to the electrical poles in the water molecules.

The osmolality of contrast media affects the incidence of side-effects. The early contrast media had very high osmolalities (1500–2000 mosm per kg) and subsequently agents of lower osmolality have been developed. Contrast media may be divided into high-, low- and iso-osmolar agents. An indication of the osmolality of an agent is given by the contrast medium ratio which is derived by dividing the number of iodine atoms in solution by the number of particles in solution:

$$\textit{Contrast medium Ratio} = \frac{\textit{Number of iodine atoms}}{\textit{Number of particles in solution}}$$

The higher osmolality agents have more particles per iodine atom and therefore have lower ratios. Thus the ionic monomers have a ratio of 1.5 (three iodine atoms per two particles in solution), the nonionic monomers and the ionic dimers have a ratio of 3 (three iodine atoms per particle in solution) and the nonionic dimers have a ratio of 6 (six iodine atoms per particle in solution) (Fig. 1.1). The nonionic dimers are iso-osmolar with blood (300 mosm per kg) at all concentrations.

Using these properties four different classes of iodinated contrast may be defined (Fig. 1.1):

1. Ionic monomeric contrast media (high-osmolar contrast media, HOCM), e.g. amidotrizoate, iothalamate, ioxithalamate
2. Ionic dimeric contrast media (low-osmolar contrast media, LOCM), e.g. ioxaglate
3. Nonionic monomeric contrast media (low-osmolar contrast media, LOCM), e.g. iohexol, iopentol, ioxitol, iomeprol, ioversol, iopromide, iobitridol, iopamidol
4. Nonionic dimeric contrast media (iso-osmolar contrast media, IOCM), e.g. iotrolan, iodixanol

1.2.2 Barium Contrast Media

Barium sulphate preparations used to visualize the gastrointestinal tract consist of a suspension of insoluble barium sulphate particles which are not absorbed from the gut. Differences between the different commercially available agents are very minor and relate to the additives in the different barium sulphate preparations.

1.3 MR Contrast Media

Magnetic resonance (MR) imaging contrast agents contain paramagnetic or superparamagnetic metal ions which affect the MR signal properties of the surrounding tissues. They are used to enhance contrast, to characterize lesions and to evaluate perfusion and flow-related abnormalities. They can also provide functional and morphological information.

1.3.1 Paramagnetic Contrast Agents

Paramagnetic contrast agents are mainly positive enhancers which reduce the T1 and T2 relaxation times and increase tissue signal intensity on T1-weighted MR images.

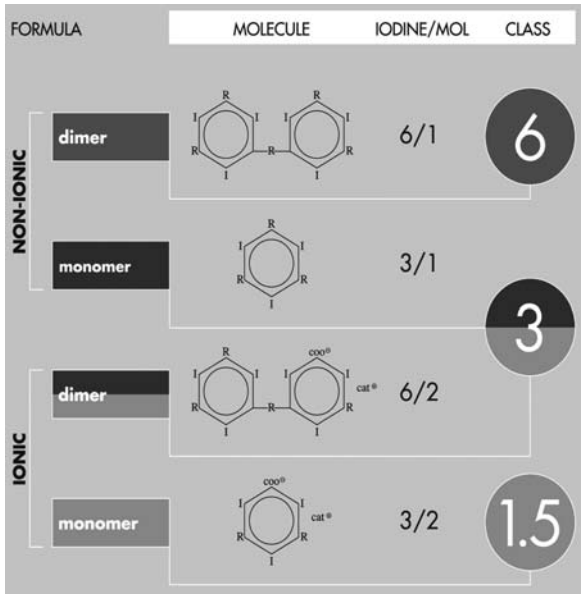


Fig. 1.1. Classification of iodinized contrast media

The most widely used paramagnetic contrast agents are non-specific extracellular gadolinium chelates. Their active constituent is gadolinium, a paramagnetic metal in the lanthanide series, which is characterized by a high magnetic moment and a relatively slow electronic relaxation time. Non-specific extracellular gadolinium chelates can be classified by their chemical structure, macrocyclic or linear, and by whether they are ionic or nonionic (Fig. 1.2). They are excreted via the kidneys.

Paramagnetic contrast agents also include liver specific gadolinium based agents (gadobenate dimeglumine, Gd-BOPTA and gadoxetate, Gd-EOB-DTPA) and manganese-based preparations [manganese chelate (mangafodipir trisodium) and free manganese combined with vitamins and amino acids (to promote the uptake) for oral intake]. These hepatobiliary contrast agents are taken up by hepatocytes and then there is variable biliary excretion. The gadolinium based liver specific contrast media are also excreted by the kidneys.

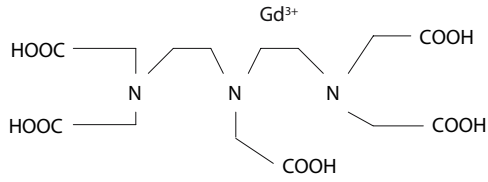
1.3.2 Superparamagnetic Contrast Agents

Superparamagnetic contrast agents include superparamagnetic iron oxides (SPIOs) and ultra small superparamagnetic iron oxides (USPIOs). Two preparations of SPIOs are available: ferumoxides and ferucarbotran. These particulate agents are composed of an iron oxide core, 3–5 mm in diameter, covered by low molecular weight dextran for ferumoxides and by carbodextran for ferucarbotran. SPIOs are approved for liver imaging and USPIOs are under consideration for MR lymphography.

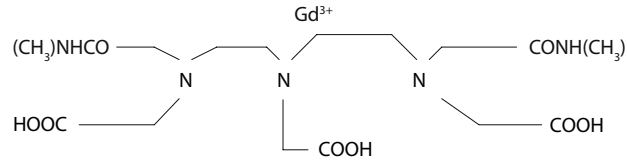
After injection, SPIO and USPIO particles are metabolised into a soluble, non superparamagnetic form of iron. Iron is incorporated into the body pool of iron (e.g. ferritin, hemosiderin and hemoglobin) within a few days.

1.4 Ultrasound Contrast Media

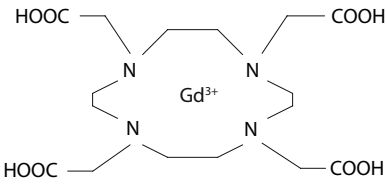
Ultrasound contrast agents produce their effect by increased back-scattering of sound compared to that from blood, other fluids and most tissues. On grey-scale images microbubble contrast agents change grey and dark areas to a brighter tone, when the contrast enters in fluid or blood. The spectral Doppler



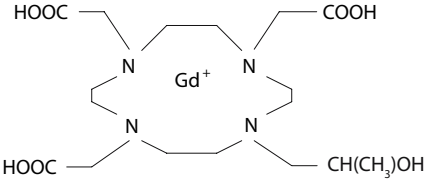
Ionic and linear Gd-DTPA (gadopentetate dimeglumine)



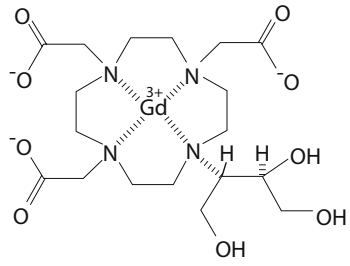
Non-ionic and linear Gd-DTPA–BMA (gadodiamide)



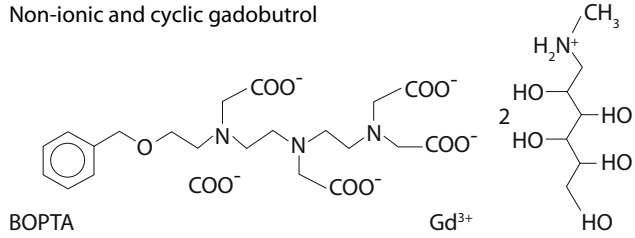
Ionic and cyclic Gd-DOTA (gadoterate meglumine)



Non-ionic and cyclic Gd-HP-DO3A (gadoteridol)



Non-ionic and cyclic gadobutrol



Ionic and linear Gd-BOPTA (gadobenate dimeglumine)

Fig. 1.2. Structures of the organic ligands of Gadolinium chelates approved for clinical use.

intensity is also increased, with a brighter spectral waveform displayed and a stronger sound heard. Using color Doppler technique, ultrasound contrast agents enhance the frequency or the power intensity giving rise to stronger color encoding. The level of enhancement of the Doppler signals may be in the order of up to 30 dB.

Ultrasound contrast agents can be used to enhance Doppler signals from most main arteries and veins. They may be useful for imaging solid organs, e.g. liver, kidney, breast, prostate and uterus. They can also be used to enhance cavities e.g. bladder, ureters, Fallopian tubes, abscesses.

1.4.1 Classification

Ultrasound contrast agents can be divided into five different classes: (1) Nonencapsulated gas microbubbles (e.g. agitated or sonicated), (2) stabilised gas microbubbles (e.g. with sugar particles), (3) encapsulated gas microbubbles (e.g. by protein, liposomes or in polymers), (4) microparticle suspensions or emulsions [perfluorooctyl bromide (PFOB), phase-shift], and (5) gastrointestinal (for ingestion). Products are not commercially available from all classes.

Ultrasound contrast agents (USCA) can also be classified based on their pharmacokinetic properties and efficacy: (1) Non-transpulmonary USCAs which do not pass the capillary bed of the lungs following a peripheral intravenous injection, show on B-mode only in the right ventricle, and have a short duration effect, (2) transpulmonary blood pool USCAs with a short half-life (< 5 min after an intravenous bolus injection), which produce low signals using harmonic imaging at low acoustic power, (3) transpulmonary blood pool USCAs with a longer half-life (> 5 min after an intravenous bolus injection), which produce high signals using harmonic imaging at low acoustic power, (4) transpulmonary USCAs with a specific liver and spleen phase which can be short- or long-lived. They lodge in the small vessels of the liver or spleen, or are taken up by either the reticuloendothelial system or by the hepatocytes.

Agents which are currently available commercially or are close to being available commercially are listed in Table 1.1.

Table 1.1. Some ultrasound contrast agents on or close to the market in various parts of the world (officially available data per April, 2005)

Product name	Some properties
Definity™ (DMP 115)	Fluorocarbon gas in liposomes
SonoVue® (BR1)	Sulphur hexafluoride gas in polymer with phospholipid
Optison™ (FS069)	Octafluoropropane-filled albumin microspheres
Sonazoid™ (NC100100)	Perfluorinated gas-containing microbubbles
Levovist® (SHU 508A)	Galactose-based, palmitic acid stabilised air-bubbles

2 Off-Label Use of Medicines – Legal Aspects

June M. Raine

CONTENTS

In Europe, subject to certain exemptions explained below, no medicine can be marketed for human use without a Marketing Authorisation granted either by a Member State competent authority or by the European Commission. The regulatory system exists to protect patients by ensuring that marketed medicines meet acceptable standards of safety, quality and efficacy in their indications. Nonetheless, for a range of reasons use of medicines outside their authorised indications, commonly known as off-label use, and use of unlicensed medicines (i.e. medicines without a marketing authorisation) are common. This chapter outlines the definition of a medicine and the current regulatory framework; reviews the legal position of prescribers of off-label use and the use of unlicensed medicines; considers special populations and therapeutic areas where off-label use or the use of unlicensed medicines is common; and provides some general guidance for prescribers considering off-label use or the use of unlicensed medicines.

J. M. Raine, MD
Medicines Control Agency, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ, UK

2.1 Definition of a Medicine

As diagnostic agents, contrast media fall within the definition of a medicine in European law, since the definition includes:

"Any substance or combination of substances which may be used in or administered to human beings … with a view to … making a medical diagnosis".

The legislation also encompasses radiopharmaceuticals:

"Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose".

Marketing authorisation is required for radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals. A marketing authorisation is not required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorised, according to national legislation, to use such medicinal products in an approved health case establishment exclusively from authorised radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.

European medicines legislation does not apply to:

O Medicines prepared in a pharmacy in accordance with a medical prescription for an individual patient (the "magistral formula").
- Medicines prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy (the "officinal formula").
- Medicines for research and development trials [covered by the Directive 2001/20/EC on good clinical practice in the conduct of clinical trials for human use ("the Clinical Trials Directive")].
- Intermediate products intended for further processing by an authorised manufacturer.
- Any radionuclides in the form of sealed sources.

2.2 The European Regulatory System

The European regulatory system governing the marketing of medicines for human use is set out in Directive 2001/83/EC as amended, Regulation (EC) No.726/2004 and associated legislation. The Regulation lays down Community procedures for the authorisation, supervision and pharmacovigilance of medicines, establishes a European Medicines Agency, and sets up a scientific committee attached to the Agency, the Committee for Human Medicinal Products. It makes provision for medicines to be approved by the European Commission via centralised authorisations valid in all member states.

The centralised procedure must be used for certain specified categories of medicines and can also be used for medicines which contain a new active substance or which constitute a significant therapeutic, scientific or technical innovation. It is therefore unsurprising that a number of new diagnostic imaging agents have been authorised by the centralised route. The Directive sets in place decentralised and mutual recognition systems, enabling authorisations to be granted nationally by Member States. For the foreseeable future, depending on the route by which a medicine has been authorised, differences may exist in Europe between member states' authorisations for the same product, and in availability of medicines. The result is that use may be within an authorisation in one country and off-label in another.

The terms in which a marketing authorisation is granted are specified in the Summary of Product Characteristics (SPC), with which all advertising must comply. The SPC contains detailed provisions covering indications, recommended dosage, contra-indications, special warnings and precautions, and adverse effects associated with the medicine. Copies of SPCs are available from the marketing authorisation holder, from the European Medicines Agency, from the some Member State competent authorities and via the Electronic Medicines Compendium on www.medicines.org.uk. The SPC also forms the basis for the Patient Information Leaflet (PIL) which accompanies the medicine and is written in terms which are understandable by patients. Clearly, a medicine which is unlicensed will not have an SPC or PIL. Marketing authorisation holders are required to keep their authorisations up to date as new information accrues in clinical use, and there is naturally a particular focus on safety data. New evidence on efficacy may not be so readily identified and manufacturers may legitimately decline to market a medicine for a purpose they do not wish to support.

2.3 Definition of Off-Label Use

The term "off-label use" applies to prescribing or administration outside any of the terms of the marketing authorisation, generally in relation to indications, dosage, or contra-indications. The expression relates to a term used in the US authorisation process: the Food and Drug Administration (FDA) approves product labelling. A medicine which is prescribed off-label will be accompanied by information which may not be consistent with its off-label use, creating the potential for concern or confusion on the part of the patient, parent or carer.

In the light of the regulatory framework, there are a number of situations where off-label use or the use of unlicensed medicines occurs:

- Products for which a marketing authorisation application or variation has yet to be made. These include drugs in development and undergoing clinical trials.
- Medicines for which a marketing authorisation application or variation has been refused.
- Medicines which no longer have a relevant marketing authorisation because it has been suspended, revoked, not renewed or compulsorily varied.
- Products prepared in formulations specially adapted to special populations such as lower strengths for children or liquids for the elderly, or without particular excipients for patients allergic to them.

The use of unlicensed medicines may also occur in clinical trials; i.e. where the drug is still under development. The use of such medicines is subject to the provisions of the Clinical Trials Directive and is not dealt with in this chapter.

2.4 Special Populations and Special Therapeutic Areas

Off-label prescribing of medicines, and the prescribing of unlicensed medicines, is common in the areas of oncology, obstetrics, and infectious disease (HIV/AIDS) and is particularly common in the paediatric population. Hospital based studies have shown that many drugs used in children are either not licensed

or are prescribed off-label. On general paediatric surgical and medical wards 36% of children received at least one drug that was unlicensed or off-label during their in-patient stay. In paediatric intensive care this figure was 70% and in neonatal intensive case 90%. A study of children's wards in five European countries found almost half of all prescriptions were either unlicensed or off label. This is consistent with the UK licensing position on contrast media – of around 90 licensed products; about 50% are indicated in children.

This situation has resulted from practical, ethical and commercial considerations relating to conducting clinical trials in children. There are difficulties in developing formulations appropriate for children, and funding for research into the paediatric use of established medicines is lacking. Following initiatives taken by the FDA in 1997 and 1999 to create incentives and obligations to conduct trials in children, the position is changing. In 2004 the European Commission published proposals for a Paediatric Regulation establishing a system of incentives and requirements, drawing on the experience of the US legislation. Importantly the European draft Regulation contains provisions for improved information on the use of medicines in children and publication of information from clinical trials in children. It is not expected to be adopted before 2006.

2.5 Legal Position of the Prescriber

The regulatory system aims to control the activities of pharmaceutical companies manufacturing, selling or supplying medicines. It is not intended to impact on the practice of medicine. European legislation does not require member states to prohibit the prescription or administration of medicines outside their authorised indications. Medicines prescribed outside the terms of the marketing authorisation may be dispensed by pharmacists and administered by nurses or midwives. In addition, the legislation contains a specific exemption which enables Member States to permit the supply of unlicensed medicines for individual patients at the order of their doctor – Article 5 of Directive 2001/83/EC provides that: "A Member State may, in accordance with the legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility". This provision is the basis for what is referred to as the "specials" regime. The exemption helps preserve the clinical freedom to act in what is judged to be in the best interests of the individual patient.

The way in which European legislation is framed means that doctors can:

- Prescribe medicines off-label.
- Prescribe unlicensed products for individual patients, either under the "specials" regime (i.e. when no suitable licensed alternative available) or where they are specially prepared in a pharmacy.
- Supply another doctor with an unlicensed medicine, in accordance with the "specials" regime.
- Use unlicensed medicines in clinical trials.
- Use or advise the use of licensed medicines for indications or in doses or by routes of administration outside the recommendations given in the licence (i.e. off-label).
- Subject to the points made below, prescribe or recommend the use of a medicine contrary to any warnings or precautions given in the marketing authorisation.

While European legislation and the regulatory system permits the off-label use or, in certain circumstances, the use of unlicensed medicines, consideration also needs to be given to potential civil liability of the prescriber, in particular for negligence, in the event that such use results in an injury to a patient.

Even in relation to an unlicensed product, manufacturers retain a responsibility for the efficacy and safety of their product under Directive 85/374/EEC on the liability for defective products (in the UK, see the Consumer Protection Act 1987), subject to the product being stored and administered correctly. A manufacturer is however unlikely to be liable if injury results not from an inherent defect in the product or its accompanying information, but from the decision of the doctor to use the product off-label, or to use an unlicensed product for a particular patient.

The law relating to medical negligence differs in different Member States, but generally provides for the imposition of liability on individual prescribers in certain circumstances. In the UK, a doctor owes a duty of care to his individual patients; if he breaches that duty by failing to take reasonable care and a patient is injured as a result, he will be liable for negligence. A doctor will generally not be considered negligent if his actions would be accepted as proper by a responsible body of medical professional opin-

ion. The courts will not however consider a body of opinion as responsible if that opinion is not capable of withstanding logical analysis.

A doctor if also responsible for obtaining the consent of the patient to the treatment in question. Failure to obtain fully informed consent may amount to negligence.

2.6 Guidance for Prescribers

The responsibility for prescribing any medicine falls on the prescribing physician or health care professional. If the prescription is for an unlicensed medicine or for off-label use, these responsibilities are enhanced.

First, when prescribing an unlicensed medicine or a medicine for off-label use the prescriber is responsible for determining whether it is appropriate to use the medicine as proposed for the individual patient. Where the proposed use is not covered by the terms of a marketing authorisation, the prescriber should consider the safety, and efficacy of the product in relation to the proposed use. The prescriber needs to be satisfied that there is sufficient evidence and/or experience of using the medicine in order to demonstrate its safety and efficacy. The prescriber should consider any relevant published literature, clinical guidance, or clinical trial data made available by regulatory authorities or companies themselves. Prescribers can also rely on information and guidance from a responsible body of medical opinion. In the area of paediatrics for example, the UK publication "Medicines for Children" produced by the Royal College of Paediatrics and Child Health has been generally cited as representing the respected body of knowledge derived from a large number of UK paediatricians. A further example is the guideline on safe sedation of children undergoing diagnostic and therapeutic procedures published in 2004 by the Scottish Intercollegiate Guideline Network.

In relation to unlicensed medicines, other than a medicine prepared in a pharmacy in accordance with a prescription, the doctor must also be satisfied that an alternative licensed medicine would not meet the patient's needs.

The second responsibility of prescribers undertaking off-label prescribing or the prescribing of unlicensed medicines is to ensure that the patient, parent or carer is adequately informed about the risks and benefits of the medicine, in the absence of authorised product information. It has been recommended that, when obtaining consent to treatment, the doctor should tell the patient of the drug's licence status, and that for an unlicensed medicine its effects will be less well known and understood than those of a licensed product. The provision of information by the prescriber is particularly important in relation to off-label use, where the patient information leaflet may provide conflicting information or information not relevant to such use, and in relation to unlicensed medicines, where no such leaflet is available. In relation to off-label use, the prescriber should have access to the up-to-date Summary of Product Characteristics, in order to give appropriate information and advice.

Providing a full verbal or written explanation to the patient and recording that in writing, helps ensure that the patient understands the risks involved and gives genuine and informed consent. This also reduces the risk of liability on the part of the prescriber in the event of injury to the patient.

Thirdly, prescribers have a professional responsibility for monitoring the safety of medicines and for submission of reports of any suspected adverse drug reactions to the competent authority of the Member State. This applies to unlicensed medicines no less than authorised products. Some Member States have introduced a legal requirement requiring health professionals to report suspected adverse drug reactions, but this does not appear to have resulted in higher reporting rates.

2.7 Conclusion

The use of medicines according to the terms of the marketing authorisation is supported by evidence of safety, quality and efficacy which has satisfied regulatory authorities of Member States or the European Commission. It is generally understood and accepted that there are clinical situations where off-label use or the use of unlicensed medicines may be judged by the prescriber to be in the patient's best interests, on the basis of the evidence available indicating a likely favourable benefit:risk balance. In such cases, the onus is on the prescriber to be familiar with the available evidence of risk and benefit, to make appropriate information available to the patient, parent or carer, and to monitor safety in use. If appropriate care is taken, information provided and decisions related to off-label use or use of unlicensed medicines recorded, the risk of a prescriber being found liable for any mishap should be minimised.

Section I:
General Adverse Reactions

3 Prevention of Acute Reactions

Judith A. W. Webb

CONTENTS

3.1 Introduction

Most of this chapter is concerned with acute idiosyncratic reactions to iodinated contrast media, particularly the factors predisposing to these reactions and the measures that may be taken to prevent them. At the end of the chapter acute reactions to gadolinium contrast media are also discussed.

J. A. W. Webb
Department of Diagnostic Radiology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK

3.2 Iodinated Contrast Media

3.2.1 Types and Frequency of Acute Reactions

Acute idiosyncratic systemic reactions (also described as allergy-like or anaphylactoid) are defined as unpredictable reactions which occur within 1 h of contrast medium administration, and which are unrelated to the amount of contrast medium above a certain level. This definition aims to distinguish them from chemotoxic reactions, which are dose-related and dependent on the physico-chemical properties of the contrast medium. However, in clinical practice, some reactions such as cardiovascular collapse may be difficult to characterise definitely into one or other group.

The mechanisms by which idiosyncratic reactions occur are not fully understood. However, they do appear to involve the release of active mediators, such as histamine, bradykinin, leucotrienes, prostaglandins and complement factors. Available evidence suggests that there are a variety of complex interactions between the complement, contact, coagulation and immune systems (Lasser 1985, 1987; Almen 1994).

Acute idiosyncratic reactions are usually characterised as mild, moderate or severe. Mild or minor reactions include nausea, mild vomiting, urticaria and itching. Moderate reactions include more severe vomiting, marked urticaria, bronchospasm, facial or laryngeal oedema, and vasovagal reactions. Severe reactions include hypotensive shock, respiratory arrest, cardiac arrest and convulsions (Bush and Swanson 1991).

3.2.2 Risk Factors for Acute Idiosyncratic Reactions

3.2.2.1 Type of Contrast Agent

With the older high osmolality ionic agents the rate of reactions of all types is in the range 5%–12% (Ansell

et al. 1980; Witten et al. 1973; Shehadi 1975; Katayama et al. 1990; Cochran et al. 2001). The majority of reactions in these series were mild with moderate reactions occurring in 1%–2% and severe reactions in approximately 0.10%–0.15% (Ansell et al. 1980; Witten et al. 1973). Mortality with the ionic agents is in the range 1 in 14,000 to 1 in 169,000 (Shehadi 1975; Katayama et al. 1990) with 1 in 75,000 an often quoted figure (Hartman et al. 1982).

With the newer low osmolality nonionic agents, the reaction rates are lower, by a factor of approximately four to five times (Katayama et al. 1990; Palmer 1988; Wolf et al. 1991; Bettman et al. 1997). Thus in Katayama's series of over 300,000 patients the reaction rates for ionic and nonionic agents were overall 12.66% and 3.13%, with severe reactions in 0.22% and 0.04%, respectively (Katayama et al. 1990). Based on a meta-analysis of all data published between 1980 and 1991, Caro et al. (1991) concluded that 80% of contrast media reactions could be prevented by using low osmolality agents. The very low mortality means that accurate mortality figures are not yet available for the nonionic agents. In Katayama et al.'s (1990) series there was no significant difference in mortality between the ionic and nonionic agents, but other data suggests a lower mortality with nonionic agents (Lasser et al. 1997).

3.2.2.2 Previous Contrast Medium Reaction

A previous reaction to an iodinated contrast medium is the most important patient factor predisposing to an acute idiosyncratic reaction (Bettman et al. 1997). With ionic agents, the risk of a reaction in a patient who reacted previously has been stated to be 16%–35% (Witten et al. 1973; Shehadi 1975) and to be eleven times greater than the risk in a non-reactor (Ansell et al. 1980). When a patient who previously reacted to an ionic agent is given a nonionic agent, the risk of a repeat reaction is reduced to approximately 5% (Siegle et al. 1991).

3.2.2.3 Asthma

Asthma is another important risk factor. Shehadi (1975) found that 11% of asthmatics had a reaction to ionic contrast media and Ansell et al. (1980) stated that the risk of reaction to ionic agents was increased five times in an asthmatic. In patients with asthma, Katayama et al. (1990) described an 8.5 times increased risk with ionic agents and a 5.8 times increased risk with nonionics. Other conditions, such as hayfever, eczema, etc. are associated with an increased risk of reaction, but by a lesser amount than asthma (Ansell et al. 1980; Witten et al. 1973; Shehadi 1975).

3.2.2.4 Allergy

A history of allergy to foods, drugs or other substances is associated with an increased risk of contrast medium reaction, usually by a lesser amount than a history of asthma. Thus, Shehadi (1975) and Katayama et al. (1990) found a two-fold increase in risk of a reaction and Ansell et al. (1980) a four times increase in risk of a reaction.

Allergy to foodstuffs which contain iodine, e.g., seafood, often causes particular anxiety. However, the available data suggests that allergy to seafood is no more significant than allergy to other foodstuffs (Witten et al. 1973; Shehadi 1975; Leder 1997).

Allergy to topical iodine skin preparations is a type of contact dermatitis and does not seem to predispose to acute idiosyncratic contrast medium reactions (Thomsen and Bush 1998).

3.2.2.5 Drugs

Whether or not β blockers affect the incidence of idiosyncratic contrast medium reactions is controversial. Greenberger et al. (1987) reported that neither β blockers nor calcium antagonists given separately or together increased the risk of reaction. Subsequently, however, Lang et al. (1991) found that β blockers did increase the risk of reaction. It is however agreed that the use of β blockers can impair the response to treatment if a reaction does occur (Thomsen and Bush 1998; Greenberger et al. 1987; Lang et al. 1991).

Patients who are receiving or have received interleukin-2 are at increased risk of adverse events following iodinated contrast media. Some of these adverse events appear to recall the side-effects of interleukin-2 (e.g., fever, nausea, vomiting, diarrhoea, pruritus and rash) (Zukiwski et al. 1990; Fishman et al. 1991; Oldham et al. 1991; Choyke et al. 1992). Reactions are often late, occurring more than one hour after contrast medium, but can occur within the first hour (Choyke et al. 1992).

3.2.3 Prevention of Acute Idiosyncratic Reactions

In any patient at increased risk of contrast medium reaction, especially if there has been a previous reaction to an iodinated contrast agent, the possibility of obtaining the necessary diagnostic information from another test not using iodinated contrast medium (e.g., ultrasonography, magnetic resonance imaging) must be considered. If iodinated contrast medium is still deemed essential the risk of an acute reaction can be reduced by an appropriate choice of contrast medium and premedication.

Since the majority of severe reactions occur within the first 20 min after contrast medium injection (Hartman et al. 1982; Shehadi 1985), patients should remain in the Radiology Department for at least this period. In high-risk subjects, monitoring for the first hour is recommended.

3.2.3.1 Choice of Contrast Medium

The single most important method of reducing the risk of idiosyncratic contrast medium reactions is to use nonionic low osmolality agents which are associated with a four to five times lower risk of reactions (Katayama et al. 1990; Palmer 1988; Wolf et al. 1991; Bettman et al. 1997). In many countries nonionic agents are used for all intravascular administration of contrast material. Where this is not possible, selective use of nonionic agents in patients at increased risk of reaction is recommended (King 1999). The principal categories of increased risk are previous contrast medium reaction, asthma or a history of allergy (Ansell et al. 1980; Witten et al. 1973; Katayama et al. 1990; Morcos et al. 2001). When there has been a previous reaction to nonionic iodinated contrast medium, the use of a different agent is appropriate (Thomsen and Bush 1998).

3.2.3.2 Premedication

3.2.3.2.1 Possible Regimes and Evidence for Their Efficacy

To reduce the incidence of idiosyncratic contrast medium reactions, a variety of premedication regimes have been used. Most frequently steroids with or without additional H1 antihistamines have been recommended, and other drugs, such as ephedrine and H2 antagonists have also been tried.

With ionic agents, there is good evidence that steroids reduce the rate of reactions. In a randomised study of 6763 unselected patients, Lasser et al. (1987) showed a reduction in the incidence of reactions to ionic contrast media from 9% to 6.4% when methylprednisolone was given 12 and 2 h before the contrast agent. In patients who have previously reacted to ionic contrast media, a combination of steroid and H1 antihistamine reduces the repeat reaction rate, estimated to be 16%–35% without premedication (Witten et al. 1973; Shehadi 1975). Greenberger et al. (1984) evaluated 657 procedures in 563 previous reactors using two premedication regimes before ionic contrast media. In patients given prednisone and antihistamine the repeat reaction rate was reduced to 9.0% and the addition of ephedrine further reduced the repeat reaction rate to 3.1%. However, because of anxieties about the possible adverse effects of ephedrine in patients with hypertension or cardiovascular disease, the use of ephedrine has not been widely adopted (Thomsen and Bush 1998). The addition of the H2 antagonist cimetidine to the steroid, antihistamine and ephedrine premedication was associated with a higher risk of reaction (Greenberger et al. 1985). With the ionic low osmolality agent meglumine ioxaglate, Bertrand et al. (1992) found that the antihistamine hydroxyzine reduced the risk of urticaria from 12.5% to 1.0% in 200 subjects.

With the nonionic low osmolality agents there is less evidence about the value of premedication, but the available evidence does indicate that premedication can further reduce the incidence of reactions. In a randomised study of 1155 unselected patients, Lasser et al. (1994) found a statistically significant decrease in the total number of reactions from 4.9 to 1.7% when patients given nonionic contrast media were premedicated with methylprednisolone given 12 and 2 h before the contrast agent. The numbers of moderate and severe reactions were also less after steroids but the numbers were small and no statistically significant difference was found. In previous reactors, Greenberger and Patterson (1991) found that the combined use of a nonionic agent together with both prednisone and antihistamine or prednisone, antihistamine and ephedrine reduced the repeat reaction rate to 0.5% in 181 patients. In patients who had previously reacted, or who had a history of allergy or severe cardiopulmonary disease, H1 and H2 antagonists reduced the reaction rate to 1.57% in 1047 patients, as compared to a reac-

tion rate of 4.37% in those who were not premedicated (Fink et al. 1992).

When steroid premedication is used, the steroids should be given at least 12 h before contrast medium. The minimal effective time interval between steroids and contrast medium is considered unlikely to be less than 6 h (Lasser et al. 1987; Morcos et al. 2001). To be effective, steroids require time to affect the complex processes which underlie anaphylactoid reactions. For example, steroids cause induction of the C1 esterase inhibitor, which affects the production of the mediator bradykinin. The rise in C1 esterase inhibitor levels occurs over a 12-h period (Lasser et al. 1981).

3.2.3.2.2 Controversies

With the ionic agents, the higher risk of reaction and the stronger evidence for the value of premedication meant that steroid premedication was widely recommended and used (Greenberger et al. 1984; Lasser et al. 1987). With the nonionic agents the use of premedication is more controversial and practice is variable (Dawson and Sidhu 1993; Lasser 1994, 1995; Dore et al. 1994 and 1995; Lasser and Berry 1994; Seymour et al. 1994; Cohan et al. 1995; Dawson 2005; Radhakrishnan et al. 2005).

One point of view is that the risk of reaction with nonionic agents is very low and the evidence of the value of steroid premedication not sufficiently strong and therefore that premedication is no longer warranted (Dawson and Sidhu 1993; Dawson 2005).

An alternative point of view is that the admittedly imperfect evidence indicates that steroid premedication further reduces the likelihood of a reaction to nonionic agents (Greenberger and Patterson 1991; Lasser et al. 1994; Lasser 1994; American College of Radiology 2004). Furthermore, high doses of steroids are used in the treatment of anaphylaxis where their effect is attributed to the fact that they stabilise cell membranes and reduce the release of chemical mediators involved in anaphylaxis (Bush and Swanson 1991).

It is not possible to be dogmatic about whether patients at increased risk of reaction should receive steroid premedication before they are given nonionic contrast media. In emergency situations the risk of not undertaking the investigation immediately often outweighs the potential benefit of using steroids. Radiologists may also be influenced by the setting in which they practice. While facilities for resuscitation should be available in all settings where intravascular contrast medium is administered, additional support facilities are more readily available in larger hospitals. The American College of Radiology Manual on Contrast Media (2004) states that the higher the risk of reaction, the stronger the case that can be made for premedication. The European Society of Urogenital Radiology guidelines indicate that opinion on this topic is divided and therefore do not issue a directive.

It must be remember that, even with steroid premedication, reactions to nonionic contrast media still occur, and are commoner in subjects with a history of allergy (Freed et al. 2001).

3.2.3.3 Pretesting and Injection Rate

The practice of pretesting – giving a small preliminary test dose of contrast medium intravenously before the full dose is given – has been shown to be of no value (Shehadi 1975; Fischer and Doust 1972; Yamaguchi et al. 1991). Fischer and Doust (1972) found the mortality after contrast medium was unaffected by pretesting and that deaths could occur following a negative pretest or following the pretest itself. Yamaguchi et al. (1991) found no benefit of pretesting either with ionic or nonionic agents.

Injection rate does not appear to have any effect on the rate of adverse reactions (Jacobs et al. 1998).

3.2.4 Summary: Iodinated Contrast Media

To reduce the risk of an acute reaction to intravascular iodinated contrast media, the important measures for all patients are:

- Use nonionic contrast media.
- Keep the patient in the Radiology Department for 30 min after contrast medium injection.
- Have the drugs and equipment for resuscitation readily available.

There is an increased risk of an acute reaction to intravascular iodinated contrast media in patients with a history of:

- Previous generalised reaction to iodinated contrast medium, either moderate (e.g. urticaria, bronchospasm) or severe (e.g. hypertension, severe bronchospasm, pulmonary oedema, cardiovascular collapse, convulsions).
- Asthma.
- Allergy requiring medical treatment.

In patients with an increased risk of a reaction to intravascular iodinated contrast media:

- Is the use of iodinated contrast medium essential? Would another test (e.g. ultrasonography, magnetic resonance imaging) give the diagnostic information needed?
- Use a different iodinated agent for previous reactors to contrast medium.
- Practice for the use of premedication is variable. It should be considered for previous reactors to iodinated contrast media and high risk patients.

A suitable corticosteroid premedication regime is:

- Prednisolone 30 mg orally (or methylprednisolone 32 mg orally) given 12 and 2 h before contrast medium.
- H2 antihistamines may also be used.

3.3 Gadolinium Contrast Media

3.3.1 Types of Reaction and Frequency

Adverse events following intravenous gadolinium contrast media are less common than following iodinated agents and are usually estimated to occur in less than 5% of patients. The majority of these adverse events are minor and self-limiting (Runge 2000). Only a small proportion of patients develop allergy-like or anaphylactoid reactions. Reactions such as rash, urticaria or bronchospasm have been estimated to occur in 0.004%–0.7% and severe life-threatening anaphylactoid reactions to occur in between 1 in 10,000 and 1 in 300,000 (ACR Manual 2004; Niendorf et al. 1991; Murphy et al. 1996). Anaphylactoid reactions occur within the first 30 min of contrast medium injection (Murphy et al. 1996). Only one fatal reaction definitely attributable to gadolinium has been reported (Jordan and Mintz 1995).

3.3.2 Risk Factors for Reactions

3.3.2.1 Type of Contrast Medium

There appears to be no significant difference between the incidence of reactions with the different gadolinium agents, both ionic and nonionic (Kirchin and Runge 2003).

3.3.2.2 Patient Risk Factors

A previous reaction to gadolinium contrast media was reported to increase the risk of adverse events from 2.4% to 21.3%, and a previous reaction to an iodinated contrast medium to increase the risk to 6.3% (Nelson et al. 1995). A history of asthma or allergy increased the risk to 3.7% in the same series (Nelson et al. 1995).

3.3.3 Prevention of Reactions

No evidence is available in the literature to indicate what measures should be taken to prevent a reaction to gadolinium. The measures to be taken when a patient has previously had a reaction to gadolinium or is considered to be at high risk are therefore based on similar principles to those for iodinated contrast agents (see ACR Manual 2004 and Sect. 3.3.4 below).

3.3.4 Summary: Gadolinium Contrast Media

The risk of an acute reaction to gadolinium contrast media is very low, and much lower than the risk of a reaction to iodinated contrast media. Nonetheless, for all patients the following is recommended:

- Keep the patient in the Radiology Department for 20 min after contrast medium injection.
- Have the drugs and equipment for resuscitation readily available.

The type of contrast medium, ionic or nonionic, does not appear to affect the incidence of reactions to gadolinium agents.

In patients with a previous reaction to a gadolinium agent or who are considered at very high risk:

- Is the use of gadolinium contrast medium essential? Would an unenhanced scan or other test give the diagnostic information needed?
- Choose a different gadolinium agent to that used before in previous reactions.
- Consider premedication.

A suitable corticosteroid premedication regime is:

- Prednisolone 30 mg (or methylprednisolone 32 mg) orally given 12 and 2 h before contrast medium.
- H2 antihistamines may also be used.

References

ACR Committee on Drugs and Contrast Media (2004) Manual on contrast media, 5th edn. American College of Radiology, Reston, VA

Almen T (1994) The etiology of contrast medium reactions. Invest Radiol 19 [Suppl]:S37–S45

Ansell G, Tweedie MCK, West CR et al (1980) The current status of reactions to intravenous contrast media. Invest Radiol 15 [Suppl]:S32–S39

Bertrand PR, Soyer PM, Rouleau PJ et al (1992) Comparative randomised double-blind study of hydroxyzine versus placebo as premedication before injection of iodinated contrast media. Radiology 184:383–384

Bettman MA, Heeren T, Greenfield A, Gondey C (1997) Adverse events with radiographic contrast agents: results of the SCVIR Contrast Agent Registry. Radiology 203:611–620

Bush WH, Swanson DP (1991) Acute reactions to intravascular contrast media: types, risk factors, recognition and specific treatment. AJR Am J Roentgenol 157:1153–1161

Caro JJ, Trindade E, McGregor M (1991) The risks of death and severe nonfatal reactions with high-vs low- osmolality contrast media: a meta-analysis. AJR Am J Roentgenol 156:825–832

Choyke PL, Miller Dl, Lotze MT et al (1992) Delayed reactions to contrast media after interleukin-2 immunotherapy. Radiology 183:111–114

Cochran ST, Bomyea K, Sayre JW (2001) Trends in adverse events after iv administration of contrast media. AJR Am J Roentgenol 176:1385–1388

Cohan RH, Ellis JH, Dunnick NR (1995) Use of low-osmolar agents and premedication to reduce the frequency of adverse reactions to radiographic contrast media: a survey of the Society of Uroradiology. Radiology 194:357–364

Dawson P (2005) Commentary: repeat survey of current practice regarding corticosteroid prophylaxis for patients at increased risk of adverse reaction to intravascular contrast agents. Clin Radiol 60:56–57

Dawson P, Sidhu PS (1993) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 48:225–226

Dore CJ, Sidhu PS, Dawson P (1994) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 49:583–584

Dore CJ, Sidhu PS, Dawson P (1995) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 50:198–199

Fink U, Fink BK, Lissner J (1992) Adverse reactions to nonionic contrast media with special regard to high-risk patients. Eur Radiol 2:317–321

Fischer HW, Doust VL (1972) An evaluation of pretesting in the problem of serious and fatal reactions to excretory urography. Radiology 103:497–501

Fishman JE, Aberle DR, Moldawer NP et al (1991) Atypical contrast reactions associated with systemic interleukin-2 therapy. AJR Am J Roentgenol 156:833–834

Freed KS, Leder RA, Alexander C et al (2001) Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. AJR Am J Roentgenol 176:1389–1392

Greenberger PA, Patterson R (1991) The prevention of immediate generalised reactions to radiocontrast media in high-risk patients. J Allergy Clin Immunol 87:867–872

Greenberger PA, Patterson R, Radin RR (1984) Two pre-treatment regimens for high-risk patients receiving radiographic contrast media. J Allergy Clin Immunol 74:540–543

Greenberger PA, Patterson R, Tapio CM (1985) Prophylaxis against repeated radiocontrast media reactions in 857 cases. Arch Intern Med 145:2197–2200

Greenberger PA, Meyers SN, Kramer BL et al (1987) Effects of beta-adrenergic and calcium antagonists on the development of anaphylactoid reactions from radiographic contrast media. J Allergy Clin Immunol 80:698–702

Hartman GW, Hattery RR, Witten DM, Williamson B (1982) Mortality during excretory urography: Mayo Clinic experience. AJR Am J Roentgenol 139:919–922

Jacobs JE, Birnbaum BA, Langlotz CP (1998) Contrast media reactions and extravasation: relationship to intravenous injection rates. Radiology 209:411–416

Jordan RM, Mintz RD (1995) Fatal reaction to gadopentetate dimeglumine. AJR Am J Roentgenol 164:734–744

Katayama H, Yamaguchi K, Kozuka T et al (1990) Adverse reactions to ionic and nonionic contrast media. Radiology 175:621–628

King BF (1999) Intravascular contrast media and premedication. In: Bush WH, Krecke KN, King BF, Bettman MA (eds) Radiology life support (RAD-LS): a practical approach. Arnold, London/University Press, New York, p 15

Kirchin MA, Runge VM (2003) Contrast agents for magnetic resonance imaging: safety update. Top Magn Reson Imaging 14:426–435

Lang DM, Alpern MB, Visintainer PF, Smith ST (1991) Increased risk for anaphylactoid reaction from contrast media in patients on β-adrenergic blockers or with asthma. Ann Intern Med 115:270–276

Lasser EC (1985) Etiology of anaphylactoid responses: the promise of nonionics. Invest Radiol 20 [Suppl]:S79–S82

Lasser EC (1987) A coherent biochemical basis for increased reactivity to contrast material in allergic patients: a novel concept. AJR Am J Roentgenol 149:1281–1285

Lasser EC (1994) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 49:582–583

Lasser EC (1995) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 50:199

Lasser EC, Berry CC (1994) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 49:584

Lasser EC, Lang JH, Lyon SG (1981) Glucocorticoid-induced elevations of C1-esterase inhibitor: a mechanism for protection against lethal dose range contrast challenge in rabbits. Invest Radiol 16:20–23

Lasser EC, Berry CC, Talner LB et al (1987) Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. N Engl J Med 317:845–849

Lasser EC, Berry CC, Mishkin MM et al (1994) Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. AJR Am J Roentgenol 162:523–526

Lasser EC, Lyon SG, Berry CC (1997) Reports on contrast media reactions: analysis of data from reports to the US Food and Drug Administration. Radiology 203:605–610

Leder R (1997) Letter. AJR Am J Roentgenol 169:906–907
Morcos SK, Thomsen HS, Webb JAW et al (2001) Prevention of generalised reactions to contrast media: a consensus report and guidelines. Eur Radiol 11:1720–1728
Murphy KJ, Brunberg JA, Cohan RH (1996) Adverse reactions to gadolinium contrast media: a review of 36 cases. AJR Am J Roentgenol 167:847–849
Nelson KL, Gifford LM, Lauber-Huber C et al (1995) Clinical safety of gadopentetate dimeglumine. Radiology 196:439–443
Niendorf HP, Haustein J, Cornelius I et al (1991) Safety of gadolinium-DTPA: extended clinical experience. Magn Reson Med 22:222–228
Oldham RK, Brogley J, Braud E (1991) J Clin Oncol 8:942–943
Palmer FJ (1988) The RACR survey of intravenous contrast media reactions: final report. Austr Radiol 32:426–428
Radhakrishnan S, Manoharan S, Fleet M (2005) Repeat survey of current practice regarding corticosteroid prophylaxis for patients at increased risk of adverse reaction to intravascular contrast agents. Clin Radiol 60:58–63
Runge VM (2000) Safety of approved MR contrast media for intravenous injection. J Magn Reson Imaging 12:205–213
Seymour R, Halpin SF, Hardman JA et al (1994) Corticosteroid prophylaxis in patients with increased risk of adverse reactions to intravascular contrast agents: a survey of current practice in the UK. Clin Radiol 49:791–795
Shehadi WH (1975) Adverse reactions to intravascularly administered contrast media. AJR Am J Roentgenol 124:145–152
Shehadi WH (1985) Death following intravascular administration of contrast media. Acta Radiol Diagn 26:457–461
Siegle RL, Halvorsen RA, Dillon J et al (1991) The use of iohexol in patients with previous reactions to ionic contrast material. Invest Radiol 26:411–416
Thomsen HS, Bush WH (1998) Adverse effects of contrast media: incidence, prevention and management. Drug Safety 19:313–324
Witten DM, Hirsch FD, Hartman GW (1973) Acute reactions to urographic contrast medium. AJR Am J Roentgenol 119:832–840
Wolf GL, Miskin MM, Roux SG et al (1991) Comparison of the rates of adverse drug reactions: ionic contrast agents, ionic agents combined with steroids and nonionic agents. Invest Radiol 26:404–410
Yamaguchi K, Katayama H, Takashima T et al (1991) Prediction of severe adverse reactions to ionic and nonionic contrast media in Japan: evaluation of prestesting. Radiology 178:363–367
Zukiwski AA, David CL, Coan J et al (1990) Increased incidence of hypersensitivity to iodine-containing radiographic contrast media after interleukin-2 administration. Cancer 65:1521–1524

4 Management of Acute Adverse Reactions to Contrast Media

Henrik S. Thomsen

CONTENTS

4.1 Introduction

Improvements in the physico-chemical properties of contrast medium molecules have been followed by a significant decrease in the frequency of acute adverse reactions (Pollack 1999; Thomsen and Morcos 2000). Nevertheless, serious reactions still may occur and remain a source of concern. A local audit in Australia demonstrated deficient acute management of anaphylactoid/anaphylactic reactions in radiology departments by both consultants and trainees (Bartlett and Bynevelt 2003). A poorly managed resuscitation situation and adverse outcome will be costly to practice as well as the individual in terms of financial loss and professional respect. All radiologists should be prepared to give immediate treatment for acute contrast medium reactions. Thus first line management should be simple and suitable for the current era when acute adverse reactions are rare. The subsequent management of severe adverse reactions including administration of second line drugs should be handled by the resuscitation team.

H. S. Thomsen, MD
Professor, Department of Diagnostic Radiology, Copenhagen University Hospital at Herlev, 2730 Herlev, Denmark

4.2 Risk Factors

A history of previous moderate or severe adverse reaction to contrast media is an important risk factor (Morcos et al. 2001; Katayama et al. 1990). In Katayama et al.'s (1990) series of over 330,000 patients there was a six-fold increase in reactions to both ionic and nonionic contrast media following a previous severe adverse reaction. Asthma is also an important risk factor with a reported six- to ten-fold increase in the risk of a severe reaction in such patients (Katayama et al. 1990). Patients treated with interleukin-2 are at increased risk of adverse reactions to contrast media whereas whether or not β-adrenergic blockers affect the incidence of idiosyncratic contrast medium reactions is controversial (Lang et al. 1991, 1993; Vervloet and Durham 1998; Taylor 1998; Fishman et al. 1991; Oldham et al. 1990; Choyke et al. 1992; Greenberger et al. 1987). Greenberger et al. (1987) reported that neither β-blockers nor calcium antagonists given separately or together increased the risk of reaction. Subsequently, however, Lang et al. (1991, 1993) found that β-blockers did increase the risk of reaction. Today, β-adrenergic blockers are seldom stopped before giving intravascular contrast medium (Morcos et al. 2001).

In patients who have had a previous severe reaction to contrast medium, most radiologists avoid giving intravascular contrast media if at all possible (Morcos et al. 2001). If the examination is considered essential, nonionic contrast media are the agents of choice based on the evidence in the literature that with nonionic agents the risk of reaction is reduced by a factor of four to five (Katayama et al. 1990). The potential risks of the procedure should be explained to the patient, and the resuscitation team should be present when the contrast medium is given (Morcos et al. 2001).

4.3 Acute Adverse Reactions

An acute adverse reaction is defined as an adverse event that occurs within 60 min of an injection of contrast medium. Reactions can be divided into mild, moderate and severe. The mild reactions include flushing, nausea, arm pain, pruritus, vomiting, headache, and mild urticaria. They are usually of short duration, self-limiting and generally require no specific treatment. Moderate reactions include more serious degrees of the above symptoms and/or moderate degrees of hypotension and bronchospasm. They usually respond readily to appropriate treatment. Severe life-threatening reactions include severe manifestations of all of the symptoms included under mild and moderate reactions in addition to symptoms such as convulsions, unconsciousness, laryngeal edema, pulmonary edema, cardiac dysrhythmias and arrest, cardiovascular and pulmonary collapse (Grainger 1997).

4.4 Incidence

Mild adverse reactions are encountered in as many as 15% of patients after intravenous ionic high-osmolar contrast media agents (1000-2000 mOsm/kg H_2O) and up to 3% of patients after nonionic low-osmolality contrast media (500-1000 mOsm/kg H_2O). Severe and very severe reactions occur much less frequently with an incidence of 0.22% and 0.04% (respectively) in patients after intravenous high osmolar contrast media and 0.04% and 0.004% in patients after low-osmolality contrast media. Thus, the incidence of contrast reactions with low-osmolar contrast media is lower than with high-osmolar contrast media by a factor of five for mild reactions and a factor of ten for severe reactions. Fatal reactions to both types of contrast media are exceedingly rare (1:170,000) with no difference in mortality reported between the two agents (Katayama et al. 1990; Thomsen and Dorph 1993; Thomsen and Bush 1998).

4.5 Mechanisms and Pathophysiology

Adverse reactions to drugs are generally classified into those that occur only in susceptible subjects and those that may occur in anyone. Reactions occurring in susceptible subjects include drug intolerance (low threshold to the normal pharmacological action of a drug), drug idiosyncrasy (a genetically determined, qualitatively abnormal reaction to a drug related to metabolic or enzyme deficiency), drug allergy (an immunologically mediated reaction, characterized by specificity, prior exposure, transferability by antibodies or lymphocytes and recurrence on re-exposure), and pseudoallergic reactions which are the same as allergic reactions but are lacking immunological specificity (non-specific complement activation and non specific histamine release mimicking type 1 allergic reactions) (Stacul 1999).

Although some reactions are difficult to categorize, the majority of non-renal side effects of intravascular contrast media are considered idiosyncratic or pseudoallergic reactions. They are unpredictable, not dose dependent and may involve the release of histamine and other active biological mediators such as serotonin, prostaglandins, bradykinin, leukotrienes, adenosine and endothelin (Almen 1994). Activation and inhibition of several enzyme systems have also been implicated. There is no conclusive evidence to indicate that reactions to iodinated contrast media are allergic in nature since antibodies against contrast media including IgE have not been consistently demonstrated (Almen 1994; Siegle 1999; Laroche et al. 1998).

Chemotoxic-type effects may also occur and are determined by dose, the molecular toxicity of each agent and the physiological characteristics of the contrast agents (i.e. osmolality, viscosity, hydrophilicity, affinity to proteins, calcium binding properties and sodium content). Chemotoxic effects of iodinated contrast media are more likely to occur in patients who are debilitated or medically unstable. High osmolality (osmotoxicity) causes shift of

fluids from the intracellular to extracellular space leading to cell dehydration and an increase in intracellular fluid viscosity precipitating cellular dysfunction (Almen 1994; Siegle 1999). Low hydrophilicity may reduce the biological tolerance to iodinated contrast media since it is associated with an increase in lipophilicity and higher affinity of the contrast medium molecule to plasma proteins and cell membrane. High hydrophilicity of nonionic contrast media is produced by hydroxyl (-OH) groups which are symmetrically distributed thereby offering a good coverage of the benzene ring and restricting access to lipophilic areas of the iodinated contrast molecule (Almen 1994; Siegle 1999; Bonnemann et al. 1990).

4.6 Treatment

The vast majority of patients with severe anaphylactoid-type reactions recover if they are treated quickly and appropriately. Most patients have reactions while they are still in the radiology department and 94%-100% of severe and fatal reactions occur within 20 min of the contrast medium injection (Shehadi 1985). The ability to assess and treat the contrast reaction effectively is an essential skill that the radiologist should have and maintain. The first line drugs and equipment should be readily available in rooms in which contrast material is injected and a list of recommended drugs and equipment is given in the Appendix. A recent survey has shown that most departments have these items available (Morcos et al. 2001).

The radiologist should remain nearby for at least the first critical minutes following contrast injection and should remain in the immediate vicinity for the next 30–45 min. If there is an increased risk of an adverse reaction venous access should be left in place.

Important first line management includes establishment of an adequate airway, oxygen supplementation, administration of intravascular physiological fluids, and measuring the blood pressure and heart rate. Talking to the patient as you check their pulse rate provides useful initial information: breathing is assessed, the possibility of a vagal reaction (bradycardia) is determined, and a rough estimate of systolic pressure is obtained (a palpable radial artery pulse approximates a systolic pressure of 80-90 mm Hg).

4.6.1 Drugs, Fluid and Oxygen

The first line drugs and most important emergency equipment (see Appendix) should be available either in or just outside the room where contrast media are given.

4.6.1.1 Oxygen

Oxygen by mask at relatively high rate (6-10 l/min) is very important in the initial treatment of all severe reactions to intravascular contrast media and for other emergencies unrelated to contrast media that occur in the radiology department or angiography suite (e.g. vagal reaction, hypotension, cardiac ischemia). Hypoxia can be a major complicating factor in all these situations, and can be induced by drugs such as adrenaline used for treating reactions. A ”non-rebreather” mask is optimal; nasal ”prongs” are much less effective and should be avoided in acute situation for preventing hypoxemia. Oxygen should be used for all patients; a history of chronic obstructive pulmonary disease or emphysema is not a contraindication to starting oxygen therapy for an acute reaction.

4.6.1.2 Intravascular Fluid Administration

Intravascular fluid administration is very important and it alone has been reported to be the most effective treatment for hypotension (van Sonnenberg et al. 1987). Starting intravenous fluid early before drug treatment is the highest priority in treating hypotension.

4.6.1.3 Adrenaline

Adrenaline is an effective drug for treating certain serious contrast reactions. The α-agonist effects of adrenaline increase blood pressure and reverse peripheral vasodilatation. The vasoconstriction induced decreases angioedema and urticaria. The β-agonist actions of adrenaline reverse bronchoconstriction, produce positive inotropic and chronotropic cardiac effects (increase in strength and rate of cardiac contractions), and may increase intracellular cyclic adenosine monophosphate (AMP) (Smith

and Corbascio 1970; Hoffman and Lefkowitz 1990). Increments in baseline cyclic AMP levels are generally considered to inhibit mediator release from inflammatory cells.

The use of adrenaline demands careful attention (Bush and Swanson 1991). For example, in individuals with a fragile intracerebral or coronary circulation, the α-agonist effects of a *large* dose of adrenaline may provoke a hypertensive crisis that could produce a stroke or myocardial ischemia (Barach et al. 1984). β-Receptor sites usually respond to lower doses of adrenaline than α-sites, but if a patient is on β-blockers, the refractory response that may occur might encourage the radiologist to increase the dose of adrenaline to the point that there were unwanted α-effects. Patients with chronic asthma may simulate patients receiving β-blockers since they may have a systemic β-adrenergic hyporesponsiveness. When chronic asthmatics develop an anaphylaxis-like reaction with asthmatic symptoms requiring β-receptor stimulation, one option is to use isoproterenol as the primary adrenergic drug, combined with more conservative doses of adrenaline (Ingall et al. 1984; Bush 1996).

When possible adrenaline should be avoided for treating the pregnant patient with a severe contrast reaction and hypotension (Entman and Moise 1984). Because uterine vessels are sensitive the α-effect of adrenaline, the combination of hypotension plus adrenaline can cause harmful sequelae to the fetus. Ephedrine is a possible alternative.

Only one concentration (1:1000) of adrenaline should be available in the radiology department to avoid confusion under stressful emergency conditions, where ampoules of different concentrations can be misidentified. The 1:1000 preparation should be given intramuscularly only. Intravenous administration of adrenaline by non experienced staff can be dangerous. Furthermore dilution of adrenaline for intravenous use is time consuming and delays treatment. Only 43% of the participants in an Australian audit knew the recommended dose of adrenaline (Bartlett and Bynevelt 2003). This enforces the need of a standard dose such as 0.5 mg in adults (see Appendix).

4.6.1.4
H2 Antihistamines and H2 Receptor Blockers

H2 antihistamines and H2 receptor blockers have a limited role in treating contrast media reactions. They are used primarily to reduce symptoms from skin reactions.

4.6.1.5
Corticosteroids

High-dose intravenous corticosteroids do not play a role in the first line treatment of the acute adverse reaction. However, very high doses of corticosteroids may have an immediate stabilizing effect on cell membranes and may be used in the second line treatment. Standard doses can be effective in reducing delayed recurrent symptoms, which can be observed for as long as 48 h after an initial reaction. It takes 6 h before corticosteroids are fully active (Lasser et al. 1977; Gillenberger et al. 1986).

4.6.1.6
Inhaled β-2-Adrenergic Agonists

Inhaled β-2-adrenergic agonists such as albuterol, metaproterenol, and terbutaline deliver large doses of bronchodilating β-2-agonist drugs directly to the airways with minimal systemic absorption and therefore, minimal cardiovascular effects.

4.6.1.7
Atropine

Atropine blocks vagal stimulation of the cardiac conduction system. Large doses of atropine (0.6-1.0 mg) are indicated, since low doses (e.g. less than 0.5 mg) of atropine can be detrimental for treating bradycardia associated with contrast media-induced vagal reactions (Bush and Swanson 1991; Chamberlain et al. 1967; Stanley and Pfister 1976; Brown 1990; Bush et al. 1993).

4.6.2
Treatment of Specific Reactions

4.6.2.1
Nausea and Vomiting

Nausea and vomiting, though usually self-limited, may be the first signs of a more severe reaction. With urography using ionic high-osmolar contrast media, 15%-20% of fatal reactions began with nausea and vomiting (Lalli 1980). For this reason, the patient should be observed closely for systemic symptoms, while intravenous access is maintained. The injection should be slowed or stopped. In severe, pro-

tracted cases, injection of an anti-emetic may be used (see Appendix).

4.6.2.2 Cutaneous Reactions

Treatment is usually not necessary if there are only a few scattered hives or pruritus. However, the patient should be observed closely for other systemic symptoms which may develop and intravenous access should be maintained. Treatment be given only if the urticaria is extensive or bothersome to the patient (see Appendix).

4.6.2.3 Bronchospasm

Bronchospasm without co-existing cardiovascular problems should be treated with oxygen and inhaled bronchodilators (see Appendix). Using a metered dose inhaler, treatment typically involves two to three deep inhalations. Adrenaline may be used if bronchospasm is not relieved by the inhaled bronchodilators.

4.6.2.4 Laryngeal Edema

Laryngeal edema does not respond well to inhaled β-agonists and these agents may actually worsen it. Therefore, careful clinical evaluation of the patient before beginning treatment is extremely important to differentiate laryngeal edema from bronchospasm. Adrenaline is the primary treatment for laryngeal edema (see Appendix). Oxygen supplementation is also important in the management of this condition.

4.6.2.5 Hypotension

Profound hypotension may occur without respiratory symptoms. Normal sinus rhythm and tachycardia differentiate this reaction from the so-called vagal reaction (hypotension plus sinus bradycardia). Initially, the patient's legs should be elevated since this returns about 700 ml of blood to the central circulation (van Sonnenberg et al. 1987). Isolated hypotension is best treated first by rapid intravenous fluid replacement rather than vasopressor drugs (see Appendix). A total volume of up to 3000 ml may be required to reverse the hypotension.

4.6.2.6 Vagal Reaction

Vagal reactions are characterized by the combination of prominent sinus bradycardia (pulse rate <60 beats per min.) and hypotension (systolic pressure <80 mmHg). Although their exact cause is unknown, vagal reactions seem to be elicited or accentuated by anxiety. Proper recognition of this reaction and the associated bradycardia is vital so that the correct treatment of increasing intravascular fluid volume plus reversing the vagal stimulation is used. Elevation of the patient's legs and rapid infusion of intravenous fluids treat the vasodilatation and expanded vascular space. The bradycardia is treated by intravenous administration of atropine to block vagal stimulation of the cardiac conduction system (see Appendix).

4.6.2.7 Generalized Anaphylactoid Reactions

These are acute, rapidly progressing, systemic reactions characterized by multisystem involvement with pruritus, urticaria, angioedema, respiratory distress (bronchospasm and/or laryngeal edema), and profound hypotension that require prompt response. Initial treatment includes maintenance of the airway, administration of oxygen, rapid infusion of intravenous fluids, and administration of adrenergic drugs (see Appendix). Adrenaline is the drug of choice. Intramuscular injection of 0.5 ml of 1:1000 adrenaline preparation is recommended in preference to intravenous administration, which requires careful ECG monitoring and slow administration, ideally by people experienced in its use. According to the Project Team of the Resuscitation Council in the United Kingdom, adrenaline 1:1000 should never be used intravenously because of the risk of arrhythmia, and subcutaneous administration is not helpful in acute life threatening situations (Project Team of the Resuscitation Council (UK) 1999; Hughes and Fitzharris 1999).

Hypoxia increases the risk of severe cardiac arrhythmias. Also, the amount of adrenaline should be limited in patients who are receiving noncardioselective β-blocking medications (e.g. propranolol)

as discussed above. Adrenaline should be avoided, if possible, in the pregnant patient experiencing an anaphylactoid reaction with hypotension. When adrenaline is contraindicated, bronchospasm can be treated with a β-2 agonist inhaler (β-2 with no α-effects).

4.7 Be Prepared

Prompt recognition and treatment can be invaluable in blunting an adverse response of a patient to radiographic contrast material and may prevent a reaction from becoming severe or even life-threatening. Radiologists and their staff should review treatment protocols regularly (e.g. at 6-12 monthly intervals) so that each can accomplish his or her role efficiently (Bush and Swanson 1991; Gillenberger et al. 1986; Bush et al. 1993; Cohan et al. 1996; Emergenct Cardiac Care Committee and Subcommittes 1992; Bartlett and Bynevelt 2003; Berden et al. 1993). Knowledge, training, and preparation are crucial for guaranteeing appropriate and effective treatment if there is an adverse contrast-related event.

References

Almen T (1994) The etiology of contrast medium reactions. Invest Radiol 29 [Suppl]:S37-S45

Barach EM, Nowak RM, Tennyson GL, Tomlanovich MC (1984) Epinephrine for treatment of anaphylactic shock. JAMA 251:2118-2122.

Bartlett MJ, Bynevelt M (2003) Acute contrast reaction management by radiologists: a local audit study. Austr Radiol 47:363-367

Berden HJJM, Willems FF, Hendrick JMA, Pijls NH, Knape JT (1993) How frequently should basic cardiopulmonary resuscitation training be repeated to maintain adequate skills? Br J Med 306:1576-1577

Bonnemain B, Meyer D, Schaffer M, Dugast-Zrihen M (1990) New iodinated low osmolar contrast media. A revised concept of hydrophilicity. Invest Radiol 25 [Suppl]: S104-S106

Brown JH (1990) Atropine, scopolamine and antimuscarinic. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds) The pharmacological basis of therapeutics. Pergamon/McGraw-Hill, New York, pp 150-165

Bush WH (1996) Risk factors, prophylaxis and therapy of X-ray contrast media reactions. Adv X-Ray Contrast 3:44-53

Bush WH, Swanson DP (1991) Acute reactions to intravascular contrast media: types, risk factors, recognition, and specific treatment. AJR Am J Roentgenol 157:1153-1161

Bush WH, McClennan BL, Swanson DP (1993) Contrast media reactions: prediction, prevention, and treatment. Postgrad Radiol 13:137-147

Chamberlain DA, Turner P, Sneddon JM (1967) Effects of atropine on heart-rate in healthy man. Lancet 2:12-15

Choyke PL, Miller DL, Leder MT et al (1992) Delayed reactions to contrast media after interleukin-2 immunotherapy. Radiology 183:111-114

Cohan RH, Leder RA, Ellis JH (1996) Treatment of adverse reactions to radiographic contrast media in adults. Radiol Clin North Am 34:1055-1060

Emergency Cardiac Care Committee and Subcommittess (1992) American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care, III: Adult Advanced Cardiac Life Support. JAMA 268:2199-2241

Entman SS, Moise KJ (1984) Anaphylaxis in pregnancy South Med J 77:402

Fishman J, Aberle D, Moldawer N et al (1991) Atypical contrast reactions associated with systemic interleukin-2 therapy. AJR Am J Roentgenol 156:833-834

Gillenberger PA, Halwig TM, Patterson R et al (1986) Emergency administration of a radiocontrast media in high risk patients. J Allergy Clin Immunol 77:630-635

Grainger RG (1997) Intravascular contrast media. In: Grainger RG, Allison D (eds) Grainger and Allison's diagnostic radiology: a textbook of medical imaging. Churchill Livingstone, New York, pp 40-41

Greenberger PA, Meyers SN, Kramer BL et al (1987) Effects of beta-adrenergic and calcium antagonists on the development of anaphylactoid reactions from radiographic contrast media. J Allergy Clin Immunol 80:698-702

Hoffman BB, Lefkowitz RJ (1990) Catecholamines and sympathomimetic drugs. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds) The pharmacological basis of therapeutics. Pergamon/McGraw-Hill, New York, pp 192-198

Hughes G, Fitzharris P (1999) Managing acute anaphylaxis, new guidelines emphasize importance of intramuscular adrenaline. Br Med J 319:1-2

Ingall M, Goldman G, Page LB (1984) Beta-blockade in stinging insect anaphylaxis (letter). JAMA 251:1432

Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K (1990) Adverse reactions to ionic and nonionic contrast media. Radiology 175:621-628

Lalli AF (1980) Contrast media reactions: data analysis and hypothesis. Radiology 134: 1-12

Lang DM, Alpern MB Visintainer PF, Smith ST (1991) Increased risk for anaphylactoid reaction from contrast media in patients on β-adrenergic blockers with asthma. Ann Intern Med 115:270-276

Lang DM, Alpern MB, Visintainer PF, Smith ST (1993) Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. Arch Intern Med 153:2033-2040 (Erratum in: Arch Intern Med 1993, 153:2412)

Laroche D, Aimone-Gastin I, Dubois F et al (1998) Mechanisms of severe, immediate reactions to iodinated contrast material. Radiology 209:183-190

Lasser EC, Lang JH, Sovak M et al (1977) Steroids: theoretical and experimental basis for utilization in prevention of contrast media reactions. Radiology 125:1-9

Morcos SK, Thomsen HS, Webb JAW (2001) Prevention of generalized reactions to contrast media: a consensus report and guidelines. Eur Radiol 11:1720-1728

Oldham R, Biogley J, Braud E (1990) Contrast media "recalls" interleukin-2 toxicity (letter to the editor). J Clin Oncol 8:942

Pollack HM (1999) History of iodinated contrast media. In: Thomsen HS, Muller RN, Mattrey RF (eds) Trends in contrast media. Springer, Berlin Heidelberg New York, pp 1-19

Project Team of the Resuscitation Council (UK) (1999) Emergency medical treatment of anaphylactic reactions. J Accid Emerg Med 16:243-247

Shehadi WH (1985) Death following intravascular administration of contrast media. Acta Radiol Diagn 26:457-461

Siegle RL (1999) Mechanisms of reactions to contrast media. In: Dawson P, Cosgrove DO, Grainger RG (eds) Textbook of contrast media. Isis Medical Media, Oxford, pp 95-98

Smith NT, Corbascio A (1970) The use and misuse of pressor agents. Anesthesiology 33:58-101

Stacul F (1999) Currently available iodinated contrast media. In: Thomsen HS, Muller RN, Mattrey RF (eds) Trends in contrast media. Springer, Berlin Heidelberg New York, pp 71-72

Stanley RJ, Pfister RC (1976) Bradycardia and hypotension following use of intravenous contrast media. Radiology 121:5-7

Taylor AJN (1998) Asthma and allergy. BMJ 316:997-999

Thomsen HS, Bush WH Jr (1998) Adverse effects of contrast media. Incidence, prevention and management. Drug Safety 19:313-324

Thomsen HS, Dorph S (1993) High-osmolar and low-osmolar contrast media. An update on frequency of adverse drug reactions. Acta Radiol 34:205-209

Thomsen HS, Morcos SK (2000) Radiographic contrast media. BJU Int 86 [Suppl 1]:1-10

Van Sonnenberg E, Neff CC, Pfister RC (1987) Life-threatening hypotensive reactions to contrast administration: comparison of pharmacologic and fluid therapy. Radiology 162:15-19

Vervloet D, Durham S (1998) ABC of allergies. Adverse reactions to drugs. BMJ 316:1511-1514

5 Late Adverse Reactions to Intravascular Iodinated Contrast Media

Fulvio Stacul

CONTENTS

5.1 Introduction

Late adverse reactions to intravascular iodinated contrast media are defined as reactions occurring between 1 h and 1 week after contrast medium injection. They were first recognized in the mid-1980s (Panto and Davies 1986) and since then have been widely studied, particularly reactions to low osmolality contrast media. However, many aspects remain controversial and there is widespread uncertainty among radiologists about the incidence, significance and management of late reactions.

5.2 Reaction Type and Severity

In reports of late reactions, the symptoms most commonly described are headache, skin rash, itching, nausea, dizziness, urticaria, fever, arm pain and gastrointestinal disturbances. When late reactions to enhanced and unenhanced CT were compared, only the skin reactions occurred more frequently in the group who received contrast medium (nonionic monomer or dimer) (Schild 1996; Yasuda and Munechika 1998) and skin reactions appear to account for the majority of true late reactions. The types of late skin reactions and their relative frequencies are similar to those which occur with many other drugs (Bigby et al. 1986). Maculopapular rash is observed in more than 50% of affected patients (Hosoya et al. 2000). Other frequently occurring skin reactions are angioedema, urticaria, erythema, macular exanthema and scaling skin eruption (Bigby et al. 1986; Christiansen et al. 2000; Kanny et al. 2005; Rydberg et al. 1998; Sutton et al. 2001, 2003; Vernassiere et al. 2004).

In most cases the skin reactions are mild or moderate, i.e. they may cause discomfort and may require specific treatment (steroids, antihistamines, topical emollients) (Hosoya et al. 2000; Munechika et al. 2003; Rydberg et al. 1998; Sutton et al. 2001, 2003). Depending on their site, these reactions cause more or less disturbance to the patient, the most troublesome being those affecting to the palms, soles of the feet or face (Sutton et al. 2001). Severe delayed reactions needing hospital treatment and/or leading to persistent disability or death have been reported, but are very rare. In the eight cases Christiansen et al. (2000) collected from the literature, four had underlying serious medical conditions (Goodfellow et al. 1986; Reynolds et al. 1993; Sadi et al. 1995; Savill et al. 1988) and there are only a few other case reports of serious reactions (Atasoy et al. 2003; Conroy et al. 1994; Lafitte et al. 2004; Rosado et al. 2001; Vavricka et al. 2002).

A number of pathophysiological mechanisms have been proposed for late skin reactions. Although the pathogenesis is still not fully understood, it appears that many are type IV hypersensitivity reactions, i.e. they are T-cell mediated (Brockow et al. 2005; Christiansen et al. 2000; Christiansen 2002). The skin reactions often show typical features of late hypersensitivity including exanthematous rash, positive skin tests and lymphocyte rich dermal perivascular infiltrate sometimes accompanied by eosinophils on skin biopsy.

F. Stacul, MD
Institute of Radiology, Ospedale di Cattinara, 34149 Trieste, Italy

If there is doubt about whether contrast medium is responsible for the skin reaction, skin testing (patch and delayed intradermal tests) may be attempted (Akiyama et al. 1998; Brockow et al. 1999, 2005; Courvoisier and Bircher 1998; Gall et al. 1999; Kanny et al. 2001; Schick et al. 1996; Sedano et al. 2001; Watanabe et al. 1999). However, the low negative predictive value of such tests should be borne in mind (Brockow et al. 2005; Vernassiere et al. 2004). Moreover, it remains to be established if skin testing is also a suitable tool for selection of an alternative contrast medium (Brockow et al. 2005).

5.3 Frequency

Determining the true frequency of late adverse reactions to contrast media from the literature is difficult. First, a variety of different methodologies have been used, with different methods of data collection (questionnaires, patient interviews in person or by phone), different start points (at a variety of times from 30 min after contrast medium injection) and different data collection periods (from 1–7 days).

A further problem is the fact that the greater the time interval between the contrast medium injection and the onset of symptoms, the more difficult it is to be sure that the symptoms are contrast medium-induced. This has been highlighted by studies of "background noise" by several investigators who have shown a high incidence of late symptoms after radiological investigations not using contrast medium. In one study late adverse reactions occurred in 12.4% of patients who had contrast medium enhanced CT, and in 10.3% who had unenhanced CT (Yasuda and Munechika 1998), and in another study approximately 50% of late adverse reactions were found to be unrelated to contrast media (Beyer-Enke and Zeitler 1993). Ueda et al. (2001) reported late reactions in 8.4% of patients having enhanced CT, and in 7.9% having plain CT. Schild (1996) reported more late adverse reactions following plain CT than enhanced CT, with the exception of skin reactions which were more common after enhanced CT.

The frequency of late adverse reactions to nonionic monomers has been reported to be between 0.52% and 23% (Bartolucci et al. 2000; Choyke et al. 1992; Cochran et al. 1993; Higashi and Katayama 1990; Hosoya et al. 2000; Mikkonen et al. 1995; Munechika et al. 2003; Pedersen et al. 1998; Rydberg et al. 1998; Ueda et al. 2001; Yasuda and Munechika 1998; Yoshikawa 1992). Several studies suggest that the incidence in the 1- to 24-h period is 4% or less (Beyer-Enke and Zeitler 1993; Choyke et al. 1992; Pedersen et al. 1998) and in four large studies the frequency of late skin reactions was 1%–3% over a period of 7 days (Hosoya et al. 2000; Munechika et al. 1999; Rydberg et al. 1998; Yasuda and Munechika 1998). There do not appear to be significant differences in the incidence of late reactions between ionic and nonionic agents (McCullough et al. 1989; Panto and Davies 1986; Pedersen et al. 1998; Yamaguchi et al. 1992), nor between the different nonionic monomers (Panto and Davies 1986; Pedersen et al. 1998; Yamaguchi et al. 1992). No significant differences have been found between the nonionic monomers and the ionic dimer ioxaglate either (Bertrand et al. 1995; Mikkonen et al. 1995; Oi et al. 1997).

The available evidence suggests that late skin reactions are more common with nonionic dimers. In two studies conducted by the same group the nonionic dimer iodixanol caused more late skin reactions than either the ionic dimer ioxaglate or the nonionic monomers iopamidol and iomeprol (Sutton et al. 2001, 2003). In another study, the frequency of late skin reactions with iodixanol was similar to that with nonionic monomer, but more of the iodixanol patients were treated with hydrocortisone or antihistamine (Rydberg et al. 1998). Fransson et al. (1996), however, found no difference in the frequency of late skin reactions between iodixanol and ioxaglate. The nonionic dimer iotrolan was withdrawn in 1995 because of the high incidence of late reactions, particularly skin reactions, initially reported from Japan but subsequently also from the USA (Hosoya et al. 2000; Niendorf 1996).

5.4 Reaction Onset and Duration

Late skin reactions after contrast medium develop within 1–7 days with the majority occurring within the first 3 days (Hosoya et al. 2000). Most reactions are self-limiting and have resolved by 7 days, with up to three-quarters resolving within 3 days (Hosoya et al. 2000; Yoshikawa 1992).

5.5 Predisposing Factors

A number of factors appear to predispose to the development of late adverse reactions. A previous

reaction to contrast medium is an important predisposing factor increasing the risk by a factor of 1.7–3.3 (Hosoya et al. 2000; Mikkonen et al. 1995; Yoshikawa 1992). However, there is no evidence that patients with a previous late reactions are at increased risk for a subsequent immediate anaphylactic reaction (Hosoya et al. 2000; Yamagughi et al. 1992; Yoshikawa 1992). A history of allergy is a further risk factor (Higashi and Katayama 1990; Hosoya et al. 2000; Munechika et al. 1999, 2003; Oi et al. 1997; Yoshikawa 1992), increasing the likelihood of a reaction approximately twice. A history of drug and contact allergy especially seems to predispose to late skin reactions after contrast medium exposure (Aoki and Takemura 2002; Kanny et al. 2005; Vernassiere et al. 2004). A seasonal variation in the incidence of late skin reactions has been described with 45% of reactions occurring in the period April to June in Finland (Mikkonen et al. 2000). A relation to the pollen season and/or to the possible photosensitizing effect of contrast media have been postulated. A significantly higher incidence of late adverse reactions during the pollen season was confirmed by Munechika et al. (2003). Females are more likely to develop late adverse reactions than males (Bartolucci et al. 2000; Higashi and Katayama 1990; Hosoya et al. 2000; Mikkonen et al. 1995; Oi et al. 1997). Coexisting diseases also appear to predispose to late reactions, especially renal disease, but also cardiac and liver disease and diabetes mellitus (Bartolucci et al. 2000; Hosoya et al. 2000; Mikkonen et al. 1995). Some of the most severe skin reactions reported occurred in patients with systemic lupus erythematosus or patients who were taking hydralazine which induces a lupus-like syndrome in some patients (Goodfellow et al. 1986; Reynolds et al. 1993; Savill et al. 1988). Bone marrow transplantation patients were reported to be another risk group for severe contrast medium induced skin eruptions (Vavricka et al. 2002).

The increased incidence of late reactions to contrast media in patients who have received interleukin-2 (IL-2) immunotherapy is well documented, with an increased frequency of two to four times (Choyke et al. 1992; Fishman et al. 1991; Oldham et al. 1990; Shulman et al. 1993; Zukiwski et al. 1990). Skin rash, pruritus and flu-like syndrome were all more frequent in patients who had received IL-2 (Choyke et al. 1992).

5.6 Prophylaxis

In view of the infrequent and self-limiting nature of the great majority of late reactions, it does not seem appropriate to warn patients with no special risk factors about the possibility of a late reaction. However, it is recommended that patients who have had a previous late skin reaction after contrast medium administration who suffer from major drug or contact allergy or who have received interleukin-2 are warned about the possibility of a late skin reaction and told to contact a doctor if they have a problem.

If patients who have previously had a late skin reaction to iodinated contrast medium require further contrast medium, it is recommended that an alternative contrast medium is chosen and steroid prophylaxis is given (Watanabe et al. 1999). However, because of frequent cross-reactivity among different contrast media, change of contrast agent is no guarantee against a repeat reaction (Brockow et al. 2005).

5.7 Conclusion

Late adverse reactions to iodinated contrast media have been recognized for 20 years. They are mainly mild or moderate skin reactions which develop from 1 hour to 7 days after contrast medium administration and usually resolve within 3–7 days. The majority of these cutaneous reactions are T-cell mediated allergic reactions. A simple guideline can be found in the Appendix.

References

Akiyama M, Nakada T, Sueki H et al (1998) Drug eruption caused by nonionic iodinated X-ray contrast media. Acad Radiol 5 [Suppl 1]:S159–S161

Aoki Y, Takemura T (2002) Allergies correlated to adverse reactions induced by non-ionic monomeric and ionic dimeric contrast media for contrast enhanced CT examination. Radiol Technol 58:1245–1251

Atasoy M, Erdem T, Sari RF (2003) A case of acute generalized exanthematous pustulosis (AGEP) possibly induced by iohexol. J Dermatol 30:723–726

Bartolucci F, Cecarini M, Gabrielli G et al (2000) Reazioni tardive a un mezzo di contrasto radiologico (iopamidolo - Bracco). Radiol Med 100:273–278

Bertrand P, Delhommais A, Alison D, Rouleau P (1995) Immediate and delayed tolerance of iohexol and ioxaglate in lower limb phlebography: a double-blind comparative study in humans. Acad Radiol 2:683–686

Beyer-Enke SA, Zeitler E (1993) Late adverse reactions to non-ionic contrast media: a cohort analytic study. Eur Radiol 3:237–241

Bigby M, Jick S, Jick H, Arndt K (1986) Drug induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975-1982. JAMA 256:3358–3363

Brockow E, Becker EW, Worret W-I, Ring J (1999) Late skin test reactions to radiocontrast medium. J Allergy Clin Immunol 104:1107–1108

Brockow K, Christiansen C, Kanny G et al (2005) Management of hypersensitivity reactions to iodinated contrast media. Allergy 60:150–158

Choyke PL, Miller DL, Lotze MT et al (1992) Delayed reactions to contrast media after Interleukin-2 immunotherapy. Radiology 183:111–114

Christiansen C (2002) Late-onset allergy-like reactions to X-ray contrast media. Curr Opin Allergy Clin Immunol 2:333–339

Christiansen C, Pichler WJ, Skotland T (2000) Delayed allergy-like reactions to X-ray contrast media: mechanistic considerations. Eur Radiol 10:1965–1975

Cochran ST, Cugley AL, Kiourmehr F (1993) Delayed reactions in patients receiving non-ionic contrast media. Adv X-Ray Contrast 1:61–62

Conroy RM, Bjartveit K, Sheppick A et al (1994) Iodixanol in intravenous urography: a comparison of iodixanol 270 mg I/ml, iodixanol 320 mg I/ml and iopamidol 300 mg I/ml (NIOPAM). Clin Radiol 49:337–340

Courvoisier S, Bircher AJ (1998) Delayed-type hypersensitivity to a nonionic, radiopaque contrast medium. Allergy 53:1221–1224

Fishman JE, Aberle DR, Moldawer NP et al (1991) Atypical contrast reactions associated with systemic interleukin-2 therapy. Am J Roentgenol 156:833–834

Fransson SG, Stenport G, Andersson M (1996) Immediate and late adverse reactions in coronary angiography. A comparison between iodixanol and ioxaglate. Acta Radiol 37:218–222

Gall H, Pillekamp H, Peter R-U (1999) Late-type allergy to the X-ray contrast medium Solutrast (iopamidol). Contact Dermatitis 40:248–250

Goodfellow T, Holdstock GE, Brunton FJ, Bamforth J (1986) Fatal acute vasculitis after high-dose urography with iohexol. Br J Radiol 59:620–621

Higashi TS, Katayama M (1990) The delayed adverse reactions of low osmolar contrast media. Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiol 50:1359–1366

Hosoya T, Yamaguchi K, Akutzu T et al (2000) Delayed adverse reactions to iodinated contrast media and their risk factors. Radiat Med 18:39–45

Kanny G, Marie B, Hoen B et al (2001) Delayed adverse reaction to sodium ioxaglic acid-meglumine. Eur J Dermatol 11:134–137

Kanny G, Pichler WJ, Morisset M et al (2005) T cell-mediated reactions to iodinated contrast media: evaluation by skin and lymphocyte activation tests. J Allergy Clin Immunol 115:179–185

Laffitte E, Nevadov Beck M, Hofer M et al (2004) Severe Stevens-Johnson syndrome induced by contrast medium iopentol (Imagopaque). Br J Dermatol 150:376–378

McCullough M, Davies P, Richardson R (1989) A large trial of intravenous Conray 325 and Niopam 300 to assess immediate and delayed reactions. Br J Radiol 62:260–265

Mikkonen R, Kontkann T, Kivisaari L (1995) Acute and late adverse reactions to low-osmolal contrast media. Acta Radiol 36:72–76

Mikkonen R, Vehmas T, Granlund H, Kivisaari L (2000) Seasonal variation in the occurrence of late adverse skin reactions to iodine-based contrast media. Acta Radiol 41:390–393

Munechika H, Hiramatsu M, Nakamura H et al (1999) Large-scale study of delayed adverse events to non-ionic contrast medium, iohexol: incidence and risk factors of adverse events following non-interventional radiography. Eur Radiol 9 [Suppl 1]:S440

Munechika H, Hiramatsu Y, Kudo S et al (2003) A prospective survey of delayed adverse reactions to iohexol in urography and computed tomography. Eur Radiol 13:185–194

Niendorf HP (1996) Delayed allergy-like reactions to X-ray contrast media. Problem statement exemplified with iotrolan (Isovist) 280. Eur Radiol 6 [Suppl 3]:S8–S10

Oi H, Yamazaki H, Matsushita M (1997) Delayed vs. immediate adverse reactions to ionic and non-ionic low-osmolality contrast media. Radiat Med 15:23–27

Oldham RK, Brogley J, Braud E (1990) Contrast medium "recalls" interleukin-2 toxicity. J Clin Oncol 8:942–943

Panto PN, Davies P (1986) Delayed reactions to urographic contrast media. Br J Radiol 59:41–44

Pedersen SH, Svaland MG, Reiss A-L, Andrew E (1998) Late allergy-like reactions following vascular administration of radiography contrast media. Acta Radiol 39:344–348

Reynolds NJ, Wallington TB, Burton JL (1993) Hydralazine predisposes to acute cutaneous vasculitis following urography with iopamidol. Br J Dermatol 129:82–85

Rosado A, Canto G, Veleiro B, Rodriguez J (2001) Toxic epidermal necrolysis after repeated injections of iohexol. Am J Roentgenol 176:262–263

Rydberg J, Charles J, Aspelin P (1998) Frequency of late allergy-like adverse reactions following injection of intravascular non-ionic contrast media. A retrospective study comparing a non-ionic monomeric contrast medium with a non-ionic dimeric contrast medium. Acta Radiol 39:219–222

Sadi AM, Toda T, Kiyuna M et al (1995) An autopsy case of malignant lymphoma with Lyell's syndrome. J Dermatol 22:594–599

Savill JS, Barrie R, Ghosh S et al (1988) Fatal Stevens-Johnson syndrome following urography with iopamidol in systemic lupus erythematosus. Postgrad Med J 64:392–394

Schick E, Weber L, Gall H (1996) Delayed hypersensitivity reaction to the non-ionic contrast medium iopromid. Contact Dermatitis 35:312

Schild H (1996) Delayed allergy-like reactions in patients: monomeric and dimeric contrast media compared with plain CT. Eur Radiol 6 (Insert to Issue 5: Delayed allergy-like reactions to X-ray contrast media):9–10

Sedano E, Vega JM, Rebollo S et al (2001) Delayed exanthema to nonionic contrast medium. Allergy 56:1015–1016

Shulman KL, Thompson JA, Benyunes MC et al (1993) Adverse reactions to intravenous contrast media in patients treated with interleukin-2. J Immunother 13:208–212

Sutton AGC, Finn P, Grech ED et al (2001) Early and late reactions after the use of iopamidol 340, ioxaglate 320 and iodixanol 320 in cardiac catheterization. Am Heart J 141:677–683

Sutton AGC, Finn P, Campbell PG et al (2003) Early and late

reactions following the use of iopamidol 340, iomeprol 350 and iodixanol 320 in cardiac catheterization. J Invas Cardiol 15:133–138

Ueda S, Mori H, Matsumoto S et al (2001) True delayed adverse reactions to non-ionic contrast media: does it really exist? Eur Radiol 11 [Suppl 1]:377

Vavricka SR, Halter J, Furrer K et al (2002) Contrast media triggering cutaneous graft-versus-host disease. Bone Marrow Transplant 29:899–901

Vernassiere C, Trechot P, Commun N et al (2004) Low negative predictive value of skin tests in investigating delayed reactions to radio-contrast media. Contact Dermatitis 50:359–366

Watanabe H, Sueki H, Nakada T et al (1999) Multiple fixed drug eruption caused by iomeprol (Iomeron), a nonionic contrast medium. Dermatology 198:291–294

Webb JAW, Stacul F, Thomsen HS et al (2003) Late adverse reactions to intravascular iodinated contrast media. Eur Radiol 13:181–184

Yamaguchi K, Takanashi I, Kanauchi T et al (1992) A retrospective survey of delayed adverse reactions to ionic and nonionic contrast media. Nippon Igaku Hoshasen Gakkai Zasshi – Nippon Acta Radiol 52:1565–1570

Yasuda R, Munechika H (1998) Delayed adverse reactions to nonionic monomeric contrast-enhanced media. Invest Radiol 33:1–5

Yoshikawa H (1992) Late adverse reactions to nonionic contrast media. Radiology 183:737–740

Zukiwski AA, David CL, Coan J et al (1990) Increased incidence of hypersensitivity to iodine-containing radiographic contrast media after interleukin-2 administration. Cancer 65:1521–1524

Section II:
Renal Adverse Effects

6 Reducing the Risk of Contrast Medium Induced Nephropathy

Henrik S. Thomsen

CONTENTS

6.1 Introduction

Acute renal failure is a sudden and rapid deterioration in renal function which results in the failure of the kidney to excrete nitrogenous waste products and to maintain fluid and electrolyte homeostasis. It may be a result of intravascular administration of radiographic and MR contrast media (see also Chap. 17). The term contrast medium induced nephropathy is widely used to refer to the reduction in renal function induced by contrast media. It implies impairment in renal function [an increase in serum creatinine by more than 25% or 44 µmol/l (0.5 mg/dl)] which occurs within 3 days following the intravascular administration of contrast media in the absence of an alternative etiology (Morcos et al. 1999). Contrast medium induced nephropathy ranges in severity from asymptomatic, nonoliguric transient renal dysfunction to oliguric severe acute renal failure necessitating dialysis. Serum creatinine often peaks within 3–4 days after the administration of contrast media (Morcos 1998; Katzberg 1997). Fortunately, most episodes of contrast medium induced nephropathy are self-limited and resolve within 1–2 weeks. Many non-anuric episodes are probably undetected, because the serum creatinine is rarely measured after administration of contrast media if the patients have no symptoms, especially if they are outpatients, who are given intravenous contrast medium. Permanent renal damage is very rare.

Diagnostic and interventional procedures using contrast media are performed with increasing frequency. The patient population subjected to these procedures is progressively older with more comorbid conditions (Solomon 1998). These are some of the reasons why contrast medium induced nephropathy is still an important cause of hospital acquired renal failure (Hou et al. 1983; Nash et al. 2002). Prevention is important to avoid the substantial morbidity and even mortality that sometimes may be associated with contrast medium induced nephropathy. Even a small decrease in renal function may greatly exacerbate morbidity and mortality caused by coexisting conditions (Gruberg et al. 2000; McCullough et al. 1997). Patients with contrast medium induced nephropathy have a higher mortality rate (31%) than patients without contrast medium induced nephropathy (0.6%) after primary angioplasty for acute myocardial infarction (Marenzi et al. 2004). The 30-day mortality is higher in patients with contrast medium induced nephropathy (16.2%) than in those without (1.2%) and the difference is maintained at 1 year (23.3% versus 3.2%) (Sadeghi et al. 2003). Sepsis, bleeding, coma, and respiratory failure are frequently observed in patients with acute renal failure.

H. S. Thomsen, MD
Professor, Department of Diagnostic Radiology, Copenhagen University Hospital at Herlev, 2730 Herlev Denmark

6.2 Radiographic Features

A persistent nephrogram on plain radiography or CT of the abdomen at 24–48 h after contrast medium injection has been described as a feature of contrast medium induced nephropathy (Berns 1989; Love at al. 1994). However, its presence is not always associated with a reduction in renal function (Jakobsen et al. 1992; Yamazaki et al. 1997a). Also, opacification of the gall bladder is not necessarily related to the occurrence of contrast medium induced nephropathy (Yamazaki et al. 1997b). However, if these signs are present, renal function should be assessed and the administration of further doses of contrast media should be avoided if the results are abnormal.

6.3 Incidence

Contrast medium induced nephropathy is rare in people with normal renal function with an incidence varying from 0%–2% (Morcos et al. 1999; McCullough et al. 1997; Rudnick et al. 1995). In acute myocardial infarction, contrast medium induced nephropathy occurred after primary angioplasty in 13% of patients who had normal S-creatinine levels before the angioplasty (Marenzi et al. 2004). However, it is unclear whether it was the contrast medium or the cardiac dysfunction which reduced the renal function temporarily. Nearly all recent studies of contrast medium induced nephropathy involve arterial injection (coronary or peripheral angiography and angioplasty). The contrast medium was given intravenously in only one of the 15 studies which Pannu et al. (2004) included in their meta-analysis of the effect of N-acetylcysteine on the prevention of contrast medium induced nephropathy. The incidence of temporary contrast medium induced nephropathy after CT scanning in oncologic patients treated with nephrotoxic drugs is unknown.

Pre-existing renal impairment increases the frequency of contrast medium induced nephropathy. An incidence of contrast induced nephropathy ranged from 3%–33% in several prospective controlled studies (Morcos et al. 1999; Solomon 1998; Rudnick et al. 1995; Bettman 2005). The incidence is significantly higher in patients with diabetic nephropathy (19.7%) than in patients with other types of nephropathy (5.7%) (Rudnick et al. 1995). In patients with a serum creatinine level below 132 μmol/l (1.5 mg/dl), the incidence of contrast medium induced nephropathy was less than 1%. The long-term effects of contrast media on renal function in man are not known.

6.4 Renal Handling of Contrast Media

After intravascular administration contrast medium molecules move across capillary membranes (except an intact blood–brain barrier) into the interstitial, extracellular space. Reverse movement from the extracellular space into the intravascular compartment occurs and a state of equilibrium is generally reached within 2 h. Continuous elimination through the glomeruli also occurs. Less than 1% is excreted extrarenally in patients with normal renal function (Thomsen et al. 1993). Following intravascular administration in patients with normal renal function the elimination half-life is about 2 h and 75% of the administered dose is excreted in the urine within 4 h (Katzberg 1997). After 24 h 98% of the injected contrast medium has been excreted. After approximately 150 min the concentration of contrast medium decreases in a monoexponential way in patients with normal renal function, but in patients with severely reduced renal function this phase is delayed (Almén et al. 1999).

6.5 Pathophysiology of Contrast Medium Induced Nephropathy

There are three relatively distinct mechanisms or pathways *proposed* for the pathophysiology of contrast medium induced nephropathy: (1) reduction in renal perfusion (hemodynamic effects), (2) toxicity directly affecting the tubular cells, and (3) endogenous biochemical disturbances (Katzberg 2005). Most clinical attention has focused on the hemodynamic effects of contrast media because tubular hypoxic injury is considered to play a central role in the renal dysfunction (Heyman et al. 2005). The mechanisms responsible for hemodynamic effects are believed to involve tubular and vascular events. The importance of direct effects of contrast media on tubular cells is debated although evidence of a

direct tubular cell toxicity of the contrast agents independent of either hemodynamic mechanisms or osmolality has been reported (Heinrich et al. 2005). An increase in oxygen-free radicals or a decrease in antioxidant enzyme activity triggered by contrast medium administration as the third potential pathway is speculative. There has been no clinical substantiation of the suggestion that the liberation of oxygen-free radicals is the mechanism of contrast medium induced nephropathy (Katzberg 2005). The lack of understanding of the cause of contrast medium induced nephropathy makes prevention of the condition difficult.

6.6 Predisposing Factors

The patients at highest risk for developing contrast induced acute renal failure are those with pre-existing renal impairment [> 132 μmol/l (1.5 mg/dl)], particularly when the reduction in renal function is secondary to diabetic nephropathy (Morcos et al. 1999; Rudnick et al. 1995). Diabetes mellitus per se without renal impairment is not a risk factor (Rudnick et al. 1995). The degree of renal insufficiency present before the administration of contrast media to a great extent determines the severity of contrast medium induced nephropathy. Baseline renal insufficiency in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention is associated with a markedly increased mortality as well as with bleeding and restenosis (Sadeghi et al. 2003). The extent to which the contrast medium contributes to the clinical deterioration is unknown since for ethical reasons the studies did not include a control group.

Large doses of contrast media and multiple injections within 72 h increase the risk of developing contrast medium induced nephropathy. The route of administration is also important and contrast media are less nephrotoxic when administered intravenously than when given intra arterially into the renal arteries or the aorta proximal to the origin of the renal blood vessels. The acute intrarenal concentration of contrast media is much higher after intra-arterial than after intravenous administration.

Dehydration and congestive cardiac failure are risk factors because they are associated with a reduction in renal perfusion, which enhances the ischemic insult of the contrast media. The concurrent use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAID) and amino glycosides potentiates the nephrotoxic effects of contrast media. Renal dysfunction is found more frequently in patients with hypertension, hyperuricemia or proteinuria than in patients without these conditions (Choyke et al. 1998). The type of contrast medium is also an important predisposing factor. High osmolar contrast media are more nephrotoxic than low and iso osmolar contrast media (Morcos 1998; Katzberg 1997; Rudnick et al. 1995).

Multiple myeloma has been considered in the past to be a risk factor for contrast medium induced nephropathy. However, if dehydration is avoided, contrast media administration rarely leads to acute renal failure in patients with myeloma (McCarthy and Becker 1992).

6.7 Identifying Patients at Risk of Contrast Medium Induced Nephropathy

Patients with preexisting renal impairment are at particularly high risk of contrast medium induced nephropathy. Serum creatinine is often used to determine the renal function and to identify high risk patients. Several studies have shown that, despite its limitations, serum creatinine is an adequate marker for identifying patients at the greatest risk of developing contrast medium induced nephropathy because patients with severely reduced renal function are at the greatest risk (Rudnick et al. 1995; McCullough et al. 1989; Parfrey et al. 1989; Thomsen et al. 2005).

6.7.1 Validation of Serum Creatinine Measurements

Serum creatinine is not an ideal marker of renal function. The serum creatinine level depends on muscle mass and is not usually raised until the glomerular filtration rate has fallen by at least 50%. Endogenous serum creatinine clearance as a measure of glomerular filtration rate is also inaccurate, especially when renal function is low, because of a compensatory increase in tubular secretion of creatinine which limits its validity as a glomerular filtration marker. Radionuclide techniques are preferable (Blaufox et al. 1996) but are labor-intensive and therefore not suitable to use in all patients receiving contrast medium. Alternatively, renal function

can be estimated using specially derived predictive equations. The most accurate results are obtained with the Cockroft-Gault equation whereas the most precise formula is the Modification of Diet in Renal Disease (MDRD) study equation (Cockroft and Gault 1976; Levey et al. 1999). Although the predictive capabilities of these formulae are suboptimal for ideal patient care (Bostrom et al. 2002), these methods are far superior to serum creatinine measurement for assessing renal function. Another possibility is to use cut-off values for serum creatinine to indicate several levels of renal impairment. However, low cut-off levels will include some patients with normal renal function and high cut-off levels will exclude some patients with renal impairment (Couchoud et al. 1999). Despite the inaccuracies of serum creatinine it is an adequate measure for identifying those patients at risk for contrast medium induced nephropathy because patients with normal serum creatinine [< 132 μmol/l (1.5 mg/dl)] have minimal risk (Rudnick et al. 1995; McCullough et al. 1989; Parfrey et al. 1989; Thomsen et al. 2005).

6.7.2 When Should Serum Creatinine Be Measured?

A questionnaire designed to elicit a history of renal disorders as well as additional risk factors for contrast medium induced nephropathy may be used to identify patients with normal serum creatinine in whom blood testing would be unnecessary (Choyke et al. 1998). The majority of patients (85%) in Choyke et al.'s 1998 study had normal serum creatinine values [< 114 μmol/l (1.3 mg/dl) for women, 123 μmol/l (1.4 mg/dl) for men]. All except two patients (99%) who gave negative answers to the questionnaire had serum creatinine levels < 150 μmol/l (1.7 mg/dl). There was a strong association between raised serum creatinine values and a history of renal disease, proteinuria, prior kidney surgery, hypertension, gout and diabetes. Only 6% of patients with negative answers to the six questions had abnormal serum creatinine levels.

In a study of 2034 consecutive outpatients referred for CT examinations, only 3.2% (66 patients) had a raised serum creatinine level [> 176 μmol/l (2.0 mg/dl)] and the majority of these patients (97%) had risk factors for contrast medium induced nephropathy (Tippins et al. 2000). Two of the 66 patients with a raised serum creatinine (0.1% of the total number of patients) had no identifiable risk factors. Serum creatinine was measured in a prospective study of 640 consecutive adult patients presenting to the emergency department with a clinical indication for intravenous administration of iodinated contrast medium (Olsen and Salomon 1996). A total of 35 (5.5%) patients had abnormal serum creatinine [> 141 μmol/l (1.6 mg/dl)]. Of these 35 patients, 77% (27) were considered to have risk factors for renal insufficiency. The remaining eight patients (1.3% of the total number) had no identifiable risk factors for renal insufficiency.

Thus, the majority of patients at risk of contrast medium induced nephropathy can be identified by appropriate questions but a questionnaire does not completely exclude the presence of renal insufficiency. The Contrast Media Safety Committee of the European Society of Urogenital Radiology guideline indicates that serum creatinine should be measured in 7 days before an investigation using iodinated contrast medium if the response to any part of the questionnaire is positive, if the serum creatinine is known to be abnormal at the time of referral or if contrast medium is to be given intra-arterially (see Appendix).

6.7.3 Risk Stratification

Risk stratification of patients to identify those susceptible to contrast medium induced nephropathy has not been fully evaluated. Based on two cohorts [one derivation cohort (1993 to 1998) and one validation cohort (1999 to 2002)] of 20,479 patients Bartholomew et al. (2004) proposed a contrast medium induced nephropathy risk score with good predictive ability for identifying patients in whom preventive strategies are indicated. Independent variables (with weighted scores) include estimated creatinine clearance < 60 ml/min (2), urgent percutaneous coronary intervention (2), intra-aortic balloon pump use (2), diabetes mellitus (1), congestive heart failure (1), hypertension (1), peripheral vascular disease (1) and contrast volume > 260 ml (1). The incidence of contrast medium induced nephropathy after percutaneous coronary intervention increased with each unit increase in score. No patient with a score ≤ 1 developed contrast medium induced nephropathy, whereas 26% of patients with a score ≥ 9 developed contrast medium induced nephropathy.

Mehran et al. (2004) also developed a simple risk score for contrast medium induced nephropathy

after percutaneous coronary intervention. Based on 8357 patients they identified eight variables, which were assigned a weighted integer: Hypotension (5), intra-aortic balloon pump (5), congestive heart failure class III/IV by New York Heart Association classification and/or a history of pulmonary edema (5), age > 75 years (4), anemia (3), diabetes (1), contrast media volume (1 for each 100 ml), serum creatinine > 132 µmol/l (1.5 mg/dl) (4) or estimated creatinine clearance < 20 ml/min/1.73m^2 (6), 20–40 ml/min/1.73m^2 (4) and 40–60 ml/min/1.73m^2 (2). In patients with a risk score ≤ 5 the risk of contrast medium induced nephropathy was 7.5% and the risk of dialysis was 0.04%, whereas the figures for patients with a risk score ≥ 16 were 57.3% and 12.6%, respectively.

Methods of stratifying patients being given contrast media appear to have potential but need further evaluation. Currently it is not known whether they are applicable to examinations where the contrast medium is injected intravenously.

6.8 Measures to Reduce the Incidence of Contrast Medium Induced Nephropathy

A number of measures (Table 6.1) have been recommended to reduce the incidence of contrast medium induced nephropathy (Thomsen 1999; Morcos 2004, 2005). The main methods that have been used are extracellular volume expansion, administration of nonionic contrast media, and the use of a variety of drugs, all of which are discussed in this section. Other measures, which have been tried, include hemodialysis, hemofiltration and gadolinium based contrast media instead of iodinated agents and they are discussed in Chaps. 7 and 17.

6.8.1 Extracellular Volume Expansion

Extracellular volume expansion is the most effective of all the measures used to prevent contrast medium induced nephropathy (Morcos et al. 1999; Mueller et al. 2002; Trividi et al. 2003; Allaqaband et al. 2002; Solomon et al. 1994; Taylor et al. 1998). However, the optimal amount of fluid that should be administered to reduce the risk of contrast medium induced nephropathy remains controversial.

Taylor et al. (1998) showed no difference between outpatient oral precatheterization hydration (oral hydration with 1000 ml clear liquid over 10 h) followed by 6 h of intravenous hydration (0.45% saline solution at 300 ml/h) beginning just before contrast media exposure and overnight intravenous hydration (0.45% saline solution at 75 ml/h for 12 h before and after catheterization). Mueller et al. (2002) found that infusion (1 ml/kg body weight/h) of normal strength (0.9%) saline solution is superior to that of half-strength (0.45%) saline solution for preventing contrast medium induced nephropathy. Patients were also encouraged to drink plenty of fluids (tea and mineral water). Trivedi et al. (2003) showed a higher incidence of contrast medium induced nephropathy with oral hydration alone compared to volume expansion with intra-

Table 6.1. Current status of measures which have been proposed to decrease the risk of iodinated contrast medium induced nephropathy (June 2005).

Measures proven to decrease the risk	Measures for which evidence is equivocal	Measures proven to increase the risk or to have no effect
Extracellular volume expansion	Hemofiltration	Loop diuretics
Normal strength (0.9%) saline for intravenous hydration	Sodium bicarbonate intravenously	Mannitol
Low dose of contrast medium	Intravenous hydration in preference to controlled oral hydration	Half strength (0.45%) saline for intravenous hydration
Low- or iso-osmolar contrast medium	Iso-osmolar dimers in preference for low-osmolar monomeric contrast media	High osmolar contrast media
Imaging methods not using iodinated contrast media		Hemodialysis
		Gadolinium based contrast media
		Pharmacological manipulation: • Renal vasodilators • Blocking of intrarenal mediators e.g. endothelin and adenosine • Cytoprotective drugs e.g. acetylcysteine

venous normal saline (1 ml/kg body weight/h) for 24 h starting 12 h before contrast medium administration. However, the amount and type of fluid in the group allowed unrestricted oral fluids were not mentioned. The conclusion should be considered with some reservation since a bias (intention to treat in one arm) may be present. Volume expansion given only during contrast medium exposure appears not to be sufficient to prevent renal damage (Bader et al. 2004).

The Contrast Media Safety Committee of the European Society of Urogenital Radiology recommends intravenous infusion of 0.9% saline solution at a rate of 100 ml/h starting 4 h before contrast medium administration and continuing for 24 h afterwards (see Appendix). In areas with a hot climate more fluid should be given. This regime is suitable for patients who are not in congestive heart failure and are not allowed to drink or eat before undergoing an interventional or surgical procedure. If there is no contraindication to oral administration, free fluid intake should be encouraged. At least 500 ml of water or soft drinks orally before and 2500 ml during the 24 h following contrast medium is recommended. In addition, concurrent administration of nephrotoxic drugs such as gentamicin and non-steroid anti-inflammatory drugs should be avoided.

Mannitol and furosemide enhance the risk of contrast medium induced nephropathy and should not be used (Solomon et al. 1994).

Based on a randomized trial in 119 patients, Merten et al. (2004) suggested that sodium bicarbonate is superior to sodium chloride hydration. Rates of contrast medium induced nephropathy were lower in the sodium bicarbonate group (1.7%) than in sodium chloride group (13.6%), but only eight of the 119 patients developed contrast medium induced nephropathy. Pretreatment with sodium bicarbonate leads to an increase in the pH of the urine and the renal medulla, which reduces the generation of free radicals and protects the kidney from oxidant injury which may be associated with contrast medium induced nephropathy. Thus the protective effect is believed to result from antioxidant effects and scavenging of reactive free radicals rather than from better hydration than that provided by saline (Merten et al. 2004). However, there is no clinical evidence that the liberation of oxygen-free radicals is the mechanism of contrast medium induced nephropathy (Katzberg 2005).

The disadvantages of volume expansion include its unsuitability for patients with cardiac failure and its limited use in emergency situations because fluid administration has to start several hours before contrast medium administration.

6.8.2 Nonionic Contrast Media

The type of contrast medium used is an important risk factor for the development of contrast medium induced nephropathy since iso-osmolar and low-osmolar contrast agents are less nephrotoxic than high-osmolar contrast agents in patients with pre-existing renal impairment (Morcos 1998; Morcos et al. 1999; Katzberg 1997; Rudnick et al. 1995). Therefore low osmolar or iso osmolar nonionic contrast media are recommended in high risk patients to reduce the risk of contrast medium induced nephropathy.

Recently it has been suggested that the isoosmolar nonionic dimer is less nephrotoxic than nonionic low-osmolar monomers. A multicenter study of 129 patients with renal impairment and diabetes mellitus [serum creatinine between 132 μmol/l (1.5 mg/dl) and 308 μmol/l (3.5 mg/dl)] undergoing angiography with either the iso-osmolar dimer iodixanol or the nonionic monomer iohexol showed that contrast medium induced nephropathy developed in only 3% of the patients after the dimer compared to 26% after the monomer (Aspelin et al. 2003). It was concluded that the iso-osmolar dimer iodixanol is significantly less nephrotoxic than the nonionic monomer. In another study of patients with a variety of causes of reduced renal function, contrast medium induced nephropathy developed in 4% after the iso-osmolar nonionic dimer iodixanol and in 10% after a low-osmolar nonionic monomer (Chalmers and Jackson 1999). In a third study, contrast medium induced nephropathy developed in 17% of patients with severe renal impairment who received intravenous injection of either a nonionic monomer or an iso-osmolar dimer for body or cranial CT but full details of the study have never been published (Kolehmainen and Soiva 2003). Stone et al. (2003) reported a 33.3% incidence of contrast medium induced nephropathy with iodixanol and a 25.3% incidence with other types of low-osmolar contrast media. The difference was not statistically significant. After coronary or peripheral procedures using the nonionic isoosmolar dimer Briguori et al. (2004a) found that the incidence of contrast medium induced nephropathy in the group receiving acetylcysteine was 4.1% and in the group receiving

fenoldopam was 13.7%. Incidences of nephropathy of 12% and 21% with iodixanol were observed in the control groups in two further studies studying the effect of acetylcysteine (Boccolandro et al. 2003; Baker et al. 2003).

Whether the nonionic iso osmolar dimer rather than the nonioinic monomer should be used in high risk patients has been discussed in several recent reviews and comments (Gleeson and Bulugahapitaya 2004; Cavusoglu et al. 2004; Maeder et al. 2004; Nikolsky and Mehran 2003; Mitchell et al. 2004; Asif and Epstein 2004; Andrew and Berg 2004; Nicholson and Downes 2003; Erdogan and Davidson 2003). Further studies are necessary to determine whether there is a significant difference in nephrotoxic effects between the nonionic dimer and nonionic monomers in patients with renal impairment (Sandler 2003). It is important to remember that than contrast medium induced nephropathy may occur following injection of any of the four classes of iodinated contrast media (Chap. 1).

6.8.3 Pharmacological Manipulation

Calcium channel blockers prevent the influx of calcium ions through voltage-operated channels, so causing a vasorelaxant effect in all vascular beds including the kidney. In one study 3 days treatment with 20 mg nitrendipine prevented the development of contrast medium induced nephropathy in patients with moderate renal impairment (Neumayer et al. 1989), but in another study a single dose (20 or 10 mg) given 1 h before contrast medium administration failed to prevent contrast medium induced nephropathy (Carraro et al. 1996). The incidence of contrast medium induced nephropathy was 6.5% with 20 mg nitrendipine, 3.7% with 10 mg nitrendipine and 8.3% in the control group, and the differences were not statistically insignificant. Thus the role of calcium channel blockers remains uncertain and their protective effect in patients with advanced renal impairment has not been proven. In addition, this class of drugs is not suitable in patients with heart failure.

Use of the vasodilators dopamine and atrial natriuretic peptide may be harmful in patients with diabetic nephropathy. The frequency of contrast medium induced nephropathy in patients who were pre-treated with either drug plus hydration was 83%, whereas the frequency in the control group, who received only hydration, was 43% (Weisberg et al. 1994).

The selective dopamine-1 receptor agonist, fenoldopam, in contrast to dopamine, increases both cortical and medullary blood flow. Fenoldopam has the advantages of not stimulating α- and β-adrenergic receptors or dopamine-2 receptors, which can produce renal vasoconstriction. One study has shown that fenoldopam offers some protection against contrast medium induced nephropathy (Kini et al. 2002) but two studies indicated that it offered no protection (Allaqaband et al. 2002; Stone et al. 2003). In addition, fenoldopam has the disadvantages that it has to be given intravenously and it induces hypotension so that regular monitoring of the blood pressure is necessary (Morcos 2004).

Experimental studies have indicated that the potent endogenous vasoactive peptide endothelin may play an important role in mediating contrast medium induced nephropathy (Oldroyd et al. 1995). Therefore it was suggested that endothelin antagonists (Benigni and Remizzi 1999) would reduce the incidence of contrast medium induced nephropathy in man. However, Wang et al. (2000) found that a non-selective endothelin receptor antagonist and intravenous hydration were associated with a contrast medium induced nephropathy rate of 56% compared to 29% in the hydration only group. In addition hypotension was more frequent in the treated group. However, Wang et al.'s 2000 study has been criticized (Haylor and Morcos 2000). The choice of a nonselective endothelin receptor antagonist which blocks both endothelin-A and the endothelin-B receptors was not appropriate. Endothelin-B receptors are responsible for vasodilatation and clearance of endothelin and blocking them abolishes the vasodilatory effect and prolongs vasoconstrictor effect of endothelin, which is released in response to contrast medium. Also, the endothelin receptor antagonist was given only 12 h after contrast medium injection so that there was not sustained drug cover.

The non-selective adenosine receptor antagonist, theophylline, has also been advocated to reduce the risk of contrast medium nephrotoxicity. Adenosine is an important intra-renal mediator, which can induce a decrease in the glomerular filtration rate through vasoconstriction of the afferent arterioles and contraction of the mesangial cells of the glomeruli (Oldroyd et al. 2000). Adenosine also induces vasoconstriction in the renal cortex and vasodilatation in the renal medulla, increases the generation

of oxygen free radical cells, and is a mediator of the tubulo-glomerulo-feedback-response (TGF). However, clinical studies have given conflicting results. In one study, administration of 200 mg theophylline intravenously had a preventive effect (Huber et al. 2002), but in another study 810 mg theophylline orally daily for three days did not offer additional protection compared to hydration alone (Erley et al. 1999). Thus, the effectiveness of theophylline in preventing contrast medium induced nephropathy remains uncertain. Also theophylline may induce cardiac arrhythmias in patients with ischemic heart disease (Morcos 2004).

Acetylcysteine is an antioxidant and scavenger of oxygen free radicals. It enhances the biologic effect of the endogenous vasodilator nitric oxide by combining with nitric oxide to form S-nitrosothiol, which is a more stable and potent vasodilator than nitric oxide. Acetylcysteine also increases the expression of nitric oxide synthase, the enzyme responsible for the endogenous production of nitric oxide in the body (Safirstein et al. 2000). Nitric oxide is crucial to the maintenance of perfusion of the kidney, particularly in the vulnerable region of the renal medulla.

The first study to use acetylcysteine was carried out by Tepel et al. (2000) and demonstrated good protection against contrast medium induced nephropathy in patients with renal impairment. Low osmolar contrast medium was injected intravenously in low doses (75 ml) and the patients were hydrated (1 ml/kg body weight/h). The incidence of contrast medium induced nephropathy in the acetylcysteine group was 2% and in the control group it was 21%. This is the only study in which the contrast medium was administered intravenously. Administration of acetylcysteine has been shown both to be effective in preventing contrast medium induced nephropathy after intra arterial contrast medium in some studies (Diaz-Sandoval et al. 2002; Kay et al. 2003; Baker et al. 2003) and to ineffective in other studies (Allaqaband et al. 2002; Durham et al. 2002; Boccolandro et al. 2003). Briguori et al. (2004a) found that acetylcysteine was more effective than fenoldopam in preventing contrast medium induced nephropathy after administration of a nonionic isoosmolar contrast medium for coronary or peripheral arterial procedures. The incidence of nephropathy in the acetylcysteine group was 4.1% and in the fenoldopam group it was 13.7%. It has been suggested that it may be useful to increase the dose of acetylcysteine if high volumes of nonionic, low-osmolality contrast agents are used (Briguori et al. 2004b).

At least six meta-analyses or systematic reviews of the effects of acetylcysteine with conflicting conclusions have been published. Inconsistency of study results in a meta-analysis reduces the confidence of recommendations about treatment (Higgins et al. 2003). The first meta-analysis based on seven studies (805 patients) concluded that the use of acetylcysteine reduced the risk of contrast medium induced nephropathy by 56% (Birck et al. 2003). Alonso et al. (2004) evaluated eight studies. Based on 885 patients, the overall risk ratio for contrast medium induced nephropathy associated with the use of acetylcysteine was 0.41. Another analysis based on 12 studies (1307 patients) indicated that conclusive data showing that acetylcysteine offers effective protection are lacking since seven of the 12 studies no effect was found (Fishbane et al. 2004). Pannu et al. (2004) included 15 studies (1776 patients) in their systematic review and concluded that N-acetylcysteine may reduce the incidence of a rise in serum creatinine after administration of contrast agents, but only with borderline statistical significance. There was significant heterogeneity between the 15 trials. In a meta-analysis of 16 prospective trials (1538 patients) Kshirsagar et al. (2004) did not confirm the validity of using acetylcysteine or recommend its routine use. They commented that the nephroprotective effect of acetylcysteine may be spurious as most studies used serum creatinine level as a surrogate marker of renal function. Hoffman et al. (2004) showed that acetylcysteine can induce a decrease in serum creatinine level independent of changes in glomerular filtration rate, probably by enhancing the tubular secretion of creatinine. Thus, there is no conclusive evidence that acetylcysteine provides protection against contrast medium induced nephropathy and its use cannot be recommended. The liberation of oxygen-free radicals has not been substantiated as the mechanism for contrast medium induced nephropathy (Katzberg 2005).

6.9 Summary

A major problem in the prevention of contrast medium induced nephropathy is that the pathophysiological mechanism of the condition is not known.

Current practice for preventing contrast medium induced nephropathy relies on identifying patients

at increased risk of the complication. In such patients, the possibility of an alternative imaging method not using contrast medium should be considered. If an investigation using iodinated contrast medium is considered essential for patient management, a number of measures which have been proved to reduce the incidence of contrast medium induced nephropathy should be instituted. These are extracellular volume expansion, the choice of normal (0.9%) saline when intravenous hydration is used, the choice of low or iso osmolar nonioinic contrast medium, and lowest contrast medium dose consistent with a diagnostic conclusion or a therapeutic goal (see Appendix). Kidney function should not be used as a guide to the amount of contrast medium which can be safely given. Based on current knowledge, a weight-related fluid dose for hydration (e.g. 1 ml/kg body weight/h or more) appears to be optimal. Even when the recommended measures are used, contrast medium induced nephropathy remains a risk after both iodinated and gadolinium contrast media.

Over the past 10 years, pharmacological manipulation with renal vasodilators, receptor antagonists of endogenous vasoactive mediators and cytoprotective drugs has been widely investigated. None of the pharmacological manipulations has yet been shown to offer consistent protection against contrast medium induced nephropathy. Therefore pharmacological manipulation with the drugs evaluated so far cannot be recommended (Table 6.1).

References

Allaqaband S, Tumuluri R, Malik AM et al (2002) Prospective randomized study of N-aceyltylcysteine, fenoldopam and saline for prevention of radiocontrast-induced nephropathy. Catheter Cardiovasc Intervent 57:279–283

Almén T, Frennby B, Sterner G (1999) Determination of glomerular filtration rate (GFR) with contrast media. In: Thomsen HS, Muller RN, Mattrey RF (eds) Trends in contrast media. Springer, Berlin Heidelberg New York, pp 81–94

Alonso A, Lau J, Jaber BL, Weintraub A, Sarnak MJ (2004) Prevention of contrast nephropathy with N-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized controlled trials. Am J Kidney Dis 43:1–9

Andrew E, Berg KJ (2004) Nephrotoxic effects of X-ray contrast media. J Toxicol Clin Toxicol 42:325–332

Arakawa K, Suzuki H, Naitoh et al (1996) Role of adenosine in the renal responses to contrast medium. Kidney Int 49:1199–1206

Asif A, Epstein M (2004) Prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 44:12–24

Aspelin P, Aubry P, Fransson S-G et al (2003) Nephrotoxic effects in high-risk patients undergoing angiography. N Engl. J Med 348:491–499

Bader BD, Berger ED, Heede MB et al (2004) What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? Clin Nephrol 62:1–7

Baker CS, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ (2003) A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J Am Coll Cardiol 41:2114–2118

Bartholomew BA, Harjai KJ, Dukkipati S et al (2004) Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol 93:1515–1519

Benigni A, Remuzzi G (1999) Endothelin antagonists. Lancet 353:133–138

Berns AS (1989) Nephrotoxicity of contrast media. Kidney Int 36:730–740

Bettmann MA (2005) Contrast medium-induced nephropathy: critical review of the existing clinical evidence Nephrol Dial Transplant 20 [Suppl 1]:i12–i17

Birck R, Krzossok S, Markowetz F, Schnulle P, van der Woude FJ, Braun C (2003) Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet 362:598–603

Blaufox MD, Aurell M, Bubeck B et al (1996) Report of the Radionuclide in Nephrourology Committee on renal clearance. J Nucl Med 37:1883–1890

Boccolandro F, Amhad M, Smalling RW, Sdringola S (2003) Oral acetylcysteine does not protect protect renal function from moderate to high doses of intravenous radiographic contrast. Cathet Cardiovasc Interv 58:336–341

Bostrom AG, Kronenberg F, Ritz E (2002) Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol 13:2140–2144

Briguori C, Colombo A, Airoldi F et al (2004a) N-acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. J Am Coll Cardiol 44:762–765

Briguori C, Colombo A, Violante A et al (2004b) Standard vs. double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. Eur Heart J 25:206–211

Carraro M, Mancini W, Aretro M et al (1996) Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration. Nephrol Dial Transplant 11:444–448

Cavusoglu E, Chabra S, Marmur JD, Kini A, Sharma SK (2004) The prevention of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. Minerva Cardioangio 52:419–432

Chalmers N, Jackson RW (1999) Comparison of iodixanol and iohexol in renal impairment. Br J Radiol 72:701–703

Choyke PL, Cady K, DePollar SL, Austin H (1998) Determination of serum creatinine prior to iodinated contrast media: is it needed in all patients? Tech Urol 4:65–69

Cockroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41

Couchoud C, Pozet N, Labeeuw M, Pouteil-Noble C (1999) Screening early renal failure: cut-off values for serum creatinine as an indicator of renal impairment. Kidney Int 55:1878–1884

Diaz-Sandoval LJ, Kosowsky BD, Losordo DW (2002) Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). Am J Cardiol 89:356–358

Durham JD, Caputo C, Dokko J et al (2002) A randomized trial

of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. Kidney Int 62:2202–2207
Erdogan A, Davidson CJ (2003) Recent clinical trials of iodixanol. Rev Cardiovasc Med 4 [Suppl 5]:S43–S50
Erley CM, Duda SH, Rehfuss D et al (1999) Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. Nephrol Dial Transplant 14:1146–1149
Fishbane S, Durham JH, Marzo K, Rudnick M (2004) N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. J Am Soc Nephrol 15:251–260
Gleeson T, Bulugahapitiya S (2004) Contrast induced nephropathy. AJR Am J Roentgenol 183:1673–1689
Gruberg L, Mintz GS, Mehran R et al (2000) The prognostic implications of further renal function deterioration with 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 36:1542–1548
Haylor JL, Morcos SK (2000) Endothelin antagonism and contrast nephropathy. Kidney Int 58:2239
Heinrich MC, Kuhlmann MK, Grgic A, Heckman M, Kramann B, Uder M (2005) Cytotoxic effects of ionic high-osmolar, nonioinic monomeric, and nonionic iso-osmolar dimeric iodinated contrast media on renal tubular cells in vitro. Radiology 235:843–849
Heyman SN, Rosenberger C, Rosen S (2005) Regional alterations in renal haemodynamics and oxygenation: a role contrast medium-induced nephropathy. Nephrol Dial Transplant 20 [Suppl 1]:i6–i11
Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analysis. Br Med J 327:557–560
Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK (2004) The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. J Am Soc Nephrol 15:407–410
Hou SH, Bushinsky DA, Wish JB et al (1983) Hospital acquired renal insufficiency: a prospective study. Am J Med 74:243–248
Huber W, Ilgman K, Page M et al (2002) Effect of theophylline on contrast material-induced nephropathy on patients with chronic renal insufficiency: controlled, randomized, double-blinded study. Radiology 223:772–779
Jakobsen JA, Lundby B, Kristoffersen DT et al (1992) Evaluation of renal function with delayed CT after injection of nonionic monomeric and dimeric contrast media in healthy volunteers. Radiology 182:419–424
Katholi RE, Taylor GJ, McCann WP et al (1995) Nephrotoxicity from contrast media: attenuation from theophylline. Radiology 195:17–22
Katzberg WR (1997) Urography into the 21st century: new contrast media, renal handling, imaging characteristics, and nephrotoxicity. Radiology 204:297–312
Katzberg WR (2005) Contrast medium-induced nephrotoxicity: which pathways? Radiology 235:752–755
Kay J, Chow WH, Chan TM et al (2003) Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention. A randomized controlled trial. JAMA 289:553–558
Kshirsagar AV, Poole C, Mottl A et al (2004) N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a metaanalysis of prospective controlled trials. J Am Soc Nephrol 15:761–769
Kini AS, Mitre CA, Kim M et al (2002) A protocol for prevention of radiographic contrast nephropathy during percutaneous coronary intervention: effect of selective dopamine receptor agonist fenoldopam. Catheter Cardiovasc Interv 55:169–173
Kolehmainen H, Soiva M (2003) Comparison of Xenetix 300 and Visispaque 320 in patients with renal failure. Eur Radiol 13:B32–B33
Levey AS, Bosch JP, Lewis JB et al (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 130:461–470
Love L, Johnson MS, Bresler ME et al (1994) The persistent computed tomography nephrogram: its significance in the diagnosis of contrast-associated nephrotoxicity. Br J Radiol 67:951–957
Maeder M, Klein M, Fehr T, Rickli H (2004) Contrast nephropathy: review focusing on prevention. J Am Coll Cardiol 44:1763–1771
Manske CL, Sprafka JM, Strony JT, Wang Y (1990) Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 89:615–620
Marenzi G, Lauri G, Assanelli E et al (2004) Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 44:1780–1785
McCarthy CS, Becker JA (1992) Multiple myeloma and contrast media. Radiology 183:519–521
McCullough PA, Wolyn R, Rocher LL et al (1997) Acute renal failure after coronary intervention: incidence, risk factors and relationship to mortality. Am J Med 103:368–375
Mehran R, Aymong ED, Nikolsky E et al (2004) A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. Development and initial validation. J Am Coll Cardiol 44:1393–1399
Merten GJ, Burgess WP, Gray LV et al (2004) Prevention of contrast induced nephropathy with sodium bicarbonate: a randomized trial. JAMA 291:2328–2338
Mitchell RL, Craig JC, Webster AC (2004) Cochane renal group report. Am J Kidney Dis 43:752–756
Morcos SK (1998) Contrast media-induced nephrotoxicity – questions and answers. Br J Radiol 71:357–365
Morcos SK (2004) Prevention of contrast media nephrotoxicity – the story so far. Clin Radiol 59:381–389
Morcos SK (2005) Prevention of contrast media-induced nephrotoxicity after angiographic procedures. J Vasc Interv Radiol 16:13–23
Morcos SK, Thomsen HS, Webb JAW and members of contrast media safety committee of the European Society of Urogenital Radiology (ESUR) (1999) Contrast media induced nephrotoxicity: a consensus report. Eur Radiol 9:1602–1613
Mueller C, Burkle G, Buerkle HJ et al (2002) Prevention of contrast media-associated nephropathy. Randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 162:329–336
Nash K, Hafeez A, Hou S (2002) Hospital-acquired renal insufficiency. Am J Kidney Dis 39:930–936
Neumayer HH, Junge W, Kufner A, Wenning A (1989) Prevention of radiocontrast-media-induced nephrotoxicity by calcium channel blocker nitrendipine: a prospective randomized clinical trial. Nephrol Dial Transplant 4:1030–1036

Nicholson T, Downes M (2003) Contrast nephrotoxicity and iso-osmolar contrast agents; implications of NEPHRIC. Clin Radiol 58:659–660

Nikolsky E, Mehran R (2003) Understanding the consequences of contrast-induced nephropathy. Rev Cardovasc Med 4 [Suppl 5]:S10–S18

Oldroyd SD, Fang L, Haylor JL, Yates MS, El Nahas AM, Morcos SK (2000) Effects of adenosine receptor antagonists on the responses to contrast media in the isolated rat kidney. Clin Sci 98:303–311

Olsen JC, Salomon B (1996) Utility of the creatinine prior to intravenous contrast studies in the emergency department. J Emerg Med 14:543–546

Pannu N, Manns B, Lee H, Tonelli M (2004) Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int 65:1366–1374

Parfrey PS, Griffiths SM, Barrett BJ et al (1989) Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. N Engl J Med 320:143–149

Rudnik MR, Goldfarb S, Wexler L et al (1995) Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. Kidney Int 47:254–261

Sadeghi HM, Stone GW, Grines CL et al (2003) Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. Circulation 108:2769–2775

Safirstein R, Andrade L, Viera JM (2000) Acetylcysteine and nephrotoxic effects of radiographic contrast agents – a new use for an old drug. N Engl J Med 342:210–211

Sandler CM (2003) Contrast-agent-induced acute renal dysfunction – is iodixanol the answer? N Engl J Med 348:551–553

Solomon R (1998) Contrast medium-induced acute renal failure. Kidney Int 53:230–242

Solomon R, Werner C, Mann D, D'Elia J, Silva P (1994) Effects of saline, mannitol and furosemide on acute decreases in renal function induced by radiocontrast agents. N Engl J Med 331:1416–1420

Stone GW, McCullough PA, Tumlin JA et al (2003) CONTRAST investigators. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA 290:2284–2291

Taylor AJ, Hotchkiss D, Morse RW, McCabe J (1998) PREPARED. Preparation for angiography in renal dysfunction: a randomized trial of in patient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. Chest 114:1570–1574

Tepel M, Giet MVD, Schwarzfeld C et al (2000) Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 343:180–184

Thomsen HS (1999) Contrast nephropathy. In: Thomsen HS, Muller RN, Mattrey RF (eds) Trends in contrast media. Springer, Berlin Heidelberg New York, pp 103–116

Thomsen HS, Golman K, Hemmingsen L, Larsen S, Skaarup P, Svendsen O (1993) Contrast medium induced nephropathy: animal experiments. Front Eur Radiol 9:83–108

Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) In which patients should serum-creatinine be measured before contrast medium administration? Eur Radiol 15:749–756

Tippins RB, Torres WE, Baumgartner BR, Baumgarten DA (2000) Are screening serum creatinine levels necessary prior to outpatient CT examinations? Radiology 216:481–484

Trivedi HS, Moore H, Nasr S et al (2003) A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract 93:c29–c34

Wang A, Holcslaw T, Bashore TM et al (2000) Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. Kidney Int 57:1675-1680

Weisberg L, Kurnik PB, Kurnik RC (1994) Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 45:259–265

Yamazaki H, Matsushita M, Inoue T et al (1997a) Renal cortical retention on delayed CT after angiography and contrast associated nephropathy. Br J Radiol 70:897–902

Yamazaki H, Oi H, Matsushita M et al (1997b) Lack of correlation between gallbladder opacification in delayed CT and contrast-associated nephropathy. Eur Radiol 7:1328–1331

7 Dialysis and Contrast Media

Sameh K. Morcos

CONTENTS

7.1 Introduction

Contrast media induced nephropathy remains an important cause of hospital acquired acute renal failure. Pre-existing renal impairment, especially diabetic nephropathy, and the dose of the contrast medium are major risk factors in the development of contrast medium induced nephropathy (Morcos et al. 1999; Morcos 1998, 2004). It is generally agreed that if contrast medium injection is clinically necessary prophylactic measures should be used to reduce the risk (Morcos et al. 2002). Prophylactic hemodialysis has been proposed to prevent contrast nephrotoxicity in patients with renal impairment, but has not obtained general acceptance. In addition, there is misunderstanding about whether intravascular contrast medium injection in patients on dialysis should be scheduled in relation to the time of the hemodialysis session (Morcos et al. 2002). In this chapter the use of hemodialysis and peritoneal dialysis for the removal of water soluble iodinated or gadolinium based contrast agents in patients with end stage renal disease and the value of hemodialysis in preventing contrast media induced nephrotoxicity in patients with pre-existing renal impairment will be discussed.

S. K. Morcos, MD
Department of Diagnostic Imaging, Northern General Hospital, Sheffield Teaching Hospitals NHS Trust, Herries Road, Sheffield S5 7AU, UK

7.2 Hemodialysis in the Removal of Iodinated Contrast Media

The pharmacokinetic properties of water soluble iodinated contrast media are such that they are distributed in the extra cellular fluid only, protein binding is minimal, they are not metabolized and excretion is mainly by glomerular filtration. The half-life of iodinated contrast media in patients with normal glomerular filtration rate is approximately 2 h but in patients with severe renal dysfunction it can be prolonged to over 30 h depending on the extent of renal impairment. Therefore, in patients with end-stage renal failure the plasma contrast medium concentration remains high for a long period of time. Such patients are at risk of central nervous system reactions such as convulsions and respiratory depression. The effect on the central nervous system could be due either to contrast media or to uremia (Morcos et al. 2002). Delayed severe skin disorders including vasculitis and salivary gland swelling have also been reported in chronic renal failure patients after high dose urography (Furukawa et al. 1996). To reduce the risk of these complications it has been suggested that contrast media should be eliminated from the body as soon as possible.

Several factors influence the elimination of contrast media by hemodialysis (Table 7.1) (Furukawa et al. 1996; Sterner et al. 2000; Waaler et al. 1990; Udea et al. 1996; Matzkies et al. 1999; Moon et al. 1995). First, the size and weight of the contrast media molecules, since the smaller the solute molecule the more easily it moves across the membrane. Comparisons of dialysance (dialysance = blood flow rate of the hemodialysis X extraction

Table 7.1. Factors that influence the elimination of contrast media by hemodialysis

A) Contrast media
Molecular size and weight
Protein binding
Electrical charge
Hydrophilicity
B) Hemodialysis procedure
The permeability and surface area of the hemodialysis membrane
Dialysis membrane material
Blood flow rate
Dialysate flow rate
Duration of dialysis
C) Patient factors
Degree of hepatic and renal excretion
Contrast medium plasma concentration

ratio) values of contrast media from one study to another are usually meaningless because the time period between contrast medium injection and starting dialysis and the dialysis conditions vary from one study to another. In one study under the same conditions the dialysance of nonionic monomeric contrast media was slightly higher than that of ionic dimeric contrast media partly because of the lower molecular weight and size of the monomer (Furukawa et al. 1996). However, in another study elimination of the nonionic monomer iohexol by hemodialysis was similar to that of the nonionic dimer iodixanol which has a molecular mass almost twice that of iohexol (Sterner et al. 2000). Second, binding to plasma proteins, which have large molecular size, also decreases the efficiency of hemodialysis of contrast media. Hydrophilicity of nonionic contrast media is an important factor in determining the protein binding of their molecules. The higher the hydrophilicity the lower is the affinity of the molecules to proteins. The elimination by hemodialysis of the nonionic dimer iodixanol which has high hydrophilicity and very low protein binding was similar to that of the nonionic monomer iohexol (Sterner et al. 2000). The protein binding of the ionic dimer ioxaglate on the other hand is relatively high and amounts to 7.6 ± 1.5% whereas with iohexol it is 1.5 ± 0.3% determined by means of equilibrium dialysis. This difference may be partly responsible for the fact that iohexol was more easily eliminated than ioxaglate (Furukawa et al. 1996). Another possible factor is the molecular aggregation that occurs with ioxaglate and leads to the formation of large particles which are less permeable during hemodialysis. The electrical charge of the molecule also influences dialysance. Ioxaglate is almost completely dissociated in plasma and is negatively charged. As the cellulose diacetate membrane is slightly negatively charged solutes with a negative charge such as ioxaglate move less easily across the membrane (Furukawa et al. 1996).

The degree of hepatic and renal excretion (in patients who are not anuric) may also affect the elimination rate of contrast media during hemodialysis in patients with chronic renal failure (Waaler et al. 1990; Udea et al. 1996).

The elimination of contrast media is not dependent on the pore size of the membrane during dialysis. Under clearly defined conditions the mean clearance rate for the nonionic monomer iopromide was 108 ml/min for high and low flux membranes both with a surface area of 1.3 m^2 (Matzkies et al. 1999). The clearance rate of contrast agents for polyacrylonitrile membranes is a 1.5–3 times higher than that of cuprophan membranes (Matzkies et al. 2000), whereas there is no difference between polyamide and hemophane membranes (Matzkies et al. 1999).

Blood flow does not seem to have an important effect. Removal of contrast agents can be performed at low blood flow rates without loss of efficacy and this is preferable in uremic patients who are prone to develop disequilibrium syndrome because of the rapid removal of the low molecular waste products during intensive dialysis (Moon et al. 1995). The osmotic process contributes to the elimination. Greater amounts of substance are transported across the dialysis membrane when it is exposed to higher concentration. Thus fast reduction of contrast medium concentrations can be achieved by dialysis in patients with high initial plasma levels. A short dialysis time of 2 h can remove contrast medium efficiently (Matzkies et al. 1999).

Dialysis immediately after a procedure involving the intravascular injection of contrast material has been advocated. A prospective clinical study to evaluate this approach was carried out in ten patients on regular hemodialysis (three times a week). The patients received between 40–225 ml of nonionic contrast media and were followed up with clinical and laboratory examination. No significant adverse effects were observed and no patient had clinical features that necessitated emergency dialysis. The average time interval from contrast administration to hemodialysis was 23 h (range 16–47 h). However, immediate post procedure dialysis is unwarranted as a routine practice (Younathan et al. 1994).

7.3 Elimination of Iodinated Contrast Media by Peritoneal Dialysis

Three patients with chronic renal failure (serum creatinine 389–804 μmol/l) underwent coronary angiography with iohexol. Intermittent automated peritoneal dialysis (36–60 l dialysis fluid) was able to remove 43%–72% of the iohexol over 16–18 h (Moon et al. 1995). In another study intermittent peritoneal dialysis for 64 h removed 56% of the injected meglumine diatrizoate (Brooks and Barry 1973). Continuous ambulatory peritoneal dialysis removed 54% (range 36%–80%) of the administrated dose of iopamidol 300 (30 ml) over 7 days using 8 l of dialysis fluid daily. During the same period 27% (range: 36%–80%) of the injected contrast medium was excreted in the urine (Donally et al. 1992). Thus peritoneal dialysis is also effective for removing contrast agents from the body, but takes longer than hemodialysis. No side-effects of the contrast agents were reported in the three studies and this is important since the residual renal function in these patents must be protected.

7.4 Elimination of Gadolinium Based Contrast Media by Dialysis

Contrast enhanced MRI examinations are frequently required in patients with end stage renal disease. In normal subjects the half-life of gadolinium based contrast agent is about 1.5 h and 90% of the injected dose is removed via the kidneys within the first 24 h. The elimination half time of gadolinium-based contrast media in patients with significant reduction in renal function can be prolonged to several hours depending on the degree of renal impairment. Over 80% of the administered dose is usually excreted within 7 days in such patients. The delay in the elimination of gadolinium in patients with significant renal impairment (GFR of 30 ml/min or less) led to the recommendation that hemodialysis should be used in these patients. The extra renal elimination of gadolinium is very small and less than 2% of the injected dose is excreted in the faeces within 5 days of injection (Joffe et al. 1998).

Good hemodialysability and safety of MRI gadolinium based contrast agents have been reported (Joffe et al. 1998; Okada et al. 2001). After three consecutive hemodialysis sessions over 6 days, 97% of the initial amount of gadodiamide was eliminated (Joffe et al. 1998). In another study of 70 patients no side effects were noted (Okada et al. 2001) and there were no side-effects in six patients in whom hemodialysis was performed 3 days after the contrast medium injection. A total of four routine hemodialysis sessions were required to achieve nearly complete removal of gadolinium based contrast medium (Okada et al. 2001).

Continuous ambulatory peritoneal dialysis for 20 days eliminated 69% of the total amount of gadodiamide injected (Joffe et al. 1998) reflecting the low peritoneal clearance. No metabolism or transmetallation of gadodiamide occurred and there were no contrast related adverse events. The slow removal is probably a consequence of altered apparent volume of distribution because of dialysis fluid in the peritoneal cavity and because of the limitations of the peritoneum as a dialysis membrane. The peritoneal clearance of gadopentetate dimeglumine in patients undergoing continuous ambulatory peritoneal dialysis was about 5 ml per minute. No side effects were recorded during a 1-week observation period (Tombach et al. 2001). Injection of gadolinium based contrast media for MRI examinations (0.1–0.3 mmol/kg BW) makes no significant change in renal function (Joffe et al. 1998; Okada et al. 2001; Tombach et al. 2001; Dörsam et al. 1995).

7.5 Prophylactic Hemodialysis in the Prevention of Contrast Media Nephrotoxicity

A variety of approaches have been suggested to prevent contrast media nephrotoxicity including saline hydration, and administration of agents that cause increased renal blood flow or diuresis (Morcos et al. 1999; Morcos 1998, 2004). The role of hemodialysis in preventing contrast medium induced nephrotoxicity has not been proven (Morcos 2004). Several studies have demonstrated that haemodialysis does not offer any protection against contrast medium induced nephropathy (Dehnharts et al. 1998; Vogt et al. 2001; Huber et al. 2002). In addition, the cost of hemodialysis and the associated risks including venous cannulation and the possibility of heparin induced bleeding can only be justified if hemodialysis can be shown to prevent contrast medium induced nephrotoxicity (Morcos 2004).

A total of 30 patients with reduced renal function (mean serum creatinine concentration

212 ± 14 μmol/L) were randomly assigned to receive either hemodialysis for 3 h starting as soon as possible (63 ± 6 min) or conservative treatment with no hemodialysis after administration of a nonionic monomeric contrast medium (Dehnharts et al. 1998). All patients received intravenous infusion of 0.9% saline at the rate of 83 ml/h beginning 12 h before injection of the contrast medium (350 mgI/ml, mean dose 3 ml/kg body weight). In the control group only the infusion of saline was continued for another 12 h after the radiographic procedure. Serum concentration of the contrast agent and creatinine were followed for up to 14 days. Both groups were treated with calcium channel antagonists (nitrendipine 10 mg 12 hourly). The incidence of contrast nephrotoxicity in the hemodialysis group was 53% and in the control group was 40%, so hemodialysis did not decrease the incidence of contrast nephrotoxicity. Patients were hemodialysed as early as possible after contrast medium exposure but the poor efficacy of hemodialysis in preventing contrast nephrotoxicity is related to the very rapid onset of renal injury after administration of contrast medium (Morcos 1998).

Of 113 patients with chronic renal impairment and serum creatinine above 200 μmol/L, 55 were randomly assigned to hemodialysis and 58 to non-hemodialysis after injection of nonionic monomeric contrast media (Vogt et al. 2001). The mean dose of contrast medium injected in the non-hemodialysis group was 143 ± 15 ml and 210 ± 19 ml in the hemodialysis group. The base line serum creatinine was 316 ± 16 and 308 ± 15 μmol/L, respectively. All patients received saline infusion following the same protocol of the previous study. The hemodialysis began 30–280 min after the radiographic procedure (median time 120 min). The incidence of contrast nephrotoxicity in the hemodialysis group was 24% and in the non-hemodialysis group was 16%. There was no significant difference between the two groups in relation to clinically important events (stroke, pulmonary edema, myocardial infarction and death). The higher incidence of nephrotoxicity in the hemodialysis group could be attributed to the larger doses of contrast medium administered in these patients in comparison to the control group. In addition, hemodialysis may cause deterioration of the renal function through activation of inflammatory reactions with release of vasoactive substances that may induce acute hypotension. The strategy of performing hemodialysis immediately after administration of contrast media in patients with reduced renal function does not diminish the rate of complications including the complication of contrast medium induced nephrotoxicity.

7.6 Conclusion

Hemo- and peritoneal dialysis are effective for eliminating iodinated or gadolinium based contrast media. Relating the time of the contrast medium injection to the dialysis schedule is unnecessary. Hemodialysis does not offer any protection against contrast medium induced nephrotoxicity. The ESUR guidelines on dialysis and contrast media administration can be found the Appendix.

References

Brooks MH, Barry KG (1973) Removal of iodinated contrast material by peritoneal dialysis. Nephron 12:10–14

Dehnarts T, Keller E, Gondolf K, Schiffner T, Pavenstadt H, Schollmeyer P (1998) Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol Dial Transplant 13:358–362

Donally PK, Burwell N, McBurney A, Ward JW, Wals J, Warkin EM (1992) Clearance of iopamidol, a non-ionic contrast medium, by CAPD in patients with end-stage renal failure. Br J Radiol 65:1108–1113

Dörsam J, Knopp MV, Schad L, Peische S, Carl S, Oesingmann N (1995) Elimination of gadolinium-DTPA by peritoneal dialysis. Nephrol Dial Transplant 10:1228–1230

Furukawa T, Ueda J, Takahashi S, Sajaguchi K (1996) Elimination of low-osmolality contrast media by haemodialysis. Acta Radiol 37:966–971

Huber W, Jeschke B, Kreymann B et al (2002) Haemodialysis for the prevention of contrast-induced nephropathy. Outcome of 31 patients with severely impaired renal function, comparison with patients at similar risk and review. Invest Radiol 37:471–481

Joffe P, Thomsen HS, Meusel M (1998) The pharmacokinetics of gadodiamide in patients with severe renal insufficiency treated conservatively or undergoing hemodialysis or continuously ambulatory peritoneal dialysis. Acad Radiol 5:491–502

Matzkies FK, Tombach B, Kisters K, Schuhmann G, Hohage H, Schaefer RM (1999) Clearance of iopromide during haemodialysis with high and low flux membranes. Acta Radiol 40:220–223

Matzkies FK, Reinecke H, Tombach B et al (2000) Reduced iopromide elimination in hemodialysis with cuprophan membranes. Acta Radiol 41:671–673

Moon SS, Back S E, Kurkus J, Nilsson-Ehle P (1995) Haemodialysis for elimination of the nonionic contrast medium iohexol after angiography in patients with impaired renal function. Nephron 70:430–437

Morcos SK (1998) Contrast media induced nephrotoxicity-questions and answers. Br J Radiol 71:357–365

Morcos SK (2004) Prevention of contrast media induced nephrotoxicity-the story so far. Clin Radiol 59:381–389

Morcos SK, Thomsen HS, Webb JAW and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) (1999) Contrast media induced nephrotoxicity: a consensus report. Eur Radiol 9:1602–1613

Morcos SK, Thomsen HS, Webb JAW and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) (2002) Dialysis and contrast media. Eur Radiol 12:3026–3030

Okada S, Katagiri K, Kumazaki T, Yokoyama H (2001) Safety of gadolinium contrast agents in haemodialysis patients. Acta Radiol 42:339–341

Sterner G, Frennby B, Mansson S, Ohisson A, Prutz KG, Almen T (2000) Assessing residual renal function and efficiency of hemodialysis – an application for urographic contrast media. Nephron 85:324–333

Tombach B, Bremer C, Reimer P et al (2001) Renal tolerance of a neutral gadolinium chelate (gadobutrol) in patients with chronic renal failure. Results of a randomized study. Radiology 218:651–652

Ueda J, Furukawa T, Takahashi S, Sakaguchi K (1996) Elimination of ioversol by hemodialysis. Acta Radiol 37:826–829

Vogt B, Ferrari P, Schonholzer C et al (2001) Pre-emptive haemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. Am J Med 111:692–698

Waaler A, Svaland M, Fauchald P, Jakobsen JA, Kolmannskog F, Berg KJ (1990) Elimination of iohexol, a low osmolar nonionic contrast medium, by haemodialysis in patients with chronic renal failure. Nephron 56:81–85

Younathan CM, Kaude JV, Cook MD, Shaw GS, Peterson JC (1994) Dialysis is not indicated immediately after administration of nonionic contrast agents in patients with end-stage renal disease treated by maintenance dialysis. AJR 163:969–971

8 Non-Insulin Dependent Diabetes and Contrast Media

Henrik S. Thomsen

CONTENTS

8.1 Introduction

Reports of patients developing lactic acidosis following intravascular iodinated contrast medium administration have caused concern to many radiologists in the last decade. The recommendation of the manufacturers of biguanides that these drugs should be stopped in non-insulin dependent diabetic patients for 2–3 days before intravascular administration of contrast media added to the concern. Health authorities and professional bodies adopted the recommendation, which created practical difficulties for clinical practice in radiology departments. This chapter provides an overview of the literature on the intravascular use of contrast media and biguanide induced lactic acidosis in non-insulin dependent diabetic patients. In current decade the debate about this topic appears to have stopped.

H. S. Thomsen, MD
Professor, Department of Diagnostic Radiology 54E2, Copenhagen University Hospital at Herlev, Herlev Ringvej, 2730 Herlev, Denmark

8.2 Biguanides

The biguanide metformin (dimethylbiguanide) was introduced into clinical practice in 1957. Metformin and the other biguanide agents phenformin and buformin are structurally related to guanidine. Metformin differs in its chemical structure and pharmacological profile from both phenformin and buformin (Dunn and Peters 1995). Biguanides lower serum glucose by inducing anorexia, decreasing gastrointestinal absorption of carbohydrates, inhibiting hepatic gluconeogenesis, and increasing cellular uptake of glucose. They are primarily absorbed by the small intestine. Although there is minimal binding of these drugs to plasma proteins, they have a high affinity for protein binding cells of the gastrointestinal tract and undergo enterohepatic recirculation (Baily and Turner 1996).

The biguanides are used in non-insulin dependent diabetes mellitus in three ways: (a) as primary treatment in overweight patients inadequately controlled by diet, or (b) as adjunct therapy when sulphonurea alone fails, or (c) sometimes in combination with insulin (Monson 1993).

8.3 Renal Handling

The different biguanides have different routes of elimination. Phenformin and buformin undergo hepatic metabolism and renal excretion. Metformin is excreted unchanged in the urine. In the absence of renal or hepatic dysfunction, the half-lives of phenformin, buformin, and metformin are 12, 4, and 1.5 h, respectively. Approximately 90% of metformin is eliminated via the kidneys in 24 h. Metformin does not cause renal failure. However, metformin accumulation sufficient to produce lactic acidosis occurs only in the presence of renal failure (and rarely hepatic failure) (Wilborn and Myrhed 1993;

LaLau et al. 1994). Renal insufficiency with failure to clear metformin and failure of hepatic metabolism and excretion of phenformin lead to accumulation of these biguanides and the potential for fatal lactic acidosis (Sirtori and Parsik 1994).

8.4 Lactic Acidosis

Lactic acidosis is generally defined as a metabolic acidosis caused by accumulation of lactic acid in the blood in excess of 5 mmol with an accompanying blood pH of less than 7.25. Acute renal failure is an important causal factor (Assan et al. 1997). Phenformin was withdrawn from clinical use in many countries in the late 1970s when an association with lactic acidosis was recognized. This tarnished the reputation of biguanides, but lactic acidosis is not a major problem with metformin. The incidence of lactic acidosis associated with metformin is approximately 0.03 cases per 1,000 patients per year, with approximately 50% of cases resulting in death (Dachman 1995). From 1968 to 1991 a total of 110 cases were reported in the literature (Sirtori and Parsik 1994). The incidence is low because lactic acidosis occurs in most patients when one or more contraindications to its use are overlooked, mainly renal insufficiency, leading to high plasma metformin concentrations (Bailey and Turner 1996). It is important to realize that blood lactate concentrations rise in any patient in whom cardiogenic shock or other illness decreases tissue perfusion. In some reported cases the metformin was probably an incidental factor and not responsible for lactic acidosis. Nolan (1997) recommended that biguanides are contraindicated when renal function is markedly reduced (GFR < 70 ml/min, or serum creatinine > 140 μmol/l).

8.5 Iodinated Contrast Media

The use of iodinated contrast media in patients receiving metformin was very controversial in the 1990s (Dachman 1995; Rotter 1995; Rasuli 1996; Nawaz et al. 1998) but now seems to be less of an issue. The potential danger of lactic acidosis relates to the fact that if renal excretion is reduced, metformin accumulates. There is no evidence of interaction of contrast media and metformin. In a review of metformin-associated lactic acidosis (Sirtori and Parsik 1994) only seven of the 110 cases reported in the world literature from 1968 to 1991 had received iodinated contrast material before developing lactic acidosis. Dachman (1996) was able to find 13 documented cases of lactic acidosis after the administration of iodinated contrast material in patients receiving metformin. Most patients either had renal dysfunction before the procedure or continued to use metformin despite the development of contrast medium induced nephropathy. In 12 of the 13 cases, the patients had elevated creatinine levels or decreased creatinine clearance before administration of the contrast medium.

Patients at risk are those who may develop contrast medium-induced renal insufficiency. Patients with diabetic nephropathy – insulin and non-insulin dependent – have the highest risk of developing contrast medium induced nephropathy (Thomsen and Bush 1998; Morcos et al. 1999). The poorer the renal function the higher the risk and dehydration increases the risk even more. Despite the short half-life of metformin (from 1.5 h dependent on the renal function), it is still present in the body when the renal effects of contrast media occur. They develop instantly after the administration of contrast media, but may not be detected until 24–48 h later (Morcos et al. 1999).

Nawaz et al. (1998) showed that patients with normal serum creatinine and who received metformin before angiographic procedures did not develop lactic acidosis. Only patients with abnormal serum creatinine before angiography developed this complication.

8.6 Gadolinium Contrast Media

Although the risk of contrast medium induced nephropathy after gadolinium contrast media is very low, it has been reported to occur, even at the doses approved for MRI (Thomsen 2004). Nonetheless, the possibility of metformin induced lactic acidosis after gadolinium agents is considered to be sufficiently low that determination of serum creatinine before gadolinium is not considered necessary. No special precautions appear to be necessary when gadolinium agents are given in doses recommended for MR to patients taking metformin.

8.7 Guidelines

The drug manufacturers currently recommend that metformin should be stopped 48 h before and for 48 h after the administration of iodinated contrast media. However, there is no firm evidence for this recommendation to be applied to all patients.

Current guidelines (see Appendix) recommend that serum creatinine should be checked before iodinated contrast medium administration in all diabetic patients taking metformin. In patients with a normal serum creatinine, it is recommended that metformin is stopped from the time of iodinated contrast medium administration for 48 h. The serum creatinine should be estimated at 48 h, and metformin only restarted if serum creatinine remains normal. In patients with abnormal renal function, it is recommended that metformin is stopped 48 h before iodinated contrast medium. The serum creatinine/renal function should be estimated 48 h after contrast medium and metformin should be restarted only if it is normalized as metformin is not approved for used in patients with abnormal renal function defined as abnormal serum creatinine level.

The parts of the current guidelines which are open to debate are those referring to patients with normal renal function. It is necessary to check the serum creatinine before restarting metformin and does one need to stop the metformin intake 48 h before contrast administration; can one wait until the day of contrast administration? The presence of normal function, defined as a normal serum creatinine level, does not totally exclude the possibility of lactic acidosis (Westberg 1995). However, in patients with normal serum creatinine the risk of contrast medium induced nephropathy is less than 0.5% when nonionic iodinated agents are used (Rudnick et al. 1995; Thomsen et al. 2005). The necessity for this additional blood test may cause practical difficulties in Radiology Departments. Argument sometimes occurs as to whether it is the responsibility of the referring clinician or of the radiologist. With increasing experience of the use of iodinated contrast media in patients taking metformin, it may be possible to propose that the serum creatinine estimation at 48 h after contrast medium is no longer necessary in patients with normal renal function and that intake of metformin is stopped from the time of and for 48 hours after contrast medium administration.

References

Assan R, Heuclin C, Ganeval D, Bismuth C, George J, Girard JR (1997) Metformin-induced lactic acidosis in the presence of acute renal failure. Diabetologia 13:211–217

Baily CJ, Turner RC (1996) Metformin. N Engl J Med 334:574–579

Dachman AH (1995) New contraindication to intravascular iodinated contrast material. Radiology 197:545

Dachman AH (1996) Answer. Radiology 290:289

Dunn CJ, Peters DH (1995) Metformin. A review of its pharmacological properties and therapeutic use in non-insulin dependent diabetes mellitus. Drugs 49:721–749

LaLau JD, Lacroix C, DeGagney B, Fournier A (1994) Metformin-associated lactic acidosis in diabetic patients with acute renal failure. A critical analysis of its pathogenesis and prognosis. Nephrol Dial Transplant [Suppl] 9:126–129

Mason RA, Arbeit LA, Giron F (1985) Renal dysfunction after arteriography JAMA 253:1001–1004

Monson JP (1993) Selected side-effects. II. Metformin and lactic acidosis. Prescriber J 33:170–173

Morcos SK, Thomsen HS, Webb JAW and members of Contrast Media Safety Committee of European Society Of Urogenital radiology (ESUR) (1999) Contrast media induced nephrotoxicity: a concensus report. Eur Radiol 9:587–588

Nolan DB (1997) Theophylline option for attenuating contrast media-induced nephrotoxicity in patients on metformin. Am J Health Syst Pharm 54:587–588

Nawaz S, Cleveland T, Gaines PA, Chan P (1998) Clinical risk associated with contrast angiography in metformin treated patients: a clinical review. Clin Radiol 53:342-344

Rasuli P (1996) New contradiction to intravascular contrast material. Radiology 290:289

Rotter A (1995) New contraindication to intravascular iodinated contrast material. Radiology 197:545–546

Rudnick MR, Goldfarb S, Wexler L et al (1995) Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. Kidney Int 47:254–261

Sirtori CR, Pasik C (1994) Re-evaluation of biguanide, metformin: mechanism of action and tolerability. Pharmacol Res 30:187–228

Thomsen HS (2004) Gadolinium-based contrast media may be nephrotoxic even at approved doses (case report). Eur Radiol 14:1654–1656

Thomsen HS, Bush WH Jr (1998) Adverse effects of contrast media. Incidence, prevention and management. Drugs Safety 19:313–324

Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) In which patients should serum-creatinine be measured before contrast medium administration? Eur Radiol 15:749–754

Westberg G (1995) Metformin (Glucophage) och röntgenkontrastmedel orsakade njurinsufficiens (in Swedish). Info Från Läkemedelsverket 3:170–171

Wilborn BE, Myrhed M (1993) Metformin-associated lactic acidosis lactic acidosis in Sweden. Eur J Clin Pharmacol 44:589–591

Section III:
Other Adverse Effects

9 Iodinated and Gadolinium Contrast Media During Pregnancy and Lactation

Judith A. W. Webb

CONTENTS

9.1 Pregnancy

Radiological investigations using iodinated contrast medium are not often done during pregnancy to avoid exposing the foetus to ionising radiation (Bury 2002). Occasionally, however, such investigations may be necessary for the mother's health (e.g., CT head scan, CT pulmonary angiogram) and the potential additional hazard from the contrast medium has to be considered. While magnetic resonance imaging avoids the risks of ionising radiation, the possibility of harmful effects of gadolinium contrast media during pregnancy also need to be considered.

9.1.1 Mutagenicity and Teratogenicity of Contrast Media

No mutagenic effects have been shown with ionic iodinated contrast media in vitro (Nelson et al. 1982). No mutagenic or teratogenic effects were found in vivo with nonionic iodinated contrast media tested in animals (Felder 1984; Shaw and Potts 1985; Ralston et al. 1989; Morisetti et al. 1994; Fujikawa et al. 1995; Heglund et al. 1995; Donandieu et al. 1996; Krause et al. 1994). Abnormal micronuclei indicating chromosomal damage have been detected in lymphocytes following radiological investigations using iodinated ionic and nonionic agents (Norman et al. 1978; Cochran et al. 1980; Cochran and Norman 1994). This effect, however, appears to be cytotoxic rather than genetic, and to affect only cells circulating in the blood at the time of the examination (Norman et al. 1978, 2001).

No evidence of either teratogenic effects or chromosomal damage has been shown with gadopentetate dimeglumine alone or together with magnetic resonance imaging in mice or rats (Rofsky et al. 1994, 1995). No teratogenic effects have been shown in animals after gadoteridol, gadobenate dimeglumine or gadoversetamide (Soltys 1992; Morisetti et al. 1999; Wible et al. 2001).

9.1.2 Placental Transfer of Contrast Media

In the human placenta there is only a single layer of chorionic epithelium separating maternal blood from foetal connective tissue (Broughton-Pipkin et al. 1994). Most drugs traverse the chorionic epithelium by diffusion. Current iodinated non-ionic monomers and gadolinium contrast agents which are water-soluble and have molecular weights in the range 500--850 Daltons would be expected to traverse the placenta less easily than lipid-soluble or smaller water-soluble molecules (Bloomfield and Hawkins 1991). Only small amounts of iobitridol, a nonionic iodinated agent, crossed the placenta of rabbits in the 24 h following injection (Bourrinet et al. 1995). Gadolinium agents are present in the placenta of rabbits and rats following intravenous administration to the mother. The amount of gado-

J. A. W. Webb, MD
Department of Diagnostic Radiology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK

linium declines rapidly in the first few hours and in rats reached one hundredth of the initial amount at 24 h (Novak et al. 1993; Okazaki et al. 1996). Gadolinium uptake into the placenta was sufficient for placental imaging in 11 women at 16--37 weeks of pregnancy after 0.1 mmol/kg gadopentetate dimeglumine (Marcos et al. 1997).

9.1.3 Iodinated Contrast Media During Pregnancy

Iodinated contrast agents which cross the placenta into the foetal blood are then excreted by the kidneys into the bladder. When the bladder empties they enter the amniotic fluid and when this is swallowed the contrast media reach the foetal gut. It has been known for many years that intravenous contrast media given to the mother could result in a neonatal pyelogram, or opacification of the neonatal gut (Thomas et al. 1963; Kelleher et al. 1979; Moon et al. 2000). Contrast media injected into the amniotic fluid have been used to opacify the foetal gut before intrauterine transfusion (Raphael et al. 1967). Assays of amniotic fluid for iodine when amniocentesis was done following maternal intravenous urography showed large amounts of iodine 24 h after urography, and much lower amounts 22 days later (Etling et al. 1979). This suggests that contrast media diffuse out through the placenta into the mother as well as passing from the mother into the foetus.

The most important potential harmful effect of iodinated contrast media which cross the placenta is depression of the foetal thyroid. The foetal thyroid is synthesising thyroxine (T4) by 12 weeks gestation under the influence of thyroid stimulating hormone (TSH) and from 30 weeks onwards tri-iodothyronine (T3) levels increase until birth (Ramsay 1986). Foetal thyroid function is essential for the normal development of the central nervous system (Semba and Delange 2001; Delange et al. 2001). Medicines containing iodine are usually considered contraindicated during pregnancy because of the potential for iodide uptake depressing the foetal thyroid (Bloomfield and Hawkins 1991).

When amniography was done using a mixture of lipiodol (iodised ethyl esters of the fatty acids of poppy seed oil) and water-soluble agents, elevated TSH levels were found in most of the neonates in the first week (Rodesch et al. 1976). Several infants subsequently developed hypothyroidism (Rodesch et al. 1976; Stubbe et al. 1980). The fat-soluble agent lipiodol is deposited on the vermix and can then be absorbed by the foetus over a long period. In rabbits, lipiodol crosses the placenta and accumulates in the foetal thyroid (Bourrinet et al. 1997). Lipiodol persists in the body when given intramuscularly. It is used to treat iodine deficiency and results in increased urinary iodine levels for over 12 months (Leverge et al. 2003).

When water-soluble iodinated contrast media were used alone for amniography, no abnormalities in cord blood T4 and T3 were detected (Morrison et al. 1973). The decline in amniotic fluid iodine levels over time after water-soluble iodinated contrast agents were given to the mother suggests diffusion of contrast agents back across the placenta into the mother (Etling et al. 1979). With water-soluble agents the free iodide is the potentially harmful component (van der Molen et al. 2004). In a contrast agent with 300 mg I/ml the upper level of free iodide allowed immediately after production is 50 μg/ml and at 3–5 years after production is 90 μg/ml. In practice, the free iodide concentration is usually one-tenth of these amounts (van der Molen et al. 2004). If the free iodide content of a contrast agent is 50 μg/ml, and if 150 ml of the agent is used for CT pulmonary angiography in a pregnant woman, the total free iodide dose is 7500 μg. Although there are no data about the pharmacodynamics of the free iodide, it is likely to traverse the placenta readily in both directions so that the foetal thyroid is only exposed to the iodide for a short period of time. In pregnant women with impaired renal function, blood levels of contrast medium and free iodide remain higher for longer, and exposure of the foetus is therefore likely to be longer. The neonatal thyroid appears to tolerate high doses of nonionic agents (e.g., 1500 mg I/kg iopamidol) in the first month of life without thyroid function being affected (Bona et al. 1992).

There are no reports of other adverse effects when iodinated contrast media are given during pregnancy. When arteriography and amniography were undertaken with ionic agents, no harmful effects were reported (Raphael et al. 1967; Wholey 1967; Blumberg et al. 1967).

In summary, when water-soluble iodinated contrast media are given intravascularly to pregnant women, it appears that foetal exposure to the contrast agent and any associated free iodide is short-lived. Nonetheless, it is recommended that following exposure the neonatal thyroid function is checked during the first week of life. Although in many countries it is standard paediatric practice to check neo-

natal thyroid function (Klein and Mitchell 2000), it is mandatory that this is done when the mother has received an iodinated contrast agent during pregnancy (see Appendix).

9.1.4 Gadolinium Contrast Media During Pregnancy

Iodinated and gadolinium contrast media are distributed and excreted very similarly suggesting that handling of gadolinium agents during pregnancy is likely to resemble handling of the iodinated agents. In rabbits, gadolinium can be detected in the foetal kidney in the 60 min after it has been given intravenously to the mother (Novak et al. 1993). In rats, radioactively labelled gadodiamide crossed the placenta in small amounts, with only 0.01% remaining in the foetus at 4 h and only minute traces at 24 h (Okazaki et al. 1996). This evidence indicates that gadolinium agents diffuse across the placenta in both directions.

There are relatively few clinical reports of the effects on neonates of giving gadolinium contrast media to the pregnant mother. No adverse effects on the infants were detected in a total of 24 cases reported where the mother had been given gadopentetate dimeglumine in doses of 0.1–0.2 mmol/kg (Marcos et al. 1997; Backhof et al. 1992; Shoenut et al. 1993; Spencer et al. 2000).

Although gadolinium is chelated in all gadolinium contrast media to minimise its toxicity, small amounts of free gadolinium may remain in animals following gadolinium contrast agents (Cacheris et al. 1990; Tweedle et al. 1995). No free gadolinium was detected in the blood of patients with markedly reduced renal function (GFR <10 ml/min) in the 5 days after they received gadolinium contrast media (Normann et al. 2000).

In summary, there appear to be no contraindications to the use of intravascular gadolinium contrast media in pregnant women.

9.2 Lactation

The excretion of drugs into the milk is facilitated when the drugs are lipid-soluble and bind readily to plasma and milk proteins (Wilson et al. 1980). Both iodinated and gadolinium contrast media are water-soluble with minimal protein-binding suggesting that they are likely to enter milk with difficulty. Nonetheless, the drug package inserts indicate that babies should not be breastfed for the 24–48 h after iodinated or gadolinium contrast media are given intravascularly to a lactating patient.

9.2.1 Iodinated Contrast Media in Milk

Early reports suggested that excretion of iodinated contrast media into the milk was very low or not detectable after intravenous ionic agents and an intrathecal nonionic agent (Fitzjohn et al. 1982; Ilett et al. 1981). Even after fat-soluble cholecystographic agents, iodine excretion in the milk was very low (Holmdahl 1956). A detailed study of larger doses (350 mg I/kg) of the nonionic agent iohexol and the ionic agent metrizoate showed that small amounts of these contrast agents reached the milk (Nielsen et al. 1987). It was calculated that with a milk intake of 0.15 l/kg/day, the infant would have received 1.7 mg I/kg with iohexol and 0.7 mg I/kg with metrizoate, corresponding to 0.5% and 0.3% of the maternal dose, respectively (Nielsen et al. 1987). For paediatric urography, the recommended dose is 900 mg I/kg for babies less than 6.5 kg and 600 mg I/kg for babies 7.0 kg or more (Jorulf 1983). The dose of iohexol received in the milk over 24 h is only 0.002% of the dose recommended to be given intravenously for urography. Only very small amounts of iodinated contrast agents in the gut are absorbed into blood. When the non-ionic agent metrizamide was given as an oral contrast agent, a total of 0.8% of the dose was excreted into the urine by the end of the third day (Johansen 1978).

9.2.2 Gadolinium Contrast Media in Milk

Only very small amounts of gadolinium contrast media reach the milk after intravenous administration to the mother. In 20 lactating women who received 0.1–0.2 mmol/kg, less than 0.04% of the intravenous dose was excreted into the milk over 24 h (Kubik-Huch et al. 2000). In two further case reports, the cumulative excretion of gadolinium into the milk over 24 h was 0.011% and 0.023% of the intravenous dose (Schmiedl et al. 1990; Rofsky et al. 1993). The recommended paediatric dose is 0.1–0.2 mmol/kg and this is well tolerated in infants less than 6 months (Marti-Bonmati et al. 2000;

Tsai-Goodman et al. 2004). Thus less than 1% of the recommended intravenous dose to an infant is present in the neonatal gut after the lactating mother has received gadolinium intravenously (Kubik-Huch et al. 2000). When gadolinium contrast media are given orally, very little is absorbed. In adults given gadopentetate dimeglumine (0.005 or 0.01 mmol/kg) orally with mannitol, no change in signal intensity of the urine was detected, indicating that significant gadolinium absorption was unlikely (Laniado et al. 1988). As has been described in the pregnancy section, small amounts of free gadolinium may remain in animals following gadolinium contrast agents (Cacheris et al. 1990; Tweedle et al. 1995).

9.2.3 Summary

The evidence indicates that only a very small amount of either iodinated or gadolinium contrast medium reach the infant's blood when a lactating mother is given these agents intravascularly. The amounts entering the neonatal blood are tiny compared to the amounts of these contrast media given to infants during imaging. The very low risk to the neonate suggests that the potential disruption to the mother and baby if breastfeeding is stopped for 24–48 h after contrast medium is not warranted (see Appendix). As with all drugs and foodstuffs, the baby may notice a change in the taste of the milk.

References

Backhof E, Heijboer RJJ, Algra PR (1992) Inadvertent iv administration of gadopentetate dimeglumine during early pregnancy. AJR Am J Roentgenol 158:1171

Bloomfield TH, Hawkins DF (1991) The effects of drugs on the human fetus. In: Philipp E, Setchell M (eds) Scientific foundations of obstetrics and gynaecology, 4th edn. Butterworth-Heinemann, Oxford, p 320

Blumberg ML, Wohl GT, Wiltchik S, Schwarz R, Emich JP (1967) Placental localisation by amniography. AJR Am J Roentgenol 100:688–697

Bona G, Zaffaroni M, Defilippe C, Gallina MR, Mostert M (1992) Effects of iopamidol on neonatal thyroid function. Eur J Radiol 14:22–25

Bourrinet P, Dencausse A, Havard P, Violas X, Bonnemain B (1995) Transplacental passage and milk excretion of iobitridol. Invest Radiol 30:156–158

Bourrinet P, Dencausse A, Cochet P, Chastin I, Bonnemain B (1997) Secretion in milk and transplacental transfer of two iodised oils, Lipiodol UF and Oriodol, in rabbits. Biol Neonate 71:395–402

Broughton-Pipkin F, Hull D, Stephenson T (1994) Foetal physiology. In: Lamming GE (ed) Marshall's physiology of reproduction, 4th edn. Chapman and Hall, London, p 777

Bury RF (2002) Radiation hazards in urological practice. BJU Int 89:505–509

Cacheris WP, Quay SC, Rocklage SM (1990) The relationship between thermodynamics and the toxicity of gadolinium complexes. Magn Reson Imaging 8:467–481

Cochran ST, Norman A (1994) Induction of micronuclei in lymphocytes of patients undergoing excretory urography with ioversol. Invest Radiol 29:210–212

Cochran ST, Khodadoust A, Norman A (1980) Cytogenetic effects of contrast material in patients undergoing excretory urography. Radiology 136:43–46

Delange F, de Benoist B, Pretell B, Dunn JT (2001) Iodine deficiency in the world: where do we stand at the turn of the century? Thyroid 11:437–447

Donandieu AM, Idee JM, Doncet D et al (1996) Toxicologic profile of iobitridol, a new nonionic low osmolality contrast medium. Acta Radiol [Suppl] 400:17–24

Etling N, Gehin-Fouque F, Vielh JP, Gautray JP (1979) The iodine content of amniotic fluid and placental transfer of iodinated drugs. Obstet Gynecol 53:376-380

Felder E (1984) Iopamidol toxicology. Invest Radiol 19 [Suppl]: S168–S170

Fitzjohn TP, Williams DG, Laker MF, Owen JP (1982) Intravenous urography during lactation. Br J Radiol 55:603–605

Fujikawa K, Sakaguchi Y, Harada S, Holtz, E, Smith JA, Svendson O (1995) Reproductive toxicity of iodixanol, a new non-ionic, iso-tonic contrast medium in rats and rabbits (in Japanese). J Toxicol Sci 20 [Suppl 1]:107–115

Heglund IF, Michelet AA, Blazak WF, Furuhama K, Holtz E (1995) Preclinical pharmacokinetics and general toxicity of iodixanol. Acta Radiol [Suppl] 399:69–82

Holmdahl KH (1956) Cholecystography during lactation. Acta Radiol 45:305–307

Ilett KF, Hackett LP, Paterson JW, McCormick CC (1981) Excretion of metrizamide in milk. Br J Radiol 54:537–538

Johansen JG (1978) Assessment of a non-ionic contrast medium (Amipaque) in the gastrointestinal tract. Invest Radiol 13:523–527

Jorulf H (1983) Iohexol compared with diatrizoate in pediatric urography. Acta Radiol [Suppl] 366:42–45

Kelleher J, Feczko PJ, Radkowski MA, Griscom NT (1979) Neonatal intestinal opacification secondary to transplacental passage of urographic contrast medium. AJR Am J Roentgenol 132:63–65

Klein RZ, Mitchell ML (2000) Hypothyroidism in infants and children. In: Braverman LE, Utiger RD (eds) The thyroid: a fundamental and clinical text, 8th edn. Lippincott, Williams and Wilkins, Philadelphia, pp 973–974

Krause W, Schobel C, Press WR (1994) Preclinical testing of iopromide. 2nd communication: toxicological evaluation. Arzneimittelforschung 44:1275–1279

Kubik-Huch RA, Gottstein Alama NM, Frenzel T et al (2000) Gadopentetate dimeglumine excretion into human breast milk during lactation. Radiol 216:555–558

Laniado M, Kornmesser W, Hamm B, Clauss W, Weinmann H-J, Felix R (1988) MR imaging of the gastrointestinal tract: value of Gd-DTPA. AJR Am J Roentgenol 150:817–821

Leverge R, Bergmann JF, Simoneau G, Tillet Y, Bonnemain B (2003) Bioavailability of oral vs intramuscular iodinated

oil (Lipiodol UF) in healthy subjects. J Endocrinol Invest 26 [Suppl 2]:2–6
Marcos HB, Semelka RC, Worowattanakul S (1997) Normal placenta: gadolinium-enhanced dynamic MR imaging. Radiology 205:493–496
Marti-Bonmati L, Vega T, Benito C et al (2000) Safety and efficacy of Omniscan (gadodimide injection) at 0.1 mmol/kg for MRI in infants younger than 6 months of age: phase III open multicenter study. Invest Radiol 35:141–147
Moon AJ, Katzberg RW, Sherman MP (2000) Transplacental passage of iohexol. J Pediatr 136:548–549
Morisetti A, Tirone P, Luzzani F, de Haen C (1994) Toxicological safety assessment of iomeprol, a new x-ray contrast agent. Eur J Radiol 18 [Suppl 1]:S21–S31
Morisetti A, Bussi S, Tirone P, de Haen C (1999) Toxicological safety evaluation of gadobenate dimeglumine 0.5 M solution for injection (Multihance), a new magnetic resonance imaging contrast medium. J Comput Assist Tomogr 23 [Suppl 1]:S207–S217
Morrison JC, Boyd M, Friedman BI et al (1973) The effects of Renografin-60 on the fetal thyroid. Obstet Gynecol 42:99–103
Nelson JA, Livingstone GK, Moon RG (1982) Mutagenic evaluation of radiographic contrast media. Invest Radiol 17:183–185
Nielsen ST, Matheson I, Rasmussen JN, Skinnemoen K, Andrew E, Hafsahl G (1987) Excretion of iohexol and metrizoate in human breast milk. Acta Radiol 28:523–526
Norman A, Adams FH, Riley RF (1978) Cytogenetic effects of contrast media and tri-iodobenzoic acid derivatives in human lymphocytes. Radiology 129:199–203
Norman A, Cochran ST, Sayre JW (2001) Meta-analysis of increases in micronuclei in peripheral blood lymphocytes after angiography or excretory urography. Radiat Res 15:740–743
Normann PT, Joffe P, Martinsen I, Thomsen HS (2000) Identification and quantification of gadodiamide in serum, peritoneal dialysate and faeces from end-stage renal patients dosed with gadodiamide injection by inductively coupled plasma-atomic emission spectroscopy and comparative analysis by high-performance liquid chromatography. J Pharm Biomed Anal 22:939–947
Novak Z, Thurmond A, Ross PL, Jones MK, Thornburg KI, Katzberg RW (1993) Gadolinium-DTPA transplacental transfer and distribution in fetal tissue in rabbits. Invest Radiol 28:828–830
Okazaki O, Murayama N, Masubuchi N, Nomura H, Hakasui H (1996) Placental transfer and milk secretion of gadodiamide injection in rats. Arzneimittelforschung/Drug Res 46:83–86
Ralston WH, Robbins MS, James P (1989) Reproductive, developmental and genetic toxicity of ioversol. Invest Radiol 24 [Suppl 1]:S16–S22
Ramsay I (1986) The thyroid. In: Philipp EE, Barnes J, Newton M (eds) Scientific foundation of obstetrics and gynaecology, 3rd edn. Heinemann, London, p 463
Raphael MJ, Gordon H, Schiff D (1967) Radiological aspects of intra-uterine blood transfusion. Br J Radiol 40:520–527
Rodesch F, Camus M, Ermans AM, Dodion J, Delange F (1976) Adverse effect of amniofetography on fetal thyroid function. Am J Obstet Gynecol 126:723–726
Rofsky NM, Weinreb JC, Litt AW (1993) Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. J Magn Reson Imaging 3:131–132
Rofsky NM, Pizzarello DJ, Weinreb JC, Ambrosino MM, Rosenberg C (1994) Effect on fetal mouse development of exposure to MR imaging and gadopentetate dimeglumine. J Magn Reson Imaging 4:805–807
Rofsky NM, Pizzarello DJ, Duhaney MO, Falick AK, Prendergast N, Weinreb JC (1995) Effect of magnetic resonance exposure combined with gadopentetate dimeglumine on chromosomes in animal specimens. Acad Radiol 2:492–496
Schmiedl U, Maravilla KR, Gerlach R, Dowling CA (1990) Excretion of gadopentetate dimeglumine in human breast milk. AJR Am J Roentgenol 154:1305–1306
Semba RD, Delange F (2001) Iodine in human milk: perspectives for infant health. Nutr Rev 59:269–278
Shaw DD, Potts DG (1985) Toxicology of iohexol. Invest Radiol [Suppl 1]:S10–S13
Shoenut JP, Semelka RC, Silverman R, Yaffe CS, Micflikier AB (1993) MRI in the diagnosis of Crohn's disease in two pregnant women. J Clin Gastroenterol 17:244–247
Soltys RA (1992) Summary of preclinical safety evaluation of gadoteridol injection. Invest Radiol 27 [Suppl 1]:S7–S11
Spencer JA, Tomlinson AJ, Weston MJ, Lloyd SN (2000) Early report: comparison of breath-hold MR excretory urography. Doppler ultrasound and isotope renography in evaluation of symptomatic hydronephrosis in pregnancy. Clin Radiol 55:446–453
Stubbe P, Heidermann P, Schumbraad P, Ulbrich R (1980) Transient congenital hypothyroidism after amniofetography. Eur J Pediatr 135:97–99
Thomas CR, Lang EK, Lloyd FP (1963) Fetal pyelography – a method for detecting fetal life. Obstet Gynecol 22:335–340
Tsai-Goodman B, Geva T, Odegard KC, Sena LM, Powell AJ (2004) Clinical role, accuracy and technical aspects of cardiovascular magnetic resonance imaging in infants. Am J Cardiol 94:69–74
Tweedle MF, Wedeking P, Kumar K (1995) Biodistribution of radiolabelled, formulated gadopentate, gadoteridol, gadoterate and gadodiamide in mice and rats. Invest Radiol 30:372–380
Van der Molen AJ, Thomsen HS, Morcos SK, members of Contrast Media Safety Committee of European Society of Urogenital Radiology (2004) Effect of iodinated contrast media on thyroid function in adults. Eur Radiol 14:902–907
Wholey MH (1967) Evaluation of arteriography in obstetrics. Radiol Clin North Am 5:121–131
Wible JH Jr, Troup CM, Hynes MR et al (2001) Toxicological assessment of gadoversetamide injection (OPTIMARK), a new contrast-enhancement agent for use in magnetic resonance imaging. Invest Radiol 36:401–412
Wilson JT, Brown RR, Cherek DR et al (1980) Drug excretion in human breast milk: principles, pharmacokinetics and projected consequences. Clin Pharmacokinet 5:1–66

10 Effects on the Blood and Endothelium

Peter Aspelin, Fulvio Stacul, and Sameh K. Morcos

CONTENTS

P. Aspelin, MD
Professor, Division of Radiology, Center for Surgical Sciences, Karolinska Institute, Huddinge University Hospital, 14186 Stockholm, Sweden
F. Stacul, MD
Institute of Radiology, Ospedale di Cattinara, 34149 Trieste, Italy
S. K. Morcos, MD
Department of Diagnostic Imaging, Northern General Hospital, Sheffield Teaching Hospitals NHS Trust, Sheffield S5 7AU, UK

10.1 Introduction

Iodinated contrast media are widely used either to visualize blood vessels (angiography) or to enhance the density of the parenchyma of different organs. In both instances they are administered intravascularly and ideally their effects on blood and endothelium should be minimal. However, all contrast media have some effects on the endothelium, blood and its constituents. There is a vast literature on these effects both in vitro and in vivo. The present chapter summarizes the effects from a clinical perspective in order to clarify whether there are important differences between the types of iodinated contrast media currently in current clinical use.

Iodinated contrast media may be either ionic or nonionic and they all produce various effects on blood components. These effects are thought to be caused by the chemical nature of contrast media, their electrical charge, and by the viscosity and the osmolality of the solution in which they are given. Different contrast media have varying effects on the many components of the blood.

The hematologic effects of iodinated contrast media have been divided into the following categories: red blood cells, white blood cells, endothelium, platelets, coagulation and fibrinolysis.

10.2 Red Blood Cells

The effect of contrast media on red blood cells can be divided into the effects on morphology, aggregation and rheology (flow properties of the blood). When iodinated contrast media come into contact with red blood cells, the normal discoid shape of the red blood cells changes (Aspelin et al. 1980; Nash and Meiselman 1991). Two changes caused by extraction of water may occur: either shrinkage of the red blood cells producing a dessicocyte or changes in shape called echinocyte or stomatocyte deformation.

10.2.1 Red Cell Morphology

Dessicocyte formation is an in vitro effect of dehydration of the red blood cell and is proportional to the osmolality of the contrast media to which it is exposed (Aspelin et al. 1980). It is only observed in a fraction of red blood cells if exposed to almost undiluted high-osmolar contrast medium.

Echinocyte formation in vitro is dependent on the chemotoxicity (including electrical charge, pH or salt concentration) (Chronos et al. 1993) and not the osmolality of the contrast agent. All contrast media including the iso-osmolar dimers may induce some degree of echinocyte formation (Hardeman et al. 1991; Aspelin et al. 1987).

10.2.2 Red Blood Cell Aggregation

Contrast media in vitro cause disaggregation of red blood cell rouleaux and not aggregation as sometimes believed (Aspelin et al. 1987). The reason for the misunderstanding could be that contrast media make red cells more rigid causing precapillary stasis which can be mistaken for increased red blood cell aggregation (Aspelin and Schmid-Schönbein 1978; Aspelin 1992).

10.2.3 Blood Rheology

As compared with normal red blood cells the combined effect of the dessicocyte, echinocyte and stomatocyte is reduced plasticity of the red blood cells (Aspelin and Schmid-Schönbein 1978; Aspelin 1992; Losco et al. 2001). Plasticity is essential for the smooth flow of red blood cells through small capillaries and when it is lost there is a decrease in blood flow especially after intraarterial injections (Dawson et al. 1983; Le Mignon et al. 1988; Strickland et al. 1992b; Pugh 1996). Pure echinocyte and stomatocyte formation without any dehydration of red blood cells produces only minor rheological change (Aspelin et al. 1980; Nash and Meiselman 1991). However, the overall in vivo effect is a mixture of the effect of contrast media on red blood cell morphology, rigidity, viscosity and vascular tone. Contrast media can induce both vasoconstriction and vasodilatation in different organs (Morcos et al. 1998; Mills et al. 1980; Almén et al. 1980; Liss et al. 1996). In the pulmonary circulation contrast media can induce red cell rigidity and pulmonary arterial vasoconstriction leading to an increase in pulmonary vascular resistance (Pugh 1996; Morcos et al. 1998; Mills et al. 1980; Almén et al. 1980). In the kidney contrast media can reduce the blood flow in the vasa recta in the medulla (Liss et al. 1996). It is not clear whether this effect is mainly caused by stasis due to vasoconstriction or by increased red blood cell aggregation in vivo. The morphological red cell changes may also affect the capacity for oxygen delivery and pH buffering (Galtung et al. 2002). However, these effects have not been proven to be of importance in clinical studies (Strickland et al. 1992a).

The overall effect of contrast media on red blood cells has not been shown to be of clinical importance.

10.3 White Blood Cells

The function of the white blood cells is mainly host defense, but their interactions with the endothelial cells and platelets are also important. White blood cells must be able to adhere to the endothelium and migrate through the vessel wall in order to phagocytize and inactivate toxic products. This involves adherence, chemotaxis, degranulation and phagocytosis. In vitro studies have shown that all these processes are affected by contrast media.

10.3.1 Phagocytosis

Contrast media reduce the ability of white blood cells to exhibit phagocytosis (Rasmussen et al. 1988, 1992b; Rasmussen 1998). This effect has only been studied with ionic high osmolar contrast media. It may also be caused by calcium chelating agents in the solution. The clinical importance of these in-vitro observations is not known.

10.3.2 Chemotaxis, Granulocyte Adherence and Inflammation

Contrast media have been shown in vitro to inhibit the chemotoxic response of white blood cells. In vivo

studies have not shown this finding to be significant (Rasmussen et al. 1992c). All contrast media decrease the adherence property of white blood cells (Rasmussen et al. 1992a; Barani et al. 2002; Blann et al. 2001; Zhan et al. 1998). Contrast media may interfere with the inflammatory response of white blood cells in the body (Hernanz-Schulman et al. 2000; Fanning et al. 2002; Laskey and Gellman 2003).

There are no clinical data to suggest that any of these interactions between contrast media and white blood cells are of clinical importance.

10.4 Endothelium

Endothelial cells contribute to the regulation of many aspects of vascular homeostasis, including coagulation, fibrinolysis and platelet function. In addition they are important modulators of vascular tone, primarily by the regulated secretion and rapid clearance of powerful vasoactive mediators such as prostacyclin, nitric oxide, endothelin and adenosine. The endothelium also controls solute permeability and leukocyte movement during the generation of inflammatory and immune responses (Pearson 1991).

Endothelial cells are exposed transiently to high concentrations of contrast media following intravascular administration. The endothelial effects of contrast media may contribute to the hemodynamic disturbances, thrombosis and pulmonary edema associated with the intravascular use of these agents.

Modulation of the production of endothelial vasoactive substances plays an important role in mediating the hemodynamic effects of contrast media particularly in the kidney (Morcos 1998). Contrast media can increase the release and expression of the potent vasoconstrictor peptide endothelin by the endothelial cells (Oldroyd and Morcos 2000). In addition, contrast media may decrease the endothelial production of nitric oxide by reducing the activity of the enzyme nitric oxide synthase which is responsible for the endogenous synthesis of this vasodilator (Schwartz et al. 1994; Heyman et al. 1998). How contrast media increase the release of endothelin or reduce the production of nitric oxide is not fully understood.

Contrast media, particularly high osmolality ionic agents, have cytostatic and cytotoxic effects on endothelial cells which may precipitate thrombosis (Barstad et al. 1996; Wilson and Sage 1994; Laerum 1983; Morgan and Bettmann 1989; Fauser et al. 2001; Gabelman et al. 2001; Sumimura et al. 2003). In addition, contrast media can induce apoptosis (programmed cell death) of endothelial cells (Zhang et al. 2000). An increase in the frequency of apoptosis in the endothelium may alter vascular homeostasis including coagulant and thrombotic properties, permeability and tone of the blood vessel wall as well as vessel growth and angiogenesis (Zhang et al. 2000).

The biocompatibility of contrast media is influenced both by osmolality and chemical structure, particularly the presence of carboxyl groups in the molecules of the ionic agents. In the nonionic media the absence of carboxyl groups and the presence of many hydroxyl groups which increase hydrophilicity markedly improve biocompatibility and significantly reduce cytotoxicity (Heptinstall et al. 1998; Eloy et al. 1991; Labarthe et al. 2003; Albanese et al. 1995). Ionic contrast media, in particular high osmolar agents, have greater effects on enzymes, higher affinity to proteins and lipids in comparison to nonionic media and can induce injury to cell membranes and interfere with cell metabolism (Krause and Niehues 1996; Dawson 1996). In addition, contrast media can penetrate endothelial cells forming dense granules on the luminal surface and pinocytotic vesicles (Nordby et al. 1989).

Ionic contrast media may increase vascular endothelial permeability leading to pulmonary edema (Morcos 2003; Furuta et al. 2001, 2002; Sendo et al. 2000; Tominaga et al. 2001; Emery et al. 2001). Subclinical pulmonary edema without obvious signs or symptoms of respiratory distress is thought to be common after intravascular use of contrast media but its true incidence is difficult to establish (Idée et al. 2002). Pulmonary edema produced by contrast media could also be responsible for the increase in the pulmonary vascular resistance (PVR) caused by these agents (Morcos 2003). Experimental studies have shown that ioxaglate induced the largest increase in PVR of the isolated rat lung preparation and more marked pulmonary edema compared to other classes of contrast media (Furuta et al. 2001, 2002; Sendo et al. 2000; Tominaga et al. 2001; Emery et al. 2001). However, these experimental observations have not been confirmed in larger clinical studies (Idée et al. 2002).

The endothelial effect of high osmolar ionic contrast media is of clinical importance in phlebography because of the increased frequency of thrombosis after the procedure.

10.5 Platelets

Briefly, platelets adhere to exposed collagen, von Willebrand factor and fibrinogen at the site of arterial injury (adhesion step). Adherent platelets are then activated by mediators such as thrombin, collagen, ADP, serotonin, etc. (activation step). Activated platelets degranulate and secrete chemotaxins, clotting factors and vasoconstrictors, thereby promoting thrombin generation, vasospasm and additional platelet accumulation (aggregation step) (Ferguson et al. 2000; Becker 2001). Therefore, when the interaction of contrast media with platelets is assessed, each step of platelet physiology should be evaluated separately.

10.5.1 Experimental Effects

10.5.1.1 Platelet Adhesion

Grabowski et al. (1991) showed that in vitro platelet adhesion/aggregation was inhibited in the order diatrizoate > ioxaglate > iohexol > saline. However, these effects were rapidly diminished because of hemodilution. In a baboon study (Markou et al. 2001), contrast media were found to inhibit platelet deposition on stents in the order ioxaglate > iohexol = iodixanol > saline. Thus, all contrast media inhibit platelet adhesion, with ionic agents being more potent than nonionics.

10.5.1.2 Platelet Activation by Thrombin

In vitro platelet activation by thrombin was inhibited by low osmolar ionic contrast media whereas nonionic monomeric and dimeric contrast media did not affect it (Li and Gabriel 1997).

10.5.1.3 Direct Platelet Activation

Direct activation of platelets (i.e. degranulation and release of the procoagulant content of dense bodies and α-granules) was induced in vitro by nonionic monomeric contrast media. Lesser activation was caused high-osmolar ionic contrast media and there was no activation low-osmolar ionic and nonionic dimeric contrast media (Chronos et al. 1993; Corot et al. 1996). Chronos et al. (1993) showed that blood from patients anticoagulated with heparin and pretreated with aspirin in preparation for percutaneous coronary angioplasty (PTCA) showed the same pattern of nonionic monomeric contrast medium-induced platelet activation as normal subjects.

10.5.1.4 Platelet Aggregation

An inhibitory effect of contrast media on platelet aggregation was first described by Zir et al. (1974) and has been widely investigated since. Ionic contrast media, both high- or low-osmolar, inhibit in vitro platelet aggregation (induced by mediators such as thrombin, ADP or collagen) more than nonionic agents (monomeric or dimeric) (Heptinstall et al. 1998; Eloy et al. 1991). Potentiation of the antithrombotic effects of clopidogrel, an anti-aggregant drug, has been found in rats with an ionic low osmolar contrast medium but not with a nonionic monomer (Labarthe et al. 2003).

10.5.2 Clinical Pharmacology Studies

Clinical pharmacology studies comparing the different categories of contrast media, however, led to more equivocal conclusions than in vitro or animal studies.

In one study of patients, no significant platelet activation (P-selectin expression) was found following left ventriculography or coronary angiography with iohexol (Albanese et al. 1995). Similarly, Arora et al. (1991) and Brzoko et al. (1997) did not find a significant difference between ionic and nonionic contrast media when platelet degranulation markers were measured in peripheral venous samples. Polanowska et al. (1992) reported an increase in the venous level of β-thromboglobulin following arteriography with a high osmolar contrast agent. Conversely, in another study (Jung et al. 2002), following cardiac catheterization, no platelet activation was found with ioxaglate whereas serotonin release was detected following injection of a nonionic monomer. Most of these studies, with the exception of Albanese et al. (1995), evaluated peripheral venous and not local blood samples. It is known that arterial catherization itself may activate platelets.

With respect to platelet aggregation, most clinical pharmacology studies have shown a higher antiaggregatory effect for ionic agents than nonionic monomers, as recently confirmed by Dalby et al. (2002; Eloy et al. 1991). However, one study did not show a difference between these categories of contrast media (Stormorken et al. 1986).

The clinical impact of these in vitro and experimental in vivo changes is debatable and is discussed in the section on coagulation.

In summary, there are no clinical data to suggest that the effect of nonionic contrast media on platelets induces increased coagulation. The mechanisms responsible for the effects of contrast media on platelets are still unclear and clinically significant effects have not been shown.

10.6 Coagulation

10.6.1 In Vitro Effects of Contrast Media

All contrast media inhibit blood coagulation but to different extents. Prothrombin time, reptilase time, activated partial thromboplastin time and recalcification clotting time are significantly increased in proportion to the dose of the contrast media (Eloy et al. 1991). Comparison of assays of fibropeptide A and thrombin-antithrombin complex between ionic agents (both monomeric and dimeric) and nonionic monomers showed that coagulation times were shorter for nonionic monomers, but were always longer than in the controls (Idée et al. 2002; Corot et al. 1989; Engelhart et al. 1988; Grabowski et al. 1991; Parvez and Moncada 1986; Parvez and Vik 1991; Rasuli et al. 1989).

The ionic dimer ioxaglate shows similar anticoagulant activity to the ionic monomers (Eloy et al. 1991). In one study the nonionic dimer iodixanol was significantly less anticoagulant than the nonionic monomer iohexol (Corot et al. 1996) while in another study it was reported that iodixanol affects the bleeding time similarly to nonionic monomers (Melton et al. 1995). However, the precise mechanisms responsible for this inhibition are still unclear. It has been suggested that the main factors are inhibition of activation of factor X, which leads to the formation of thrombin from prothrombin (Eloy et al. 1991; Fay and Parker 1998; Idée and Corot 1999) and inhibition of fibrin polymerization (Stormorken et al. 1986; Fay and Parker 1998; Dawson et al. 1986; Dawson 1999). Al Dieri et al. (2001, 2003) showed that ioxaglate blocks feedback activation of factors V and VIII, significantly inhibits platelet dependent thrombin generation and boosts the effect of abciximab, whereas iodixanol does not. Interference with the assembly of fibrin monomers by contrast media results in poor fibrin stabilization of clots (Chronos et al. 1993; Engelhart et al. 1988).

Therefore, ionic monomers and dimer have similar anticoagulant activity in vitro which is more pronounced than that of nonionic monomers and dimers. Nonionic monomers probably have more anticoagulant effect than nonionic dimers.

10.6.2 Clinical Trials

Clinical data are less easy to evaluate because of patient related and procedure related variability (state of haemostatic system, condition of the vessel wall, use of guidewires, catheters, balloons, stents). Because of the rapid clearance of contrast media, their anticoagulant effect is local rather than systemic and their effect may be not significant if measured in distant peripheral blood vessels.

Following the in vitro observation by Robertson (1987) of more frequent clot formation in blood contaminated syringes with nonionic monomers than with ionic agents, a few case reports of thrombotic complications in diagnostic angiography with nonionic monomers were published (Bashore et al. 1988; Grollman et al. 1988; Millet and Sestier 1989). However, trials have shown no clinical evidence of significant differences in thrombotic complications when ionic agents are compared to nonionic monomers for coronary angiography (Davidson et al. 1990; Schrader 1998).

Randomized trials comparing ioxaglate to nonionic monomers during PTCA have produced conflicting results (Piessens et al. 1993; Grines et al. 1996; Esplugas et al. 1991; Malekianpur et al. 1998; Schrader et al. 1999; Fleisch et al. 1999; Danzi et al. 2003). In the two studies with the largest number of patients, one showed no significant difference between ioxaglate and iomeprol in the incidence of sudden vessel occlusion (Schrader et al. 1999) while the other showed a trend toward less thromboembolic complications with ioxaglate compared to ioversol (Fleisch et al. 1999). Scheller et al. (2001) reported that patients undergoing stent placement

had fewer acute and subacute stent occlusions when imaged using ioxaglate (versus multiple nonionic agents). However, Danzi et al. (2003) recently reported that nonionic monomers (iopamidol and iopromide) did not adversely affect stent patency when compared to ioxaglate. The considerable periprocedural use of antiplatelet agents may explain their results. A meta-analysis comparing nonionic monomers to ioxaglate showed a significant reduction of coronary vessel abrupt occlusions with ioxaglate (Cucherat and Leizorovicz 1999). Iodixanol was compared to ioxaglate in three trials. In one, no significant differences with regard to major adverse cardiac events (MACE) were detected (Bertrand et al. 2000). In a second, high-risk patient group less abrupt vessel occlusions (p=0.05) were found with iodixanol (Davidson et al. 2000). This difference was more significant in patients who did not receive GpIIb/IIIa blockers. In the third, no significant differences between the two media were found and there was no clear advantage with the use of an ionic contrast agent in a large population of patients undergoing percutaneous coronary intervention for both stable and unstable coronary artery disease (Sutton et al. 2002).

10.6.3 Contrast Media Interactions with Angiographic Devices

Interactions of contrast media with angiographic devices have been investigated both in vitro and in vivo. The syringe material greatly influenced the possibility of clot formation in syringes containing contrast media and blood. Glass was a more powerful activator of coagulation than plastic and among the plastic syringes, those made of styrene acrylonitrile activated coagulation more than those made of polypropylene. Furthermore clots formed only in situations where there was very poor angiographic technique (Dawson et al. 1986).

Teflon coated catheters and guidewires are more thrombogenic than polyurethane materials and much more than polyethylene materials (Dawson 1999). Idée and Corot (1999) comprehensively reviewed the many factors influencing clotting in catheters including the length of the procedure, blood/catheter contact time, volume of blood in the catheter, size and type of the catheter, type of contrast material and degree of blood/contrast medium mixture in the catheter. Some of these factors are difficult to control or standardize in clinical studies.

Therefore catheter and guidewire materials probably play a significant role in clinical studies of contrast media and coagulation. The use of equipment with technically improved surfaces will probably largely overcome this problem.

10.7 Fibrinolysis

Contrast media impede fibrinolysis and delay the onset of lysis by recombinant tissue-type plasminogen activator (rt-PA), urokinase and streptokinase (Dehmer et al. 1995). This effect is reduced by increasing the concentration of the lysis agent. Contrast media cause fibrin to form in long/thin fibrils, which have a lower mass/length ratio and are more resistant to fibrinolysis (Gabriel et al. 1991; Parvez et al. 1982). In vitro studies have shown that diatrizoate and iohexol delay the onset of lysis induced by all lysis agents. However, ioxaglate delayed the onset of lysis by rt-PA and urokinase but not by streptokinase (Dehmer et al. 1995). Another in vitro study showed that thrombi formed with iodixanol and iohexol are larger and more resistant to thrombolysis when compared to thrombi formed with ioxaglate (Jones and Goodal 2003). In vivo studies in dogs showed that alteplase-induced thrombolysis could be delayed by iohexol and amidotrizoate whereas ioxaglate had no significant effects (Pislaru et al. 1998). In a small group of patients undergoing pulmonary angiography iohexol significantly increased plasma levels of PAI-1, an inhibitor of t-PA and urokinase, while ioxaglate did not (van Beek et al. 1994). Other effects on fibrinolysis caused by interactions of contrast media with concomitantly given drugs are described in more detail in Chap. 14.

10.8 Conclusion

All contrast agents may alter the morphology and function of red blood cells. However, the overall effect of contrast media on red cells has not been shown to be of clinical importance. Similarly the effect on white blood cells has not been shown to be clinically important.

In vitro studies have shown that nonionic monomers cause more activation of platelets than ionic contrast media. Iso-osmolar dimeric contrast media

have not been shown to activate platelet function. Clinical studies have not confirmed these in-vitro observations.

Contrast media have cytostatic, cytotoxic and apoptotic effects on endothelial cells. These effects are more evident with ionic contrast media, in particular high osmolar agents, than with nonionic media. Contrast media induced endothelial injury may play a role in the pathophysiology of the effects of contrast media. These include hemodynamic effects, thrombosis and contrast media-induced pulmonary edema.

The risk of thrombosis induced by contrast media relates to the combined effect on platelets, endothelial cells and coagulation factors. In clinical practice, high osmolar contrast media can induce thrombosis after intravenous injection mainly because of endothelial injury produced by the high osmolality. This effect is less with nonionic low-osmolar and iso-osmolar contrast media.

All contrast media have anticoagulant properties, and ionic media are more anticoagulant than nonionic compounds. Acute and subacute thrombus formation remains a topic of debate including the use of low-osmolar ionic contrast media in preference to low-osmolar nonionic contrast media in coronary interventions. However, the general consensus is that good angiographic technique is the most important factor in reducing thrombotic complications. Drugs and interventional devices that decrease the risk of thromboembolic complications during interventional procedures minimize the importance of the effects of contrast media (Aguirre et al. 1997).

References

Aguirre FV, Simoons ML, Ferguson JJ et al (1997) Impact of contrast media on clinical outcomes following percutaneous coronary interventions with platelet glycoprotein IIb/IIIa inhibition: meta-analysis of clinical trials with abciximab. Abstract. Circulation 96 [Suppl 1]:161

Albanese JR, Venditto JA, Patel GC, Ambrose JA (1995) Effects of ionic and nonionic contrast media on in vitro and in vivo platelet activation. Am J Cardiol 76:1059–1063

Al Dieri R, de Muinck E, Hemker C, Beguin S (2001) An ionic contrast agent inhibits platelet-dependent thrombin generation and boots the effect of abciximab. Thromb Haemost 85:944–945

Al Dieri R, Beguin S, Hemker C (2003) The ionic contrast medium ioxaglate interferes with thrombin-mediated feedback activation of factor V, factor VIII and platelets. J Thromb Haemost 1:269–274

Almén T, Aspelin P, Nilsson P (1980) Aortic and pulmonary arterial pressure after injection of contrast media into the right atrium of the rabbit. Comparison between metrizoate, ioxaglate and iohexol. Acta Radiol [Suppl] 362:37–41

Arora R, Khandelwal M, Gopal A (1991) In vivo effects of nonionic and ionic contrast media on beta-thromboglobulin and fibrinopeptide levels. J Am Coll Cardiol 17:1533–1536

Aspelin P (1992) Contrast media and red blood cell aggregation: interaction dangerous or harmless from a clinical view – an overview. Clin Hemorheol 12:401–406

Aspelin P, Schmid-Schönbein H (1978) Effect of ionic and nonionic contrast media on red cell aggregation in vitro. Acta Radiol Diagn (Stockh) 19:766–784

Aspelin P, Stöhr-Liessen M, Almén T (1980) Effect of Iohexol on human erythrocytes. I. Changes of red cell morphology in vitro. Acta Radiol [Suppl] 362:117–122

Aspelin P, Nilsson PE, Schmid-Schonbein H, Schroder S, Simon R (1987) Effect of four non-ionic contrast media on red blood cells in vitro. III. Deformability. Acta Radiol [Suppl] 370:89–91

Barani J, Gottsater A, Mattiasson I, Lindblad B (2002) Platelet and leukocyte activation during aortoiliac angiography and angioplasty. Eur J Vasc Endovasc Surg 23:220–225

Barstad RM, Buchmann MS, Hamers MJ et al (1996) Effects of ionic and nonionic contrast media on endothelium and on arterial thrombus formation. Acta Radiol 37:954–961

Bashore TM, Davidson CK, Mark DB (1988) Iopamidol use in the cardiac catheterization laboratory: a retrospective analysis of 3313 patients. Cardiology 5:60–100

Becker RC (2001) Markers of platelet activation and thrombin generation. Cardiovasc Toxicol 1:141–145

Bertrand ME, Esplugas E, Piessens J, Rasch W (2000) Influence of a non-ionic, iso-osmolar contrast medium (iodixanol) versus an ionic, low-osmolar contrast medium (ioxaglate) on major adverse cardiac events in patients undergoing percutaneous transluminal coronary angioplasty: a multicenter, randomized, double-blind study. Visipaque in percutaneous transluminal coronary angioplasty VIP Trial Investigators. Circulation 101:131–136

Blann AD, Adams R, Ashleigh R, Naser S, Kirkpatrick U, McCollum CN (2001) Changes in endothelial, leucocyte and platelet markers following contrast medium injection during angiography in patients with peripheral artery disease. Br J Radiol 74:811–817

Brzosko M, Cyrylowski L, Brzosko I, Domanski Z, Fiedorowicz-Fabrycy I (1997). Effects of ionic and non-ionic contrast media on platelet function as evaluated by plasma concentration on beta-thromboglobulin. Br J Radiol 70:1239–1244

Chronos NAF, Goodall AH, Wilson DJ, Sigwart U, Buller NP (1993) Profound platelet degranulation is an important side effect of some types of contrast media used in interventional cardiology. Circulation 88:2035–2044

Corot C, Chronos N, Sabattier V (1996) In vitro comparison of the effects of contrast media on coagulation and platelet activation. Blood Coagul Fibrinolysis 7:602–608

Corot C, Perrin JM, Belleville J, Amiel M, Eloy R (1989) Effect of iodinated contrast media on blood clotting. Invest Radiol 24:390–393

Cucherat M, Leizorovicz A (1999) Effects of non-ionic contrast media on abrupt vessel closure and ischaemic complications after angioplasty. A meta-analysis. Abstract. Am J Cardiol [Suppl] 84:98P

Dalby MCD, Davidson SJ, Burman JF, Clague J, Sigwart U, Davies SW (2002) Systemic platelet effects of contrast

media: implications for cardiologic research and clinical practice. Am Heart J 143:E1

Danzi GB, Capuano C, Sesana M, Predolini S, Baglini R (2003) Nonionic low-osmolar contrast media have no impact on major adverse cardiac events in patients undergoing coronary stenting with appropriate antiplatelet therapy. Catheter Cardiovasc Interv 60:477–482

Davidson CJ, Mark DB, Pieper KS et al (1990) Thrombotic and cardiovascular complications related to non-ionic contrast media during cardiac catheterization: analysis of 8517 patients. Am J Cardiol 65:1481–1484

Davidson CJ, Laskey WK, Hermiller JB et al (2000) Randomized trial of contrast media utilization in high-risk PTCA. The COURT trial. Circulation 101:2172–2177

Dawson P (1996) X-ray contrast-enhancing agents. Eur J Radiol 23:172–177

Dawson P (1999) Contrast media interactions with endothelium and the blood. In: Dawson P, Cosgrove DO, Grainger RG (eds) Textbook of contrast media. Dunitz, London, pp 191–209

Dawson P, Harrison M, Weisblatt E (1983) Effect of contrast media on red cell filtrability and morphology. Br J Radiol 56: 707–710

Dawson P, Hawitt P, Mackle IJ, Machin SJ, Amin S, Bradshaw A (1986) Contrast, coagulation and fibrinolysis. Invest Radiol 21: 248–252

Dehmer GJ, Gresalfi N, Daly D, Oberhardt B, Tate DA (1995) Impairment of fibrinolysis by streptokinase, urokinase and recombinant tissue-type plasminogen activator in the presence of radiographic contrast agents. J Am Coll Cardiol 25:1069–1075

Eloy R, Corot C, Belleville J (1991) Contrast media for angiography: physicochemical properties, pharmacokinetics and biocompatibility. Clin Mater 7:89–197

Emery CJ, Fang L, Laude EA, Morcos SK (2001) Effects of radiographic contrast media on pulmonary vascular resistance of normoxic and chronically hypoxic pulmonary hypertensive rats. Br J Radiol 74:1109–1117

Engelhart JA, Smith DC, Maloney MD, Westengard JC, Bull BS (1988) A technique for estimating the probability of clots in blood/contrast agent mixtures. Invest Radiol 23:923–927

Esplugas E, Cequier A, Jara F et al (1991) Risk of thrombosis during coronary angioplasty with low osmolality contrast media. Am J Cardiol 68:1020–1024

Fanning NF, Manning BJ, Buckley J, Redmond HP (2002) Iodinated contrast media induced neutrophil apoptosis through a mitochondrial and caspase mediated pathway. Br J Radiol 75:861–873

Fauser C, Ullisch EV, Kubler W, Haller C (2001) Differential effects of radiocontrast agents on human umbilical vein endothelial cells: cytotoxicity and modulators of thrombogenicity. Eur J Med Res 6:465–472

Fay WP, Parker AC (1998) Effects of radiographic contrast agents on thrombin formation and activity. Thromb Haemost 80:266–272

Ferguson JJ, Quinn M, Moake JL (2000). Platelet physiology. In: Ferguson JJ, Chronos NA, Harrington RA (eds) Antiplatelet therapy in clinical practice. Dunitz, London, pp 5–34

Fleisch M, Mulhauser B, Garachemani A et al (1999) Impact of ionic (ioxaglate) and non-ionic (ioversol) contrast media on PTCA-related complications. J Am Coll Cardiol 33 [Suppl A]:85A (abstract 1188–1192)

Furuta W, Sendo T, Kataoka Y, Oishi R (2001) Morphologic degeneration of human microvascular endothelial cells induced by iodinated contrast media. Acad Radiol 8:158–161

Furuta W, Yamauchi A, Dohgu S et al (2002) Contrast media increase vascular endothelial permeability by inhibiting nitric oxide production. Invest Radiol 37:13–19

Gabelmann A, Haberstroh J, Weyrich G (2001) Ionic and non-ionic contrast agent-mediated endothelial injury. Quantitative analysis of cell proliferation during endothelial repair. Acta Radiol 42:422–425

Gabriel DA, Jones MR, Reece NS, Boothroyd E, Bashore T (1991) Platelet and fibrin modification by radiographic contrast media. Circ Res 68:881–887

Galtung HK, Sörlundsengen V, Sakariassen KS, Benestad H (2002) Effect of radiologic contrast media on cell volume regulatory mechanisms in human red blood cells. Acad Radiol 9:878–885

Grines CL, Schreiber TL, Savas V et al (1996) A randomized trial of low osmolar ionic versus nonionic contrast media in patients with myocardial infarction or unstable angina undergoing percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 27:1381–1386

Grabowski EF, Kaplan KL, Halpern EF (1991a) Anticoagulant effects of nonionic versus ionic contrast media in angiography syringes. Invest Radiol 26:417–421

Grabowski EF, Rodriquez M, McDonnel SL (1991b) Platelet adhesion/aggregation and endothelial cell function in flowing blood: effect of contrast media. Semin Hematol 28 [Suppl 7]:60–65

Grollman JH Jr, Liu CK, Astone RA, Lurie MD (1988) Thromboembolic complications in coronary angiography associated with the use of non-ionic contrast medium. Cathet Cardiovasc Diagn 14:159–164

Hardeman MR, Goedhart P, Koen IY (1991) The effect of low-osmolar ionic and nonionic contrast media on human blood viscosity, erythrocyte morphology, and aggregation behavior. Invest Radiol 26:810–819

Heptinstall S, White A, Edwards N et al (1998) Differential effects of three radiographic contrast media on platelet aggregation and degranulation: implications for clinical practice? Br J Haematol 103:1023–1030

Hernanz-Schulman M, Vanholder R, Waterloos M-A, Hakim R, Schulman G (2000) Effect of radiographic contrast agents on leukocyte metabolic response. Pediatr Radiol 30:361–368

Heyman S, Goldfarb M, Carmeli F, Shina A, Rahmilewitz D, Brezis M (1998) Effects of radiocontrast agents on intrarenal nitric oxide (NO) and NO synthase activity. Exp Nephrol 6:557–562

Idée J-M, Corot C (1999) Thrombotic risk associated with use of iodinated contrast media in interventional cardiology: pathophysiology and clinical aspects. Fundam Clin Pharmacol 13:613–623

Idée JM, Prigent P, Corot C (2002) Effects of ioxaglate on cultured microvascular endothelial cells: do all in vitro studies actually reflect clinical situations? Acad Radiol 9:98–100

Jones CI, Goodal AH (2003) Differential effects of the iodinated contrast agents Ioxaglate, Iohexol and Iodixanol on thrombus formation and fibrinolysis. Thromb Res 112:65–71

Jung F, Spitzer SG, Pindur G (2002) Effect of an ionic compared to a non-ionic X-ray contrast agent on platelets and coagulation during diagnostic cardiac catheterisation. Pathophysiol Haemost Thromb 32:121–126

Krause W, Niehues D (1996) Biochemical characterization of X-ray contrast media. Invest Radiol 31:30–42
Labarthe B, Idée JM, Burnett R, Corot C (2003) In vivo comparative antithrombotic effect of ioxaglate and iohexol and interaction with the platelet antiaggregant clopidogrel. Invest Radiol 38:34–43
Laerum F (1983) Acute damage to human endothelial cells by brief exposure to contrast media in vitro. Radiology 147:681–684
Laskey WK, Gellman J (2003) Inflammatory markers increase following exposure to radiographic contrast media. Acta Radiol 44:498–503
Le Mignon MM, Ducret MN, Bonnemain B, Donadieu AM (1988) Effect of contrast media on whole blood filtrability. Acta Radiol 29:593–597
Li X, Gabriel DA (1997) Differences between contrast media in the inhibition of platelet activation by specific platelet agonists. Acad Radiol 4:108–114
Liss P, Nygren A, Olsson U, Ulfendahl HR, Erikson U (1996) Effects of contrast media and mannitol on renal medullary blood flow and red cell aggregation in the rat kidney. Kidney Int 49:1268–1275
Losco P, Nash G, Stone P, Ventre J (2001) Comparison of the effects of radiographic contrast media on dehydration and filterability of red blood cells from donors homozygous for hemoglobin A or hemoglobin S. Am J Hematol 68:149–158
Malekianpour M, Bonan R, Lespérance J, Gosselin G, Hudon G, Doucet S (1998) Comparison of ionic and non-ionic low osmolar contrast media in relation to thrombotic complications of angioplasty in patients with unstable angina. Am Heart J 135:1067–1075
Markou CP, Chronos NAF, Hanson SR (2001) Antithromotic effects of ionic and non-ionic contrast media in nonhuman primates. Thromb Haemost 85:488–493
Melton LG, Muga KM, Gabriel DA (1995) Effect of contrast media on in vitro bleeding time: assessment by a hollow fiber instrument. Acad Radiol 2:239–243
Millet PJ, Sestier F (1989) Thromboembolic complications with non-ionic contrast media. Cathet Cardiovasc Diagn 17:192
Mills SR, Jackson BF, Older RA, Heaston DK, Moore AV (1980) The incidence, aetiologies and avoidance of complications of pulmonary angiography in a large series. Radiology 136:295–299
Morcos SK (1998) Contrast media-induced nephrotoxicity-questions and answers. Br J Radiol 71:357–365
Morcos SK (2003) Effects of radiographic contrast media on the lung. Br J Radiol 76:290–295
Morcos SK, Dawson P, Pearson JD et al (1998) The haemodynamic effects of iodinated water soluble radiographic contrast media: a review. Eur J Radiol 29:31–46
Morgan DML, Bettmann MA (1989) Effects of X-ray contrast media and radiation on human vascular endothelial cells in vitro. Cardiovasc Intervent Radiol 12:154–160
Nash GB, Meiselman HJ (1991) Effect of dehydration on the viscoelastic behaviour of red cells. Blood Cells 17:517–522
Nordby A, Thorstensen K, Halgunset J, Haugen OA, Solberg S (1989) Effects on the ATP content of cultured cells after radiographic contrast media exposure – evidence for accumulation of contrast media in cultured cells. Acta Radiol 30:541–547
Oldroyd SD, Morcos SK (2000) Endothelin: what does the radiologist need to know? Br J Radiol 73:1246–1251
Parvez Z, Moncada R (1986) Nonionic contrast medium: effects on blood coagulation and complement activation in vitro. Angiology 37:358–364
Parvez Z, Vik H (1991) Nonionic contrast media and blood clotting. A critical review. Invest Radiol 26 [Suppl 1]:S103–S106; discussion S107–S109
Parvez Z, Moncada R, Messmore HL, Fareed J (1982) Ionic and nonionic contrast media interaction with anticoagulant drugs. Acta Radiol Diagn (Stockh) 23:401–404
Pearson JD (1991) Endothelial cell biology. Radiology 179:9–14
Piessens JH, Stammen F, Vrolix MC et al (1993) Effects of an ionic versus a non-ionic low osmolar contrast agent on the thrombotic complications of coronary angioplasty. Cathet Cardiovasc Diagn 28:99–105
Pislaru S, Pislaru C, Szilard M, Arnout J, van der Werf F (1998) In vivo effects of contrast media on coronary thrombolysis. J Am Coll Cardiol 32:1102–1108
Polanowska R, Wilczynska m, Slawinski W, Goch JH, Augustiniak W, Cierniewski CS (1992) Changes in platelet activity and tissue plasminogène activator during arteriography in patients with chronic limb ischaemia. Thromb Res 65:663–665
Pugh N (1996) Haemodynmic and rheological effects of contrast media: the role of viscosity and osmolality. Eur Radiol 6 [Suppl 2]:S13–S15
Rasmussen F (1998) The influence of radiographic contrast media on some granulocyte functions. Acta Radiol [Suppl] 419:7–35
Rasmussen F, Georgsen J, Grunnet N (1988) Influence of radiographic contrast media on phagocytosis. Acta Radiol 29:589–592
Rasmussen F, Antonsen S, Georgsen J (1992a) Granulocyte adherence is inhibited by radiographic contrast media in vitro. Acta Radiol 33:379–383
Rasmussen F, Georgsen J, Antonsen S, Grunnet N (1992b) Phagocytic properties of granulocytes after intravenous injection of ioxaglate or iohexol. Acta Radiol 33:271–274
Rasmussen F, Georgsen J, Pedersen JO, Antonsen S (1992c) Granulocyte chemotaxis before and after urography. Influence of four different contrast media. Acta Radiol 33:164–168
Rasuli P, McLeish WA, Hammond DI (1989) Anticoagulant effects of contrast materials: in vitro study of iohexol, ioxaglate and diatrizoate. AJR Am J Roentgenol 152:309–311
Robertson HJF (1987) Blood clot formation in angiographic syringes containing nonionic contrast media. Radiology 163:621–622
Scheller B, Hennen B, Pohl A, Schieffer H, Markwirth T (2001) Acute and subacute stent occlusion: risk reduction by ionic contrast media. Eur Heart J 22:385–391
Schrader R (1998) Thrombogenic potential of non-ionic contrast media, fact or fiction? Eur J Radiol 23 [Suppl 1]: S10–S13
Schrader R, Esch I, Ensslen R et al (1999) A randomized trial comparing the impact of a non-ionic (iomeprol) versus an ionic (ioxaglate) low osmolar contrast medium on abrupt vessel closure and ischaemic complications after coronary angioplasty. J Am Coll Cardiol 33:395–402
Schwartz D, Blum M, Peer G et al (1994) Role of nitric oxide (EDRF) in radiocontrast acute renal failure in rats. Am J Physiol 267:F374–F379

Sendo T, Kataoka Y, Takeda Y, Furuta W, Oishi R (2000) Nitric oxide protects against contrast media-induced pulmonary vascular permeability in rats. Invest Radiol 35:472–478

Stormorken H, Skalpe IO, Testart MC (1986) Effects of various contrast media on coagulation, fibrinolysis and platelet function. An in vitro and in vivo study. Invest Radiol 21:348–354

Strickland NH, Rampling MW, Dawson P, Martin G (1992a) Contrast media-induced effects on blood rheology and their importance in angiography. Clin Radiol 45:240–242

Strickland N, Rampling M, Dawson P, Martin G (1992b) The effects of contrast media on the rheological properties of blood. Clin Hemorheol 12:369–379

Sumimura T, Sendo T, Itoh Y et al (2003) Calcium-dependent injury of human microvascular endothelial cells induced by variety of iodinated radiographic contrast media. Invest Radiol 38:366–374

Sutton AGC, Ashton VJ, Campbell PG, Price DJA, Hall JA, de Belder MA (2002) A randomized prospective trial of ioxaglate 320 (Hexabrix) vs iodixanol 320 (Visipaque) in patients undergoing percutaneous coronary intervention. Catheter Cardiovasc Interv 57:346–352

Tominaga K, Kataoka Y, Sendo T, Furuta W, Niizeki M, Oishi AR (2001) Contrast media-induced pulmonary vascular hyperpermeability is aggravated in a rat climacterium model. Invest Radiol 36:131–135

Van Beek EJR, Levi M, Reekers JA, Hack CE, Buller HR, ten Cate JW (1994) Increased plasma levels of PAI-1 after administration of non-ionic contrast medium in patients undergoing pulmonary angiography. Radiology 193:821–823

Wilson AJ, Sage MR (1994) Cytochemical studies on contrast medium-induced blood-brain-barrier damage. Invest Radiol 29 [Suppl 2]:S105–S107

Zhan X, Agrawal DK, Thorpe PE (1998) Effect of iodinated contrast media on neutrophil adhesion to cultured endothelial cells. J Vasc Interv Radiol 9:808–816. Erratum in: J Vasc Interv Radiol 9:889, 1998

Zhang H, Holt CM, Malik N, Shepherd L, Morcos SK (2000) Effects of radiographic contrast media on proliferation and apoptosis of human vascular endothelial cells. Br J Radiol 73:1034–1041

Zir LM, Carvalho AC, Hawthorne JW, Colman RW, Lees RS (1974) Effect of contrast agents on platelet aggregation and ^{14}C-serotonin release. N Engl J Med 291:134–135

11 Effect of Iodinated Contrast Media on Thyroid Function

Aart J. van der Molen

CONTENTS

11.1 Introduction

The two main reasons for development of thyrotoxicosis are Graves' disease and thyroid autonomy. In Graves' disease thyroid stimulating autoantibodies enhance iodine uptake and thyroid hormone synthesis. In thyroid autonomy, the autonomous tissue is not under the control of thyroid stimulating hormone (TSH) and if subjected to high iodine loads produces and secretes excessive thyroid hormone with or without a concomitant decrease in TSH.

A. J. van der Molen
Department of Radiology, C-2S, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

From time to time, the issue of "contrast medium-induced thyrotoxicosis" is brought to the attention of radiologists. Since contrast medium solutions contain some free iodide, contrast media may induce thyrotoxicosis in the above-mentioned patient groups. Iodine deficiency is an important factor in the development of thyroid autonomy and goiter. Therefore, iodine-induced thyrotoxicosis is more commonly seen in areas where the iodine intake is low.

11.2 Terminology

The terms *iodine* and *iodide* are often used interchangeably. Iodine is often used in the generic sense as in "iodine deficiency" or in describing diseases like "iodine-induced thyrotoxicosis". Iodide refers to the metabolically important, non-organic free form that can be present in excess due to a number of factors. Iodine enters the body in the form of iodide or iodate ions. Iodate is rapidly converted to iodide which can be trapped and organically bound in the thyroid gland.

The term *hyperthyroidism* is used to describe excessive secretion of thyroid hormone from the thyroid gland which may or may not become clinically symptomatic. *Thyrotoxicosis* is the preferred term for the clinical syndrome caused by excess thyroid hormone. This excess can come from both endogenous or exogenous sources of iodide.

11.3 Iodine Deficiency Areas

As iodine deficiency is an important factor in the development of thyroid autonomy and multinodular goiter, in iodine deficient areas the number of patients at risk for iodine-induced thyrotoxicosis

is higher. Important geographical differences in iodine intake still exist because of differences in national laws, fortification programs (e.g., iodized salt) and awareness. Global WHO data covering 92% of the world's population show that prevalence is intimately related to iodized salt intake which is highest in the Americas. Therefore, prevalence of iodine deficiency in the general population in the Americas (9.8%) is significantly lower than in Europe (56.9%) which has the highest prevalence worldwide (de Benoist et al. 2003). In 2002, the International Council for Control of Iodine Deficiency Disorders (ICCIDD) designated European countries with sufficient or likely sufficient and deficient or likely deficient iodine nutrition status (Table 11.1) (Vitti et al. 2003). More than 60% of nearly 600 million Europeans live in iodine deficient countries, which include countries such as Germany, France, Belgium, Italy and Spain.

Table 11.1. Iodine nutrition status in Europe by country as designated by the International Council for Control of Iodine Deficiency Disorders (ICCIDD) (Vitti et al. 2003)

Sufficient	Likely sufficient	Deficient	Likely deficient
Austria	Iceland	Belgium	Albania
Bosnia	Luxembourg	Denmark	
Bulgaria	Norway	France	
Croatia	Sweden	Germany	
Cyprus		Greece	
Czech Republic		Hungary	
Finland		Italy	
Macedonia		Ireland	
Netherlands		Montenegro	
Poland		Romania	
Portugal		Slovenia	
Slovak Republic		Spain	
Serbia			
Switzerland			
UK			

11.4 Free Iodide

According to the quality control regulations for production of water-soluble contrast media the content of free iodide per ml is far below the total amount of (organically bound) iodine per ml. In a bottle with a contrast medium concentration of 300 mgI/ml, the upper limit of free iodide is generally below 50 μg/ml directly after production and below 90 μg/ml after 3–5 years of shelf-life. In most products the actual content of free iodide is below one-tenth of these upper limits, depending on the time between production and date of use. For instance, a 150-ml dose of a contrast medium containing 10 μg/ml provides 1500 μg free iodide, equivalent to ten times the recommended daily intake in adults.

In addition, it was shown (Rendl and Saller 2001) that iodinated contrast media molecules can be deiodinated in the body. The resulting amount of free iodide depends on the time that the contrast medium is circulating and is 0.01–0.15% (1 h – 1 week circulation time) of the amount of organically bound iodine administered. Biliary contrast media circulate longer and are metabolized at a greater rate resulting in the release of a significant amount of free iodide in the circulation. Therefore, the effects of biliary contrast media on the thyroid may be greater and persist longer than for the other water-soluble media.

11.5 Effect of Contrast Media on Thyroid Function in Normal, Euthyroid Patients

In an older review (Hehrmann et al. 1996), it was reported that within 21 days of administration of large doses of contrast medium, there is a small decrease followed by an increase within normal limits in free thyroxine (T_4) and a decrease followed by a rapid increase (< 5 days) within normal limits in TSH. More recently, in 102 euthyroid patients that underwent coronary angiography (Fassbender et al. 2001a) subgroup analyses showed small increases in TSH in small glands but decreases in larger glands. Also a discrete increase in free T_4 was seen in patients with large glands and low-normal TSH values. Another study of 22 patients specifically evaluated the early time period after contrast medium administration (Gartner and Weissel 2004). There were increases in TSH 3–5 days after contrast administration, with increases outside the normal range (18%) in patients with basal high-normal TSH values. Thyroid hormone levels were unchanged. This suggests transient subclinical hypothyroidism, a condition more frequently seen in patients with autoimmune (Hashimoto) thyroiditis (Roberts and Ladenson 2004). Thus, in the majority of normal euthyroid patients no changes in thyroid functional parameters are seen, although transient subclinical hypothyroidism or hyperthyroidism may sometimes

occur. However, administration of contrast media to a population of geriatric patients may lead to long-lasting subclinical hyperthyroidism with increased free T_4 and decreased TSH as long as 8 weeks post injection (Conn et al. 1996). This is thought to be caused by undiagnosed autonomous nodules in the thyroid glands of these elderly patients.

11.6 Contrast Medium-Induced Thyrotoxicosis

11.6.1 Mechanism of Contrast Medium-Induced Thyrotoxicosis

Iodine is an essential requirement for thyroid hormone synthesis. The recommended daily intake for adults is about 150 μg. The thyroid gland has intrinsic regulatory mechanisms that maintain thyroid function even in the presence of iodide excess. When large amounts of iodide are given to subjects with normal thyroid function, the synthesis of thyroid hormones decreases transiently for about 2 days. This acute inhibitory effect of iodide on thyroid hormone synthesis is called the Wolff-Chaikoff effect and is due to increased iodide concentration. Escape from, or adaptation to, the acute Wolff-Chaikoff effect is produced by a blockage in the thyroid iodide trap. This reduces the intrathyroidal iodide concentration due to a decrease in the sodium-iodide symporter (NIS) mRNA and protein expression.

Excess iodide ingestion also reduces the release of thyroxine (T_4) and tri-iodothyronine (T_3) from the thyroid. This results in small decreases in serum T_4 and T_3 concentrations with compensatory increases in basal and thyrotropin release hormone (TRH)-stimulated thyrotropin (TSH) concentrations. All values remain in the normal range (Roti and Uberti 2001).

Iodine-induced hyperthyroidism is not a single etiologic entity. It may occur in patients with a variety of underlying thyroid diseases, the most important of which are Graves' disease, and multinodular goiters in patients who live in areas of iodine deficiency. Rare causes of hyperthyroidism include the presence of ectopic thyroid tissue (e.g. in the tongue or thorax), or abnormal autoregulation of thyroid tissue, as can occur in patients with well-differentiated papillary and follicular thyroid carcinoma or its metastases (Roti and Uberti 2001). The exact pathophysiology and epidemiology of the complete spectrum of iodine-induced hyperthyroidism goes beyond the scope of this chapter, and has been reviewed elsewhere (Braverman 1994; Stanbury et al. 1998).

In addition to contrast media, other sources of iodide excess include disinfectants, secretolytic agents, the iodine-containing antiarrhythmic amiodarone, eye drops and ointments, seaweed, multivitamin preparations, skin ointments, toothpaste, etc. (Hehrmann et al. 1996).

11.6.2 Biochemical Diagnosis of Hyperthyroidism

Hyperthyroidism is defined as elevation of plasma free thyroxine (FT_4) or total tri-iodothyronine (T_3) level and suppression of thyroid-stimulating hormone (TSH) level (Martin and Deam 1996).

11.6.3 Prevalence of Contrast Medium-Induced Thyrotoxicosis

Little is known about the true prevalence of iodine-induced thyrotoxicosis caused by to contrast medium. It was calculated (Rendl and Saller 2001) that in an iodine deficient country, 38 cases of thyrotoxic crisis (the most severe form of thyrotoxicosis) due to contrast media are seen per year while in the same year about 5 million contrast-enhanced studies are performed (0.0008 %). Two large studies in unselected populations in an iodine deficient area showed a prevalence of 0.25%–0.34% (Nolte et al. 1996; Hintze et al. 1999), while in an iodine sufficient area this figure is tenfold lower at 0.028 % (de Bruin 1994).

11.6.4 Clinical Symptoms of Thyrotoxicosis

Hyperthyroidism caused by the free iodide in contrast media is usually self-limiting, but in rare cases (and in the presence of risk factors) the free iodide can lead to clinically significant thyrotoxicosis. Hyperthyroidism occurs more frequently in the elderly so the diagnosis may not be apparent, particularly in the presence of cognitive impairment (Martin and Deam 1996). Clinically, it cannot be differentiated from other forms of thyrotoxicosis and, depending on the underlying risk factors, may

give rise to symptoms such as weight loss, nervousness, easy fatigability, intolerance to heat, hyperkinesia, palpitations and cardiac arrhythmias.

The most important manifestations of thyrotoxicosis are cardiovascular. It can aggravate pre-existing cardiac diseases and can also lead to atrial fibrillation, congestive heart failure, worsening of angina, thromboembolism, and rarely death. In the absence of pre-existing cardiac disease, treatment of thyrotoxicosis usually returns cardiac function to normal (Dunn et al. 1998).

Palpitations are probably the most common cardiac symptom. They are caused by either sinus tachycardia or the development of supraventricular tachycardia, usually atrial fibrillation. Atrial fibrillation occurs in 15%–20% of patients with hyperthyroidism, compared with less than 1% of euthyroid adults. Angina is another common symptom. It usually occurs in patients with known coronary disease, but angina from coronary spasm in previously healthy patients has also been reported. Dyspnea on exertion, pulmonary edema and other signs of heart failure can also occur, particularly if cardiomyopathy has developed. Thromboembolic events complicating atrial fibrillation may be the presenting symptom of thyrotoxicosis (Dunn et al. 1998; Roti and Uberti 2001). Tachycardia is the most common sign of thyrotoxicosis at physical examination, occurring in more than 40% of patients on initial presentation. Other signs of a hyperdynamic circulation, such as systolic hypertension and prominent cardiac pulsations, are frequent.

11.6.5 Clinical Studies on Contrast Medium-Induced Thyrotoxicosis

There are very few studies dealing with the development of thyrotoxicosis following injection of contrast media. Patient populations and results may differ depending on whether the study was performed in iodine deficient or iodine sufficient areas.

A number of studies have been undertaken in areas without iodine deficiency. One study showed no effect on serum T_4, T_3 or FT_4 index up to 56 days after cardiac catheterization using meglumine ioxaglate (Grainger and Pennington 1981). Seven patients with multinodular goiter of a cohort of 24,600 CT scans performed over a 3-year period needed hospital admission because of clinically severe iodine-induced hyperthyroidism following administration of a total dose of 3–12 mg free iodide in nonionic contrast media (de Bruin 1994). After CT of the thyroid using 100 ml iohexol, eight of 22 patients with thyroid disease had a temporary change in thyroid function. Four patients showed increases in TSH levels, while in a further four temporary hyperthyroidism developed over a period of 1 month (Nygaard et al. 1998). In geriatric populations, iodine-induced thyrotoxicosis following contrast radiography with iopamidol 370 mgI/ml was the cause in seven of 28 cases of hyperthyroidism seen over 20 months (Martin et al. 1993). Although the condition appeared self-limited, it was associated with increased patient morbidity and prolonged hospital stay. In another study from the same group in 60 patients with hyperthyroidism over the age of 70 years, 23% had been exposed to iodinated contrast media within the previous 6 months. In 62% of the patients hyperthyroidism was not suspected at admission (Martin and Deam 1996).

In an iodine deficient area, the prevalence and pathogenesis of thyrotoxicosis following contrast media administration was evaluated between 1971 and 1979 (Stiedle 1989). In 89 (15%) of 663 patients with thyrotoxicosis the condition could be related to iodine-containing contrast media. The majority (95%) occurred after 12 weeks. Goiter was present in 63% of the patients and the majority of them were elderly. In a large study in unselected patients, only two of 788 developed hyperthyroidism within 12 weeks of coronary angiography (Hintze et al. 1999). Administration of nonionic iodinated contrast medium to 102 euthyroid patients did not lead to hyperthyroidism in any patient despite the large number of nodularly transformed glands and patients with goiter (Fassbender et al. 2001a). The same study showed that thyroid morphology at ultrasound was not a prognostic factor for the development of hyperthyroidism.

Thus, iodine-induced thyrotoxicosis does not seem to be clinically relevant in unselected patient populations or in euthyroid patients. It seems to be relevant only in patients with previous thyroid disease or in patients at risk, especially in areas of iodine deficiency and in geriatric populations.

11.7 Prevention and Prophylaxis of Contrast Media-Induced Thyrotoxicosis

Prevention of iodine-induced thyrotoxicosis in patients at high-risk is important because treatment

with thyrostatic drugs is hindered by the high iodide levels in the blood, and there are more complications associated with treatment than in other forms of thyrotoxicosis.

In patients with risk factors, a strong indication for administering iodinated contrast medium is essential. If there is manifest hyperthyroidism, administration of contrast media is contra-indicated as stated in the drug insert. In other patients at increased risk, diagnostically equivalent alternative imaging modalities not requiring iodinated contrast media should be considered, e.g. ultrasound, MRI, scintigraphy, or unenhanced CT.

In thyroid autonomy the amount of autonomous tissue is one of the key determinants of the risk of iodine-induced hyperthyroidism. The results of a previous Technetium scintigram have been used to quantify the amount of autonomous tissue to stratify risk (Hehrmann et al. 1996; Joseph 1995; Emrich et al. 1993). However, this indication for scintigraphy has fallen into disuse since very sensitive TSH assays became available into general use more recently. To reduce the incidence of iodine-induced thyrotoxicosis further, it has been suggested that prophylactic drugs could be administered, starting well before the examination. The subject of medical prophylaxis is controversial and recommendations are related to the presence or absence of iodine deficiency.

A number of indications and regimens have been suggested. Prophylaxis by perchlorate only in cardiac patients with a goiter and subnormal levels of TSH has been recommended (van Guldener et al. 1998). In a prospective randomized study in high-risk subjects with autonomy, prophylaxis with either perchlorate or thiamazole only prevented small increases in circulating thyroid hormone levels, but was not able to prevent hyperthyroidism completely and combination therapy was advised (Nolte et al. 1996). Administration of perchlorate and a thioamide class drug to elderly patients with suppressed serum TSH and/or palpable goiter has been suggested (Lawrence et al. 1999). It has been recommended that this combination is started the day before and continued for 2 weeks after contrast administration in patients with thyroid autonomy (Hehrmann et al. 1996; Lawrence et al. 1999; Rendl and Saller 2001), but others restrict its use to patients with high Tc-uptake levels (Joseph 1995). A sample combination protocol for prophylaxis is summarized in Table 11.2.

An alternative strategy is to monitor high-risk patients closely using biochemical tests (Nygaard et al. 1998). In euthyroid, not-at-risk patients, iodine-induced hyperthyroidism after coronary angiography was rare and therefore prophylactic therapy was not considered necessary (Hintze et al. 1999). The risk of side effects from medical prophylaxis in these patients is probably greater than the risk of developing iodine-induced thyrotoxicosis.

Table 11.2. Sample combination regimen for prophylaxis of contrast medium-induced thyrotoxicosis

Elective contrast-enhanced studies:		
Sodium Perchlorate	300 mg 3 times daily	Start day before and continue for 8–14 days
Thiamazole	30 mg once daily	Start day before and continue for 14 days
Emergency contrast-enhanced studies:		
Sodium Perchlorate	800 mg once daily	Directly prior to examination Continue with 3×300 mg for 8–14 days
Thiamazole	30 mg once daily	Directly prior to exam and continue for 14 days

11.8 Nuclear Medicine Studies and Contrast Media

For a long time is has been known that giving iodinated contrast media interferes with both diagnostic scintigraphy and radioiodine treatment. It is believed that the reduced uptake of the radioactive tracer is due to the amount of inorganic free iodide in the contrast medium solution which can range from 1–20 μg/ml (Coel et al. 1975; Laurie et al. 1992).

11.8.1 Effect of Contrast Media on Thyroid Scintigraphy

In the nuclear medicine literature, after intravascular (water-soluble) contrast medium administration an interval of 3–6 weeks is advocated before scintigraphy depending on the indication for the study and on whether the patient is euthyroid or hyperthyroid (Wilson and O'Mara 1997; Martin and Sandler 2003). To avoid non-diagnostic studies, some hospitals use an interval as long as 3 months. As biliary contrast agents are metabolized and excreted more slowly, a longer interval of 2 months apply. For reasons of consistency and simplicity a conservative period of 2 months for all types of water-soluble contrast media is recommended (see Appendix) (van der Molen et al. 2004).

11.8.2 Effect of Contrast Media on Radio-Iodine Treatment

Before radio-iodine treatment with ^{131}I, excess iodine should be avoided. Nuclear medicine literature and a European Association of Nuclear Medicine guideline advise that iodinated water-soluble contrast media should be withheld 1–2 months before radio-iodine treatment (Tuttle et al. 2003; European Association of Nuclear Medicine 2003), although some hospitals use even longer periods. Also, in preparation of patients iodine-containing antiseptics (e.g. povidone-iodine) should not be used 2 weeks prior to radio-iodine treatment (Tuttle et al. 2003). It seems advisable to have a period of 2 months between giving iodinated water soluble contrast media and undertaking radioiodine treatment (see Appendix) (van der Molen et al. 2004). Because of slower metabolism and excretion, biliary contrast agents should be withheld for a longer period of 3–4 months.

11.9 Effect of Impaired Renal Function

Water-soluble iodinated contrast medium molecules are almost completely eliminated from the body within 24 h after injection in patients with normal renal function. In patients with a decreased glomerular filtration rate (GFR), elimination is delayed and a longer period of interference with nuclear medicine studies can be expected. There is, however, no evidence of an increased risk of contrast medium-induced thyrotoxicosis in patients with severely reduced renal function (GFR < 20 ml/min). There is no evidence in the literature to suggest that deiodination and the resulting thyrotoxicosis occurs in patients with end-stage renal failure.

11.10 Nonvascular Routes of Administration

Very little data exists on the administration of iodinated contrast media by other routes. Most information concerns contrast administration during endoscopic retrograde cholangiopancreatography (ERCP). Administration of iodinated contrast agents into the biliary and pancreatic ducts during ERCP led to significant increases of serum levels of total iodine and free iodide and of urinary iodine excretion which returned to normal in 2–3 weeks in one study (Mann et al. 1994). Levels of TSH, free T_4, and free T_3 remained unchanged and no hyperthyroidism occurred. However, even a small amount of contrast medium given enterally can be associated with thyroid stimulation (Fassbender et al. 2001b). A decrease of TSH and an increase in total T_3, free T_4 and urinary iodine excretion was reported after ERCP, especially in patients with multinodular goiter. However, clinical symptoms of hyperthyroidism did not occur. A third study concluded that routine measurement of TSH and thyroid hormone levels before ERCP is not indicated given the relatively low iodine load administered during the procedure (Mönig et al. 1999).

10.11 Conclusions

In patients without risk factors, contrast medium-induced thyrotoxicosis is very rare. Thus, it is not necessary routinely to assess thyroid function or morphology before injection of contrast media. However, a small group of patients are at increased risk and radiologists should be aware of the potential effects on thyroid function associated with administration of iodinated contrast media. The history and physical examination are important, and risk factors should always be communicated to the radiologist via the request form.

Patients with Graves' disease and multinodular goiter with thyroid autonomy are at increased risk of developing thyrotoxicosis after iodinated contrast medium. In at-risk patients, the prevalence of contrast medium-induced thyrotoxicosis is significantly higher in iodine deficient areas (Rendl and Saller 2001). Also, iodine-induced thyrotoxicosis has been reported to occur more frequently in the elderly (Conn et al. 1996). Clinically, this thyrotoxicosis is most relevant in patients with an associated cardiovascular risk (Dunn et al. 1998). Nowadays, this geriatric population is exposed to diagnostic imaging including imaging-guided intervention more frequently than in the past because of major technological advances and increased longevity. Although thyroid stimulation is more common in these patients (even following nonvascular administration of contrast), the literature does not unequivocally prove an increased incidence of clinically relevant thyrotoxicosis in the elderly.

Nonetheless, in high risk patients knowledge of thyroid function (at least TSH) before a contrast-enhanced study is helpful. All risk patients should be monitored closely after the injection of an iodinated contrast medium, preferably by endocrinologists (Nygaard et al. 1998). Selected patients (e.g. the elderly patient with multinodular goiter and concomitant cardiac disease) may benefit from prophylactic thyrostatic therapy. In patients with established hyperthyroidism administration of iodinated contrast media is contra-indicated. It is not advisable to use intravenous cholangiographic media in patients at risk (Rendl and Saller 2001).

A more frequently observed problem in clinical practice is a decreased uptake of radioactive technetium and/or iodine in nuclear medicine studies following exposure to iodinated contrast agents. This has compromised diagnosis of thyroid disorders and treatment of thyroid carcinoma. When urgent treatment is essential, gadolinium-based contrast media up to 0.3 mmol/kg body weight may be used in diagnostic studies (Thomsen et al. 2002; Christensen et al. 2000). However, this will seldom result in satisfactory radiographic or CT examinations.

References

Braverman LE (1994) Iodine and the thyroid: 33 years of study. Thyroid 4:351–356

Christensen CR, Glowniak JV, Brown PH et al (2000) The effect of gadolinium contrast media on radioiodine uptake by the thyroid gland. J Nucl Med Technol 28:41–44

Coel M, Talner B, Lang H (1975) Mechanism of radioactive iodine uptake depression following intravenous urography. Br J Radiol 48:146–147

Conn JJ, Sebastian MJ, Deam D et al (1996) A prospective study of the effect of ionic media on thyroid function. Thyroid 6:107–110

De Benoist B, Andersson M, Takkouche B et al (2003) Prevalence of iodine deficiency worldwide. Lancet 362:1859–1860

De Bruin TW (1994) Iodide induced hyperthyroidism with computed tomography contrast fluids (letter). Lancet 343:1160–1161

Dunn JT, Semigran MJ, Delange F (1998) The prevention and management of iodine-induced hyperthyroidism and its cardiac features. Thyroid 8:101–106

Emrich D, Erlenmaier U, Pohl M et al (1993) Determination of the autonomously functioning volume of the thyroid. Eur J Nucl Med 20:410–414

European Association of Nuclear Medicine (2003) EANM procedure guidelines for therapy with iodine-131. Eur J Nucl Med 30:BP27–BP31

Fassbender WJ, Schlüter S, Stracke H et al (2001a) Schilddrüsenfunktion nach Gabe jodhaltigen Röntgenkontrastmittels bei Koronar-angiographie – eine prospektive Untersuchung euthyroiden Patienten. Z Kardiol 90:751–759

Fassbender WJ, Vogel C, Doppl W et al (2001b) Thyroid function, thyroid immunoglobulin status, and urinary iodine excretion after enteral contrast-agent administration by endoscopic retrograde cholangiopancreatography. Endoscopy 33:245–252

Gartner W, Weissel M (2004) Do iodine-containing contrast media induce clinically relevant changes in thyroid function parameters of euthyroid patients within the first week? Thyroid 14:521–524

Grainger RG, Pennington GW (1981) A study of the effect of sodium/meglumine ioxaglate (Hexabrix) on thyroid function. Br J Radiol 54:768–772

Hehrmann R, Klein D, Mayer D et al (1996) Hyperthyreoserisiko bei Kontrastmitteluntersuchungen. Aktuel Radiol 6:243–248

Hintze G, Blombach O, Fink H et al (1999) Risk of iodine-induced thyrotoxicosis after coronary angiography: an investigation in 788 unselected subjects. Eur J Endocrinol 140:264–267

Joseph K (1995) Leser fragen – Experten Antworten. Welche Empfehlungen zur Prophylaxe liegen vor für Patienten mit erhöhtem Hyperthyreoserisiko, wenn eine Untersuchung mit jodhaltigen Kontrastmitteln durchgeführt werden müß? Internist 36:1014–1015

Laurie AJ, Lyon SG, Lasser EC (1992) Contrast material iodides: potential effects on radioactive iodine thyroid uptake. J Nucl Med 33:237–238

Lawrence JE, Lamm SH, Braverman LE (1999) The use of perchlorate for the prevention of thyrotoxicosis in patients given iodine rich contrast agents. J Endocrinol Invest 22:405–407

Mann K, Rendl J, Busley R et al (1994) Systemic iodine absorption during endoscopic application of radiographic contrast agents for endoscopic retrograde cholangiopancreaticography. Eur J Endocrinol 130:498–501

Martin FIR, Deam DR (1996) Hyperthyroidism in elderly hospitalized patients. Clinical features and treatment outcomes. Med J Aust 164:200–203

Martin FIR, Tress BW, Colman PG et al (1993) Iodine-induced hyperthyroidism due to non-ionic contrast radiography in the elderly. Am J Med 95:78–82

Martin WH, Sandler MP (2003) Thyroid imaging: In: Sandler MP, Coleman RE, Patton JE, Wackers FJT, Gottschalk A (eds) Diagnostic nuclear medicine, 4th edn. Lippincott, Williams and Wilkins, Baltimore, pp 607–651

Mönig H, Arendt T, Eggers S et al (1999) Iodine absorption in patients undergoing ERCP compared with coronary angiography. Gastrointest Endosc 50:79–81

Nolte W, Müller R, Siggelkow H et al (1996) Prophylactic application of thyrostatic drugs during excessive iodine exposure in euthyroid patients with thyroid autonomy: a randomized study. Eur J Endocrinol 134:337–341

Nygaard B, Nygaard T, Jensen LI et al (1998) Iohexol: effects on uptake of radioactive iodine in the thyroid and on thyroid function. Acad Radiol 5:409–414

Rendl J, Saller B (2001) Schilddrüse und Röntgenkontrastmittel: Pathophysiologie, Häufigkeit und Prophylaxe der jodinduzierten Hyperthyreose. Dtsch Ärztebl 98:A402–A406

Roberts CGP, Ladenson PW (2004) Hypothyroidism. Lancet 363:793–803

Roti E, Uberti ED (2001) Iodine excess and hyperthyroidism. Thyroid 11:493–500

Stanbury JB, Ermans AE, Bourdoux P et al (1998) Iodine-induced hyperthyroidism: occurence and epidemiology. Thyroid 8:83–100

Stiedle B (1989) Iodine-induced hyperthyroidism after contrast media. Animal experimental and clinical studies. In: Tänzer V, Wend S (eds) Recent developments in nonionic contrast media. Thieme, New York, pp 6–14

Thomsen HS, Almén T, Morcos SK and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (2002) Gadolinium-containing contrast media for radiographic examinations: a position paper. Eur Radiol 12:2600-2605

Tuttle RM, Becker DV, Hurley JR (2003) Radioiodine treatment of thyroid disease: In: Sandler MP, Coleman RE, Patton JE, Wackers FJT, Gottschalk A (eds) Diagnostic nuclear medicine, 4th edn. Lippincott, Williams and Wilkins, Baltimore, pp 653–670

Van der Molen AJ, Thomsen HS, Morcos SK, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (2004) Effect of iodinated contrast media on thyroid function in adults. Eur Radiol 14:902–907

Van Guldener C, Blom DM, Lips P et al (1998) Hyperthyreoidie door jodiumhoudende röntgencontrastmiddelen. Ned Tijdschr Geneeskd 142: 1641–1644

Vitti P, Delange F, Pinchera A et al (2003) Europe is iodine deficient. Lancet 361:1226

Wilson GA, O'Mara RE (1997) Uptake tests, thyroid and whole body imaging with isotopes: In: Falk SA (ed) Thyroid disease: endocrinology, surgery, nuclear medicine and radiotherapy. Lippincott-Raven, Philadelpha, pp 113–133

12 Pulmonary Effects of Radiographic Contrast Media

Sameh K. Morcos

CONTENTS

12.1 Introduction

The lung is an important target organ for the effects of water soluble radiographic contrast media. The pulmonary circulation is the first important vascular bed exposed to contrast medium following intravenous injection and during the venous return after arteriographic examinations (Morcos 2003). Several pulmonary adverse effects may follow the intravascular injection of contrast media, including bronchospasm, pulmonary arterial hypertension and pulmonary edema (Morcos 2000, 2003). In this chapter the effects of contrast media on airways resistance and pulmonary circulation following intravascular administration will be discussed.

12.2 Effects of Contrast Media on Airways Resistance

The adverse respiratory reactions that have been reported with the intravascular use of contrast media include apnea, dyspnea and bronchospasm (Morcos 2000, 2003; Littner et al. 1977, 1981; Dawson et al. 1983; Longstaff and Henson 1985; Wilson and Davis 1988). Bronchospasm has been reported to be a contributory factor in 23% of moderate and 5% of severe adverse reactions to intravascular administration of radiographic contrast media (Morcos 2003). While symptomatic bronchospasm is rare, occurring in 0.01% of patients (Morcos 2003), subclinical bronchospasm detected by a fall in forced expiratory volume in 1 s (FEV1) is common. It tends to be less pronounced with low osmolar nonionic contrast media (Littner et al. 1977, 1981; Dawson et al. 1983; Lonstaff and Henson 1985). However, Wilson and Davies (1988) found that both high osmolar ionic and low osmolar nonionic contrast media produce a comparable fall in FEV_1 and forced vital capacity. Experimental studies in the guinea-pig found that the high osmolar ionic monomer diatrizoate, the low osmolar nonionic monomer iopromide and the isoosmolar nonionic dimer iotrolan did not induce significant increase in airways resistance and only the low osmolar ionic dimer ioxaglate caused bronchospasm (Table 12.1) (Cipolla et al. 1995; Laude et al. 1999). Some retrospective clinical studies also documented a higher incidence of allergy like reactions with ioxaglate in comparison to other types of contrast media (Lasser et al. 1997; Greenberger and Patterson 1991; Laroche et al. 1998). However, there are no prospective clinical studies that have confirmed these observations. In one prospective clinical study, ioxaglate was found to be less likely than conventional high osmolar agents to produce coughing during pulmonary arteriography (Smith et al. 1987).

The pathophysiology of the changes in airways resistance induced by contrast media remains obscure and could be multifactorial. The underlying mechanism may involve the release of bronchospastic mediators [such as histamine, endothelin (ET), 5-hydroxytryptamine, prostaglandins, thromboxane and bradykinin], cholinesterase inhibition, vagal reflex or a direct effect on the bronchi (Dawson et al. 1983; Laude et al. 1999; Assem et al. 1991; Peachell and Morcos 1998; Szolar et al. 1995a,b; Lasser et al. 1971; Ring and Sovak 1981). Contrast media can

S. K. Morcos FRCS, FFRRCSI, FRCR
Department of Diagnostic Imaging, Northern General Hospital NHS Trust, Sheffield S5 7AU, UK

cause the release of histamine, a potent bronchoconstrictor, from mast cells and basophils through a direct effect and indirectly by activating the complement system (Assem et al. 1991; Peachell and Morcos 1998). In vitro studies showed dose-dependent histamine release from human lung mast cells and basophils in response to all types of contrast media (Assem et al. 1991; Peachell and Morcos 1998). The high osmolar diatrizoate induced the largest histamine release from human basophils and human lung mast cells. Ioxaglate and iotrolan caused histamine release from human basophils but not from human lung mast cells. The low osmolar nonionic monomer iopromide was a relatively ineffective activator of histamine release from both human lung mast cells and basophils (Table 12.1) (Peachell and Morcos 1998). The importance of histamine in causing contrast media induced bronchospasm has not been proven conclusively. Experimental studies have shown that pretreatment with anti-histamine H1 receptor antagonist did not prevent contrast media-induced increase in airways resistance (Cipolla et al. 1995; Laude et al. 1999). Pretreatment with prednisolone did not offer any protection against contrast media induced bronchospasm in spite of using the two doses regime recommended by Lasser et al. (1987) (Cipolla et al. 1995; Laude et al. 1999; Lasser 1981, 1998). The use of corticosteroid prophylaxis in preventing contrast media reactions including bronchospasm is controversial. It has been suggested that the use of nonionic agents alone is better in preventing all categories of reactions than the use of high osmolar ionic agents with corticosteroid prophylaxis (Dawson and Sidhu 1993; Wolf et al. 1991).

The role of endothelin (ET) in mediating the bronchospastic effects of contrast media has also been investigated (Laude et al. 1999). ET is a potent smooth muscle constrictor and in the lung produces an increase in the vascular resistance and marked bronchospasm (Laude et al. 1999; Oldroyd and Morcos 2000). A pharmacologically effective dose of non-selective ET antagonist provided no protection against iodinated contrast media-induced bronchospasm in the guinea pig (Laude et al. 1999).

Leakage of fluids from the microcirculation into the lung tissues and bronchi may also cause an increase in airways resistance. Experimental studies in the guinea pig did not show fluid accumulation in the lungs and the bronchi in association with contrast medium-induced rise in airways resistance (Laude et al. 1999). Also aerosolised β_2 adrenergic agonist treatment was able to reverse contrast medium induced increases in airways resistance completely, suggesting that any airway narrowing resulting from edema is minimal (Cipolla et al. 1995; Laude et al. 1999).

A role for cholinesterase inhibition or the vagal reflex in mediating contrast medium-induced bronchospasm has not been confirmed. A direct effect of contrast medium on bronchial smooth muscle cells is possible and contribution of other bronchospastic mediators such as leucotrienes and kinins requires further investigation.

12.3 Effects of Contrast Media on Pulmonary Circulation

An increase in pulmonary artery pressure has been reported following the intravascular injection of contrast media (Frisinger et al. 1965; Mills et al. 1980; Peck et al. 1983; Schrader et al. 1987; Nicod et al. 1987; Rees et al. 1988; Tajima et al. 1994; Pitton et al. 1996; Almen et al. 1980; Sunnegardh et al. 1990; Sorenson et al. 1994). This sudden increase in pulmonary artery pressure is thought to contribute to the morbidity and mortality associated with pulmonary angiography particularly in patients suffering from pulmonary hypertension (Schrader et al. 1987; Nicod et al. 1987; Rees et al. 1998; Tajima et al. 1994; Pitton et al. 1996). There are conflicting reports in the literature about the mechanisms responsible for these effects (Peck et al. 1983; Schrader et al. 1984, 1987; Rees et al. 1988; Almen et al. 1980; Sunnegardh et al. 1990; Sorenson et al. 1994; Kuhtz-Buschbeck et al. 1997; Emery et al. 2001).

Some studies showed that the rise in pulmonary artery pressure is secondary to an increase in pulmonary vascular resistance (PVR) (Schrader et al. 1984; Emery et al. 2001), while others indicated that it is due to an increase in cardiac output associated with a decrease in pulmonary vascular resistance (Almen et al. 1980; Sunnegardh et al. 1990; Sorenson et al. 1994; Kuhtz-Buschbeck et al. 1997). In the studies which suggested a fall in the vascular resistance, the pulmonary vascular resistance was not directly measured and was calculated from the formula pulmonary vascular resistance = (pulmonary artery pressure – pulmonary venous pressure) / cardiac out put. The increase in cardiac output was attributed to reduced peripheral vascular resistance of the systemic circulation caused by

contrast medium induced vasodilatation (Peck et al. 1983; Schrader et al. 1987; Almen et al. 1980; Sunnegardh et al. 1990; Sorenson et al. 1994; Kuhtz-Buschbeck et al. 1997). The fall in pulmonary vascular resistance could be due to an increase in the capacity of the pulmonary vascular bed by recruitment of closed vessels and active vasodilatation of pulmonary arteries (Emery et al. 2001). Experimental studies have shown that contrast media can induce both dilatation and constriction of pulmonary arteries but in systemic vascular beds they induce mainly vasodilatation except in the kidney where vasoconstriction predominates (Morcos et al. 1998; Wang et al. 1997; Morcos 1998).

In the isolated blood perfused lung of the normal rat, iodinated contrast media (iotrolan, iopromide, ioxaglate and diatrizoate) and hypertonic solutions of mannitol caused an overall rise in pulmonary artery pressure reflecting an increase in the pulmonary vascular resistance. The maximum increase in pulmonary artery pressure was observed with the ionic dimer ioxaglate and the least increase with the nonionic monomer iopromide (Emery et al. 2001). In isolated lungs from chronically hypoxic rats, where baseline pulmonary artery pressure and resistance are high, a slow rise in pulmonary artery pressure was observed in response to the contrast media (ioxaglate, iotrolan and iopromide) (Emery et al. 2001). The rise in the pulmonary artery pressure observed with ioxaglate was comparable to that of iotrolan but significantly greater than that with iopromide (Emery et al. 2001).

Surprisingly the isoosmolar iotrolan with the lowest vasoactivity induced a significant increase in the pulmonary vascular resistance of the isolated blood perfused lung of both the normal and chronic hypoxic rat (Emery et al. 2001). High viscosity and rheological effects on red blood cells of iotrolan could be responsible for the observed increase in the vascular resistance of the isolated lung preparation, which is perfused with blood (table) (Emery et al. 2001). The nonionic monomer iopromide had the least effect on pulmonary vascular resistance of both the normotensive and hypertensive rat lung preparation (Emery et al. 2001). This is understandable since iopromide has low vasoactive properties including low viscosity. Its effects on the endothelium are minimal and unlikely to cause pulmonary edema leading to an increase in the pulmonary vascular resistance (Emery et al. 2001; Zhang et al. 2000). Clinical experience has also shown the absence of major hemodynamic effects with the use of low osmolar nonionic monomers in pulmonary angiography even in patients with pulmonary hypertension (Zuckerman et al. 1996; Nilsson et al. 1998).

The increase in pulmonary vascular resistance induced by contrast media is most likely caused by a combination of active vasoconstriction of the pulmonary arteries, pulmonary edema and possibly also by increased blood viscosity (Wang et al. 1997; Dawson et al. 1983; Liss et al. 1996; Spitzer et al. 1999). The increased blood viscosity could be secondary to cellular effects (increased aggregation of red blood cells with nonionic media and rigidity with high osmolar solutions) and the high viscosity of some of the contrast agents (Dawson et al. 1983; Liss et al. 1996; Spitzer et al. 1999). Contrast media may also activate adhesion of leucocytes to the endothelium causing capillary plugging and stasis of red blood cells in the small vessels precipitating an increase in vascular resistance (Emery et al. 2001).

In summary, iodinated contrast media can induce an increase in pulmonary vascular resistance and rise in pulmonary artery pressure through direct effects on the pulmonary circulation. Nonionic monomers produce the least increase in pulmonary artery pressure. The mechanisms responsible for the rise in pulmonary artery pressure remain poorly defined.

12.4 Contrast Medium-Induced Pulmonary Edema

Contrast medium-induced pulmonary edema is often secondary to endothelial injury leading to an increase in the permeability of the microcirculation and accumulation of fluid in the lung (Morcos 2003).

Pulmonary edema produced by contrast media could also be responsible for the increase in the pulmonary vascular resistance and rise in pulmonary artery pressure caused by these agents. Experimental studies have shown that ioxaglate, which induced the largest increase in the pulmonary vascular resistance of the isolated rat lung preparation, is more cytotoxic to the vascular endothelium than diatrizoate and nonionic media (see Table 12.1) (Emery et al. 2001; Zhang et al. 2000; Benyon et al. 1994). Ioxaglate induced greater pulmonary edema in the rat than did nonionic monomeric contrast media (Mare et al. 1984; Sendo et al. 2000; Tominaga et al. 2001). Interestingly, in the rat nitric oxide (Sendo et al. 2000) and estrogen (Tominaga et al. 2001) offered some protection against ioxaglate induced pulmonary edema.

Table 12.1. Summary of the different pulmonary effects of different classes of iodinated contrast media

Effect	Most marked with following categories of contrast medium	Mechanism
Bronchospasm	• Low osmolar ionic dimer	• Remains unknown
(Littner et al. 1981; Longstaff and Henson 1985; Cipolla et al. 1995; Laude et al. 1999)	• High osmolar ionic monomer	
Pulmonary edema	• Low osmolar ionic dimer	• Endothelial injury
(Morcos 2003; Mare et al. 1984; Sendo et al. 2000; Tominaga et al. 2001; Hauggaard 1996; Paul and George 2002)	• High osmolar ionic monomer	• Fluid overload in cardiac patients
Increase in pulmonary vascular resistance	• High osmolar ionic monomer	• Vasoconstriction
(Emery et al. 2001; Wang et al. 1997; Dawson et al. 1983; Liss et al. 1996; Spitzer et al. 1999)	• Low osmolar ionic dimer	• Pulmonary edema
	• Isoosmolar nonionic dimer	• Rheological effects on red blood cells
Histamine release from lung mast cells	• High osmolar ionic monomer	• Direct effect on the mast cells
(Peachell and Morcos 1998)		• Complement activation
Histamine release from basophils	• High osmolar ionic monomer	• Direct effect on basophils
(Assem et al. 1991; Peachell and Morcos 1998)	• Low osmolar ionic dimer	• Complement activation
	• Isoosmolar nonionic dimer	

Pulmonary edema may also occur in patients with incipient cardiac failure, when large doses of contrast medium, particularly when high osmolar agents are used (Morcos 2003; Frisinger et al. 1965). Pulmonary edema has been reported in 10%–20% of cases of fatal reaction to intravenous infusion of contrast media (Hauggard 1996; Paul and George 2002). Sub-clinical pulmonary edema without obvious signs or symptoms of respiratory distress is thought to be common after intravascular contrast media but its true incidence is difficult to establish (Morcos 2003). In the Appendix a simple guideline on reducing the pulmonary effects of iodinated contrast media can be found.

References

Almen T, Aspelin P, Nilsson P (1980) Aortic and pulmonary arterial pressure after injection of contrast media into the right atrium of the rabbit. Acta Radiol [Suppl] 362:37–41

Assem ES, Bray K, Dawson P (1991) The release of histamine from human basophils by radiological contrast agents. Br J Radiol 56:695–712

Benyon HLC, Walport MJ, Dawson P (1994) Vascular endothelial injury by intravascular contrast agents. Invest Radiol 29 [Suppl 2]:195–197

Cipolla P, Castano M, Kirchin MA, de Haen C, Tirone P (1995) Effects of iodinated contrast media on pulmonary airway resistance in anesthetized guinea pigs. Acad Radiol 2:306–312

Dawson P, Sidhu PS (1993) Is there a role for corticosteroid prophylaxis in patients at increased risk of adverse reactions to intravascular contrast agents? Clin Radiol 48:225–226

Dawson P, Harrison MJ, Weisblatt E (1983a) Effects of contrast media on red cell filterability and morphology. Br J Radiol 56:707–710

Dawson P, Pitfield J, Britain J (1983b) Contrast media and bronchospasm: a study with iopamidol. Clin Radiol 34:227–230

Emery CJ, Fang L, Laude EA, Morcos SK (2001) Effects of radiographic contrast media on pulmonary vascular resistance of normoxic and chronically hypoxic pulmonary hypertensive rats. Br J Radiol 74:1109–1117

Frisinger G, Schaffer J, Criley M, Gartner R, Ross J (1965) Haemodynamic consequences of the injection of radiopaque material. Circulation 31:730–740

Greenberger PA, Patterson R (1991) The prevention of immediate generalized reactions to radiocontrast media inhigh-risk patients. J Allergy Clin Immunol 87:867–872

Hauggaard A (1996) Non-cardiogenic pulmonary oedema after intravenous administration of nonionic contrast media. Acta Radiol 37:823–825

Kuhtz-Buschbeck JP, Ehrhardt K, Kohnlein S, Radtke W, Heintzen P (1997) Gadopentetate dimeglumine and iodinated contrast media. Haemodynamic side effects after bolus injection in pigs. Invest Radiol 32:111–119

Laroche D, Aimone-Gastin, Dubois F et al (1998) Mechanisms of severe immediate reactions to iodinated contrast material. Radiology 209:183–190

Lasser EC (1981) Adverse reactions to intravascular administration of contrast media. Allergy 36:369–373

Lasser EC (1998) Pretreatment with corticosteroids to prevent reactions to IV contrast material: overview and implications. AJR Am J Roentgenol 150:257–259

Lasser EC, Walter A, Reuter SR, Lang I (1971) Histamine release by contrast media. Radiology 100:683–686

Lasser EC, Berry CC, Talner LB et al (1987) Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. N Engl J Med 317:845–849

Lasser EC, Berry CC, Mishkin MM, Williamson B, Zheutlin N, Silverman JM (1994) Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. AJR Am J Roentgenol 162:523–526

Lasser EC, Lyon SG, Berry CC (1997) Reports on contrast media reactions: analysis of data from reports to the US Food and Drug Administration. Radiology 203:605-610 (erratum 876)

Laude EA, Emery CJ, Suvarna SK, Morcos SK (1999) The effect of antihistamine, endothelin antagonist and corticosteroid prophylaxis on contrast media induced bronchospasm. Br J Radiol 72:1058–1063

Liss P, Nygren A, Olsson U, Ulfendahl HR, Erikson U (1996) Effects of contrast media and mannitol on renal medullary blood flow and red cell aggregation in the rat kidney. Kidney Int 49:1268–1275

Littner MR, Rosenfield AT, Ulreich S, Putman CE (1977) Evaluation of bronchospasm during excretory urography. Radiology 124:17–21

Littner MR, Ulreich S, Putman CE, Rosenfield AT, Meadows G (1981) Bronchospasm during excretory urography: lack of specificity for the methyl glucamine. AJR Am J Roentgenol 137:477–481

Longstaff AJ, Henson JHL (1985) Bronchospasm following intravenous injection of ionic and nonionic low osmolality contrast media. Clin Radiol 36:651–653

Mare K, Violante M, Zack A (1984) Contrast media induced pulmonary edema. Comparison of ionic and nonionic agents in an animal model. Invest Radiol 19:566–5699

Mills SR, Jackson BF, Older RA, Heaston DK, Moore AV (1980) The incidence, aetiologies and avoidance of complications of pulmonary angiography in a large series. Radiology 136:295–299

Morcos SK (1998) Contrast media-induced nephrotoxicity-questions and answers. Br J Radiol 71:357–365

Morcos SK (2000) Radiological contrast media. In: Dukes MNG, Aronson JK (eds) Meyler's side effects of drugs, 14th edn, chap 46.1. Elsevier Science, Amsterdam, pp 1596–1630

Morcos SK (2003) Effects of radiographic contrast media on the lung. Br J Radiol 76:290–295

Morcos SK, Dawson P, Pearson JD et al (1998) The haemodynamic effects of iodinated water soluble radiographic contrast media: a review. Eur J Radiol 29:31–46

Nicod P, Peterson K, Levine M et al (1987) Pulmonary angiography in severe chronic pulmonary hypertension. Ann Intern Med 107:565–568

Nilsson T, Carlsson A, Mare K (1998) Pulmonary angiography: a safe procedure with modern contrast media and technique. Eur Radiol 8:86–89

Oldroyd SD, Morcos SK (2000) Endothelin: what does the radiologist need to know? Br J Radiol 73:1246–125

Paul RE, George G (2002) Fatal non-cardiogenic pulmonary oedema after intravenous non-ionic radiographic contrast. Lancet 359:1037–1038

Peachell P, Morcos SK (1998) Effect of radiographic contrast media on histamine release from human mast cells and basophils. Br J Radiol 71:24–30

Peck WW, Slutsky RA, Hackney DB et al (1983) Effects of contrast media on pulmonary hemodynamics: comparison of ionic and non-ionic agents. Radiology 149:371–374

Pitton MB, Duber C, Mayer E, Thelen M (1996) Hemodynamic effects of nonionic contrast bolus injection and oxygen inhalation during pulmonary angiography in patients with chronic major vessel thromboembolic pulmonary hypertension. Circulation 94:2485–2491

Rees CR, Palmaz JC, Garcia O, Alvarado R, Siegle RL (1988) The hemodynamic effects of the administration of ionic and nonionic contrast material into the pulmonary arteries of a canine Model of acute pulmonary hypertension. Invest Radiol 23:184–189

Ring J, Sovak M (1981) Release of serotonin from human platelets in vitro by radiographic contrast media. Invest Radiol 16:245–248

Schrader R, Wolpers HG, Korb H et al (1984) Central venous injection of large amounts of contrast media – advantages of low osmolar contrast medium in experimentally induced pulmonary hypertension. Z Kardiol 73:434–441

Schrader R, Hellige G, Kaltenbach M, Kober G (1987) The haemodynamic side-effects of ionic and non-ionic contrast media in the presence of pulmonary hypertension: experimental and clinical investigation. Eur Heart J 8:1322–1331

Sendo T, Kataoka Y, Takeda Y, Furuta W, Oishi R (2000) Nitric oxide protects against contrast media-induced pulmonary vascular permeability in rats. Invest Radiol 35:427–428

Smith DC, Lois JF, Gomes AS, Maloney MD, Yahiku PY (1987) Pulmonary angiography: comparison of cough stimulation effects of diatrizoate and ioxaglate. Radiology 162:617–618

Sorenson L, Sunnegardh O, Svanegard J, Lundquist S, Heitala SO (1994) Systemic and pulmonary haemodynamic effects of intravenous infusion of non-ionic isoosmolar dimeric contrast media. An investigation in the pig of two ratio 6 contrast media. Acta Radiol 35:383–390

Spitzer S, Munster W, Sternitzky R, Bach R, Jung F (1999) Influence of iodixanol-270 and iopentol-150 on the microcirculation in man: influence of viscosity on capillary perfusion. Clin Hemorheol 20:49–55

Sunnegardh O, Heitala SO, Wierell S et al (1990) Systemic, pulmonary and renal haemodynamic effects of intravenously infused Iopental. A comparison in the pig of a new low osmolar non-ionic medium with saline and iohexol. Acta Radiol 31:395–399

Szolar DH, Saeed M, Flueckiger F et al (1995a) Effects of Iopromide on vasoactive peptides and allergy-mediated substances in healthy volunteers. Invest Radiol 30:144–149

Szolar DH, Saeed M, Flueckiger F et al (1995b) Response of vasoactive peptides to a non-ionic contrast media in patients undergoing pulmonary angiography. Invest Radiol 30:511–516

Tajima H, Kumazaki T, Tajima N, Murakami R, Gemma K (1994) Effect of iohexol on pulmonary arterial pressure at pulmonary angiography in patients with pulmonary hypertension. Radiat Med 12:197–199

Tominaga K, Kataoka Y, Sendo T, Furuta W, Niizeki M, Oishi AR (2001) Contrast media-induced pulmonary vascular hyperpermeability is aggravated in a rat climacterium model. Invest Radiol 36:131–135

Wang YX, Emery CJ, Laude E, Morcos SK (1997) Effects of radiocontrast media on the tension of isolated small pulmonary arteries. Br J Radiol 70:1229–1238

Wilson ARM, Davis P (1988) Ventilatory function during urography: a comparison of iopamidol and sodium iosalamate. Clin Radiol 39:490–493

Wolf GL, Mishkin MM, Roux SG et al (1991) Comparison of the rates of adverse drug reactions. Ionic agents, ionic agents combined with steroids and non-ionic agents. Invest Radiol 26:404–410

Zhang H, Holt CM, Malik N, Shepherd L, Morcos SK (2000) Effects of radiographic contrast media on proliferation and apoptosis of human vascular endothelial cells. Br J Radiol 73:1034–1041

Zuckerman DA, Sterling KM, Oser RF (1996) Safety of pulmonary angiography in the 1990s. J Vasc Interv Radiol 7:199–205

13 Phaeochromocytoma

Judith A. W. Webb

CONTENTS

13.1 Introduction

Phaeochromocytomas are relatively rare tumours which originate from chromaffin cells in the adrenal medulla and which secrete the catecholamines adrenaline and noradrenaline (epinephrine and norepinephrine). Less frequently, catecholamine-secreting tumours arise from extra-adrenal chromaffin tissue in and around the sympathetic and parasympathetic chains (paragangliomas). Secretion of catecholamines by phaeochromocytomas and paragangliomas may be continuous or intermittent. Typical clinical presentations include hypertension resistant to conventional treatment and intermittent crises – attacks of hypertension, headache, sweating, anxiety and pallor or flushing. Crises occur when catecholamines are released from the tumour and may be spontaneous or precipitated by drugs or by physical compression of the tumour (Bouloux and Fakeeh 1995). When symptoms suggest the presence of a catecholamine-producing tumour, assays of catecholamines or their metabolites in the urine or plasma are used to confirm the diagnosis (Bouloux and Fakeeh 1995; Lenders et al. 2002).

Once the diagnosis has been established biochemically the tumour is localised by imaging – anatomical (CT or MR) or functional [^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy]. Usually CT of the abdomen is performed and is extended to other areas if an adrenal tumour is not found. Full evaluation necessitates the use of enhancement with intravenously injected iodinated contrast medium. If MR is used for localisation or for staging when malignancy is suspected, a gadolinium contrast agent may be used. Rarely, if tumour localisation is not possible with CT, MR or MIBG, venous sampling may be used particularly to look for extra-adrenal tumours. Venous sampling involves the use of iodinated contrast medium to identify the site of the catheter in the venous system.

Adrenal masses are not infrequently incidentally detected during abdominal imaging with CT, MR or ultrasound. Incidental adrenal masses occur in 5%–9% of the general population at autopsy (Ilias and Pacak 2004). The majority are non-functioning adrenocortical adenomas of no clinical significance (Grumbach et al. 2003). They can be identified on unenhanced CT by low density (<10 HU) scans, and/or by typical washout behaviour after iodinated contrast medium (Korobkin 2000). However, a proportion of incidentally detected adrenal masses are phaeochromocytomas and some phaeochromocytomas have as low density as adenomas on unenhanced CT (Blake et al. 2003). Full evaluation of incidentally detected adrenal masses often involves administration of iodinated agents during CT.

13.2 Iodinated Contrast Media

In the 1960s, adrenal angiography with ionic iodinated agents, usually following α-blockade with phenoxybenzamine, was reported to be relatively safe (Rossi et al. 1968; Alfidi et al. 1969). However, in some patients who had not received α-blockers, ionic iodinated contrast media used for selective angiography and adrenal venography caused significant increases in blood pressure (Alfidi et al.

J. A. W. Webb, MD
Department of Diagnostic Radiology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK

1969; Meaney and Buonocore 1966; Gold et al. 1972). The contrast media were presumed to have caused catecholamine release from the tumours.

This was supported by plasma catecholamine measurement after the ionic contrast medium meglumine iothalamate (Raisanen et al. 1984). The mean change in plasma noradrenaline 10 min after contrast medium was not significantly different between eight patients with phaeochromocytomas and 12 controls. However, in five of the patients the increase in plasma noradrenaline at 10 min was considered sufficient to have produced a rise in blood pressure if they had not already been under α-adrenergic blockade (Raisanen et al. 1984). It became standard practice for all patients with biochemically proven phaeochromocytoma to have full α- and β-adrenergic blockade (e.g., by oral phenoxybenzamine and propranolol) for at least 1 week before contrast medium injection, and to have further phenoxybenzamine intravenously in the 24 h before the procedure (Bouloux and Fakeeh 1995; Francis et al. 1992).

While this approach was safe, it had several disadvantages. The preparation for imaging localisation in biochemically proven phaeochromocytoma was time-consuming. Also, intravenous phenoxybenzamine could interfere with subsequent MIBG imaging (Patel et al. 1995), so that this had to be delayed for at least 10 days after CT. In patients with adrenal masses incidentally detected on CT it was considered unsafe to characterise them fully using enhancement with iodinated contrast medium before catecholamine assay.

More recently, the effects of lower osmolality nonionic contrast medium have been studied in ten patients with phaeochromocytomas or paragangliomas and six controls (Mukherjee et al. 1997). The patients were under full α- and β-adrenergic blockade and had received phenoxybenzamine intravenously 24 h before scanning. No significant differences were detected in the plasma noradrenaline levels between the patients and controls in the 60 min after either iohexol or saline. However, plasma catecholamine levels in the patients were variable and one patient with high basal levels (indicating a highly secretory tumour) showed both an increase in plasma catecholamine after saline and a delayed increase in plasma catecholamine at 60 min after contrast medium considered to be spontaneous. It was therefore recommended that all patients with biochemically diagnosed catecholamine-secreting tumours should have oral α- and β-blockade before intravenous iodinated contrast medium, but that intravenous phenoxybenzamine was not needed if a nonionic agent was to be used (Ilias and Pacak 2004; Mukherjee et al. 1997). Before intra-arterial contrast medium, especially if it is given selectively into the renal or adrenal arteries, full blockade including phenoxybenzamine is recommended (American College of Radiology 2004).

13.3 Gadolinium Contrast Media

There is no specific information about the effects of gadolinium contrast agents on catecholamine-producing tumours. Some of these agents are ionic with higher osmolality while others are nonionic with lower osmolality (Kirchin and Runge 2003). However, the volumes of gadolinium contrast agents injected are usually at least five to ten times less than the volumes of iodinated contrast media. Thus, even with the ionic gadolinium agents, the osmolar load is less than the osmolar load given with a nonionic iodinated agent for CT. Since the increase in plasma catecholamines caused by iodinated contrast media appears osmolality-related (Mukherjee et al. 1997), it seems very unlikely that the small osmolar load with the gadolinium agents will cause a rise in plasma catecholamines. Thus, as with the iodinated agents, it is recommended that patients with known catecholamine-producing tumours are α- and β-blockaded before gadolinium contrast media are given, but blockade with intravenous phenoxybenzamine does not seem necessary. No special precautions are necessary when gadolinium-enhanced imaging of incidentally detected adrenal masses is performed.

13.4 Guideline

The ESUR guideline can be found in the Appendix.

References

Alfidi RJ, Gill WM, Klein HJ (1969) Arteriography of adrenal neoplasms. AJR Am J Roentgenol 106:635–641

American College of Radiology Manual on Contrast Media (2004) Version 5, p 16

Blake MA, Krishnamoorthy SK, Boland GW et al (2003) Low density pheochromocytoma on CT: a mimicker of adrenal adenoma. AJR Am J Roentgenol 181:1663–1668

Bouloux P-MG, Fakeeh M (1995) Investigation of phaeochromocytoma. Clin Endocrinol (Oxf) 43:657–664

Francis I, Gross MD, Shapiro B et al (1992) Integrated imaging of adrenal disease. Radiology 184:1–13

Gold RE, Wisinger BM, Geraci AR, Heinz LM (1972) Hypertensive crisis as a result of adrenal venography in a patient with pheochromocytoma. Radiology 102:579–580

Grumbach MM, Biller BM, Braunstein GD et al (2003) Management of clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med 138:424–429

Ilias I, Pacak K (2004) Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 89:479–491

Kirchin MA, Runge VM (2003) Contrast agents for magnetic resonance imaging: safety update. Top Magn Reson Imag 14:426–435

Korobkin M (2000) CT characterisation of adrenal masses: the time has come. Radiology 217:629–632

Lenders JWM, Pacak K, McClellan MM et al (2002) Biochemical diagnosis of pheochromocytoma. Which test is best? JAMA 287:1427–1434

Meaney TF, Buonocore E (1966) Selective arteriography as a localizing and provocative test in the diagnosis of pheochromocytoma. Radiology 87:309–314

Mukherjee JJ, Peppercorn PD, Reznek RH et al (1997) Pheochromocytoma: effect of non-ionic contrast medium in CT on circulating catecholamine levels. Radiology 202:227–231

Patel V, Kaltsas G, Nageh T et al (1995) ^{123}I-MIBG imaging in chromaffin tumours: interference due to intravenous phenoxybenzamine. J Endocrinol 144 [Suppl]:P194

Raisanen J, Shapiro B, Glazer GM et al (1984) Plasma catecholamines in pheochromocytoma. Effect of urographic contrast media. AJR Am J Roentgenol 143:43–46

Rossi P, Young IS, Parke WF (1968) Techniques, usefulness and hazards of arteriography of pheochromocytoma. JAMA 205:75–81

14 Contrast Media: Interactions with Other Drugs and Clinical Tests

Sameh K. Morcos

CONTENTS

14.1 Introduction

Iodinated water soluble contrast media in clinical use are high osmolar ionic monomers, low osmolar ionic dimers, low osmolar nonionic monomers and iso-osmolar nonionic dimers. Nowadays, high osmolar contrast media are rarely used intravascularly in the developed world. Magnetic resonance imaging (MRI) contrast agents are mainly gadolinium based but new non gadolinium paramagnetic contrast agents have recently become available for clinical use. Some of the gadolinium preparations are ionic and have high osmolality; others are nonionic with varying osmolality (600–2000 mOsmol/kg H_2O). Ultrasound contrast agents are micro-bubbles which produce acoustic enhancement. They are pharmacologically almost inert and safe (Jakobsen et al. 2005).

The use of contrast media continues to grow in a wide range of imaging and interventional procedures. Also the patient population receiving contrast media has changed. Currently, many older patients with multiple medical problems who are receiving a variety of drugs are actively investigated with imaging techniques which require the administration of contrast agents.

A drug interaction is defined as the drug's possible capacity to influence the pharmacological action of another drug. Such interactions between contrast agents and therapeutic medications have not been widely investigated (Frohlich 2001). Although contrast agents are not highly active pharmacologically, interaction with other drugs may occur with possible serious consequences to the patient.

In this chapter potential interactions between drugs and contrast agents are presented based on an extensive review of the literature. The interactions are grouped together according to clinical importance and the body system involved. In addition, the effects of contrast media on isotope studies are highlighted as well as the danger of mixing contrast media with other drugs before intravascular use. Contrast media may also interfere with biochemical assays of body fluids. The aim of this chapter is to raise the awareness of both radiologists and clinicians to the possibility of such events.

14.2 Classification of Drug Interaction

The interactions between drugs and contrast agents are subdivided into the following:

- Drugs which will be retained in the body when there is contrast medium induced reduction in renal function.
- Drugs which enhance the renal effects of contrast media.

S. K. Morcos FRCS, FFRRCSI, FRCR
Department of Diagnostic Imaging, Northern General Hospital NHS Trust, Sheffield S5 7AU, UK

- Drugs which enhance allergic-like reactions to contrast media.
- Drugs which interfere with the hematological effects of contrast media.
- Contrast media and neuroleptic drugs.
- Drugs which enhance the cardiac effects of contrast media.

Additional topics dealt with in this chapter are:

- The effects of contrast media on isotope studies.
- Mixing contrast media with other drugs.
- The effects of contrast media on biochemical assays.

14.2.1 Drugs Which Will Be Retained in the Body When There Is Contrast Medium-Induced Reduction in Renal Function

Contrast media may interfere with the pharmacokinetics (distribution, metabolism and elimination of the drug) of other drugs, particularly those which are eliminated from the body through the kidneys. One of the important potential – but rare – pharmacodynamic effects of iodinated contrast media is reduction of renal function, particularly in patients with preexisting reduced renal function. This leads to retention of drugs which are excreted exclusively through the kidneys. A good example is the indirect interaction between contrast media and metformin (Thomsen et al. 1999). Significant reduction of renal function can be induced by contrast agents in the presence of pre-existing kidney disease, particularly diabetic nephropathy (Morcos 1998; Morcos et al. 1999; Thomsen and Morcos 2003). If contrast media reduce renal function, there is retention of metformin potentially leading to the serious complication of lactic acidosis (Thomsen et al. 1999). This subject is comprehensively reviewed in Chap. 8. Drugs which cause diuresis and natriuresis can be hazardous and should be avoided in patients receiving lithium. Although contrast media, especially those of high osmolality, can induce significant diuresis and natriuresis, their potential for increasing the toxicity of lithium has not been widely studied.

14.2.2 Drugs Which Enhance the Renal Effects of Contrast Media

Nephrotoxic drugs such as non-steroidal anti inflammatory drugs (NSAIDs) have the potential to increase the renal effects of contrast media. This class of drugs inhibits the intrarenal synthesis of vasodilatory prostaglandins and augments the renal vasoconstrictor effect of iodinated contrast media which may facilitate the development of contrast media nephrotoxicity (Morcos 1998; Morcos et al. 1998; Thomsen and Morcos 2003). Other nephrotoxic drugs such as gentamicin, cyclosporine and cisplatin may also augment the nephrotoxic effects of contrast media (Morcos et al. 1998). Diuretics such as acetazolamide, furosemide and spironolactone may augment the diuretic effect of contrast media, particularly those of high osmolality, leading to dehydration, increased risk of contrast medium nephropathy, electrolyte imbalance and hypotension (Swanson et al. 1990).

14.2.3 Drugs Which Enhance Allergy-Like Reactions to Contrast Media

In general, the rate of allergy-like reactions after administration of nonionic contrast media is very low. Patients receiving α-receptor blockers, interleukins or interferons have an increased tendency to develop allergy like reactions following the administration of contrast media. Delayed reactions to contrast media are more likely to develop in patients who have received interleukin-2 (IL-2) treatment (Choyke et al. 1992). Patients on hydralazine treatment, which can induce systemic lupus erythematosus (SLE) like syndrome, may develop cutaneous vasculitis several hours after intravascular administration of nonionic iodinated contrast medium. It has been suggested that injection of iodinated contrast media should be avoided in patients receiving hydralazine as they may provoke severe reactions (Reynolds et al. 1993). Hypersensitivity reactions to iodine-containing compounds have also been described in patients with systemic lupus erythematosus.

14.2.3.1 α Blockers

Anaphylaxis like reactions which may occur following the administration of contrast media require aggressive treatment including adrenaline. However, if the patient is receiving α-receptor blockers the effectiveness of the sympathomimetic drugs which are crucial in this potentially lethal situation is reduced. α blockers selectively block the α-adren-

ergic effects of adrenaline and inhibit adenylate cyclase activity which leads to increased release of anaphylactoid mediators. α blockers are often prescribed for hypertension, angina, arrhythmias and after myocardial infarction. Eye drop preparations are used for the treatment of glaucoma. To avoid the risk of exacerbating angina, acute myocardial infarction and malignant tachycardia and causing sudden death α blockers should not be stopped suddenly. Gradual withdrawal over 10–14 days is recommended (Laurence and Bennett 1992).

Whether or not β blockers affect the incidence of idiosyncratic contrast medium reactions is controversial. Greenberger et al. (1987) reported that neither β blockers nor calcium antagonists given separately or together increased the risk of reaction. Subsequently, however, Lang et al. (1991, 1993) found that β blockers did increase the risk of reaction. It is however agreed that the use of β blockers can impair the response to treatment if a reaction does occur (Thomsen and Bush 1998; Greenberger et al. 1987; Lang et al. 1991). Adrenaline may be ineffective or promote undesired α-adrenergic or vagal effects.

14.2.3.2 Interleukin-2

IL-2 is a lymphokine produced by helper T cells which acts as an antineoplastic agent. Alone or in combination with lymphokine-activated killer cells it can induce partial or complete responses in more than 20% of patients with advanced melanoma or renal cell carcinoma (Choyke et al. 1992).

In a prospective study of patients undergoing CT who had received IL-2 and intravenous nonionic low-osmolar or oral ionic high osmolar contrast media, or both, there were immediate urticarial reactions in 1.8% of the patients within 1 h of contrast administration. No acute reactions were observed in a control group who received contrast media but had not been treated with IL-2. Delayed reactions (erythema, rash, fever, flushing, pruritus and flu-like symptoms) developed in 12% of IL-2 patients and only in 4% of the control group. Two of the IL-2 patients required admission to hospital. The mean onset of symptoms was 4.5 h after injection of contrast media and the mean duration of reaction was 16.4 h. The patients had no risk factor for delayed reactions other than IL-2 therapy and all had had previous uneventful exposure to contrast media. None of the patients with immediate reactions developed delayed reactions. The average time since IL-2 therapy was 6 months (range 24 days to 2.4 years). The main concern with delayed side effects is that the patient is usually not in hospital when the reaction occurs. Previous contrast medium reaction in an IL-2 patient should be considered a relative contraindication to further contrast media administration (Choyke et al. 1992). An increased risk of contrast reactions may remain for 2 years after stopping IL-2 treatment.

The administration of contrast media may also precipitate IL-2 toxicity. Fever, diarrhea, nausea and vomiting have been observed 2–4 h after CT scanning enhanced with nonionic low-osmolar contrast media. The exact mechanism is not clear and immunologic interactions are probable. Contrast media may generate the release of endogenous IL-2 or reactivate the IL-2 receptors (Abi-Aad et al. 1991). Patients who develop these reactions should avoid further exposure to iodinated contrast media and imaging techniques such as MRI or unenhanced CT should be considered for monitoring response to treatment (Abi-Aad et al. 1991).

14.2.4 Drugs Which Alter the Hematological Effects of Contrast Media

14.2.4.1 Effects of Contrast Media on Coagulation

It is well established that contrast media interact with the coagulation mechanism, with platelet activation and degranulation and with thrombolytic drugs (Frohlich 2001). Ionic contrast media inhibit both the intrinsic and extrinsic coagulation cascades at several levels. They act as direct inhibitors of thrombin production. They also inhibit both platelet activation and aggregation, increase the bleeding time and cause enzyme inhibition of fibrinolysis. Ionic contrast media are more effective than nonionic agents at increasing the clotting time and give a four-fold increase in the whole blood clotting time when compared to nonionic agents (Frohlich 2001). Nonionic contrast media cause less significant alteration of clotting by inhibiting the coagulation cascade after the generation of thrombin at the step of fibrin monomer polymerization (Massee et al. 1991; Parvez et al. 1982). Thus, both ionic and nonionic contrast media can prolong clotting time and may exaggerate the effects of anticoagulant and antiplatelet drugs (Frohlich 2001). In addition, clotting tests will be falsely elevated after the

administration of contrast media and should only be performed 6 h or more after contrast media have been given (Parvez et al. 1982).

14.2.4.2 Effects of Contrast Media on Fibrinolysis

Contrast media impede fibrinolysis and delay the onset of lysis by recombinant tissue-type plasminogen activator (rt-PA), urokinase and streptokinase (Dehmer et al. 1995). This effect is reduced by increasing the concentration of the lysis agent. Contrast media cause fibrin to form in long/thin fibrils which have a lower mass/length ratio and are more resistant to fibrinolysis (Parvez et al. 1982). In vitro studies showed that diatrizoate and iohexol delayed the onset of lysis induced by all lysis agents. However, ioxaglate delayed the onset of lysis by rt-PA and urokinase but not by streptokinase (Dehmer et al. 1995). In vivo studies in dogs showed that alteplase-induced thrombolysis could be inhibited by iohexol and amidotrizoate (Pislaru et al. 1998).

In clinical practice, if coronary angiography is performed before starting thrombolysis, the recent administration of contrast media may reduce therapeutic success. Reocclusion of coronary arteries was more common after contrast media administration despite concomitant aspirin and heparin therapy (Pislaru et al. 1998). The hematological effects of contrast media are described in details in Chap. 10.

14.2.5 Contrast Media and Drugs Acting on the Central Nervous System

Cerebral angiography may lower the fit threshold in patients receiving antipsychotics such as phenothiazines (chlorpromazine, perfenazine, prochlorperazine, thioridazine) antihistamines (promethazine, trimeparazine), thioxanthenes (chlorprothixene, haloperidol, thiothrixene) or tricyclic antidepressants (amitryptyline, desipramine, doxepin, imipramine, protryptiline), butyrophenones, or analeptics (amphetamine, methamphetamine, cocaine, methylphenidate) (Frohlich 2001). During the time when high-osmolar content media were in general use it was suggested that these drugs should be discontinued for 48 h before and 24 h after cerebral angiography. However, stopping antipsychotics may lead to an increased rate of suicide. Today where modern nonionic contrast media are used, antipsychotics are no longer stopped.

14.2.6 Drugs which Enhance the Cardiac Effects of Contrast Media

Calcium channel blockers prevent influx of calcium ions into the cell affecting the tone of heart and vascular smooth muscle cells and leading to vasodilatation and negative inotropic effects on the myocardium. Patients receiving calcium channel blockers may develop hypotension after left ventriculography with high osmolar ionic agents since the latter can also induce peripheral vasodilatation and have a negative inotropic effect on the heart. These effects are not significant with modern low osmolar nonionic contrast media which are less vasoactive and have minimal negative inotropic effect on the myocardium (Higgins et al. 1983; Morris et al. 1985, 1998).

Harmful synergism between high osmolar contrast media and digitalis was also suggested following experimental studies in the rat (Fischer and Morris 1980). However, no human data are available to support this observation.

14.3 Effects of Contrast Media on Isotope Studies

The administration of iodinated contrast media interferes with both diagnostic scintigraphy and radioiodine treatment. The reduced uptake of the radioactive tracer is caused by free iodide in the contrast medium solution. A delay before undertaking scintigraphy of 4–6 weeks for water soluble and 12 weeks for cholangiographic contrast media is advocated, depending on the indication for scintigraphy and whether the patient is euthyroid or hyperthyroid. A more detailed report on the effects of contrast media on the thyroid gland has been produced by the Contrast Media Safety Committee of the ESUR (van der Molen et al. 2004).

Intravascular administration of contrast media shortly after injection of isotope material (^{99m}Tc-pyrophosphate) for bone imaging can interfere with the distribution of the ^{99m}Tc-pyrophosphate. Increased uptake of the isotope material in kidneys and liver with low uptake in bones was observed. The diuretic effect of contrast media may increase the elimination of the isotope material in urine so less is available for deposition in skeleton. The increased uptake in the liver is not fully explained (Crawford and Gumerman 1978).

Intravascular administration of contrast media may also interfere with red blood cell labeling with isotope material. ^{99m}Tc labeling of red blood cells should not be performed within 24 h after contrast media injection. How contrast media interfere with red blood cell labeling is not fully understood (Tatum et al. 1983).

14.4 Mixing Contrast Media with Other Drugs

Contrast media should not be mixed with other drugs before intravascular use (Kim et al. 1992). A mixture may change the stability of the drugs. It is also advisable not to inject other drugs through the same venous access used for contrast media injection. If the same venous access is used, there should be adequate flushing with normal saline first.

14.5 Effects of Contrast Media on Biochemical Assays

Measurements of clotting time and other coagulation factors can be falsely increased after the intravascular administration of contrast media. Therefore clotting tests should be avoided for 6 h or more after injection of contrast media (Parvez et al. 1982). Iodinated contrast media in the urine may also interfere with some protein assay techniques leading to false positive results (Morcos et al. 1992). Care must be exercised in interpreting tests for proteinuria for 24 h after contrast medium injection.

Gadodiamide and gadoversetamide may cause spurious hypocalcemia, particularly at doses of 0.2 mmol/kg or higher in patients with renal insufficiency (Prince et al. 2003; Choyke and Knopp 2003). These contrast media interfere with calcium measurements obtained by assay using the orthocresolphthalein complexone (OOC) method but not with the assays using the Arsenazo III method (Proctor et al. 2004; Normann et al. 1995). False measurements of serum calcium did not occur with gadopentetate dimeglumine or gadoteridol (Choyke and Knopp 2003). In very high concentrations Gd-DTPA may interfere with calcium determination when methylthymolblue is used (Junge and Troge 1991). Awareness of this effect of some MRI contrast agents on calcium measurements is important to avoid incorrect and potentially hazardous corrective treatment (Prince et al. 2003). Iodinated contrast media may interfere with determination of bilirubin, copper, iron, phosphate and proteins in blood (Junge and Troge 1991). Caution should be exercised when using colorimetric assays for angiotensin-converting enzyme, calcium, iron, magnesium, total iron binding capacity and zinc in serum samples from patients who have recently received gadolinium based contrast media (Proctor et al. 2004).

In summary, biochemical assays are better performed before contrast media injection or delayed for at least 24 h afterwards or longer in patients with renal impairment. Urgent laboratory tests performed on specimens collected shortly after contrast media injection should be carefully assessed. Accuracy of unexpected abnormal results should be questioned and discussed with colleagues from the hospital laboratories.

14.6 Conclusion

Contrast media have the potential for interaction with other drugs and may interfere with biochemical assays. Awareness of these interactions is important to avoid misinterpretation of biochemical data and causing harm to the patient following imaging and interventional procedures. Proper documentation of intravascular use of contrast media should be included in the patient's records (Barrs 2002). Simple guidelines on interaction between contrast media and other drugs which have been produced by the Contrast Media Safety Committee of the European Society of Urogenital Radiology are presented in the Appendix.

References

Abi-Aad AS, Figlin RA, Belldegrun A, de Kernion JB (1991) Metastatic renal cell cancer: interleukin-2 toxicity induced by contrast agent injection. J Immunother 10:292–295

Barrs TJ (2002) Establishing safeguards for the use of imaging related drugs. Am J Health Syst Pharm 59:1449–1553

Choyke PL, Knopp MV (2003) Pseudohypocalcemia with MR imaging contrast agents: a cautionary tale. Radiology 227:627–628

Choyke PL, Miller DL, Lotze MT, Whireis JM, Ebbitt B, Rosenberg SA (1992) Delayed reactions to contrast media after interleukin-2 immunotherapy. Radiology 183:111–114

Crawford JA, Gumerman LW (1978) Alteration of body distribution of Tc99m-pyrophosphate by radiographic contrast material. Clin Nucl Med 3:305–307

Dehmer GJ, Gresalfi N, Daly D, Oberhardt B, Tate DA (1995) Impairment of fibrinolysis by streptokinase, urokinase and recombinant tissue-type plasminogen activator in the presence of radiographic contrast agents. J Am Coll Cardiol 25:1069–1075

Fischer HW, Morris TW (1980) Possible factors in intravascular contrast media toxicity. Invest Radiol 15 [Suppl 6]: S232–S238

Frohlich JM (2001) Systematic survey of interactions between contrast media and other drugs. Special edition by Guerbet Switzerland

Greenberger PA, Meyers SN, Kramer BL et al (1987) Effects of beta-adrenergic and calcium antagonists on the development of anaphylactoid reactions from radiographic contrast media. J Allergy Clin Immunol 80:698–702

Higgins CB, Kruber M, Slutsky RA (1983) Interaction between verapamil and contrast media in coronary arteriography: comparison of standard ionic and new nonionic media. Circulation 68:628–635

Jakobsen JÅ, Oyen R, Thomsen HS, Morcos SK, members of contrast media safety committee of the European Society of Urogenital Radiology (ESUR) (2005) Safety of ultrasound contrast media. Eur Radiol 15:941–945

Junge W, Troge B (1991) Kontrastmittel als Störfaktoren in der laborchemischen Analytik. In: Peters PE, Zetler E (eds) Röntgen Kontrastmittel. Springer, Berlin Heidelberg New York, pp 76–82

Kim SH, Lee HK, Han MC (1992) Incompatibility of water-soluble contrast media and intravascular pharmacologic agents. An in vitro study. Invest Radiol 27:45–49

Lang DM, Alpern MB, Visintainer PF, Smith ST (1991) Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. Ann Intern Med 115:270–276

Lang DM, Alpern MB, Visintainer PF, Smith ST (1993) Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. Arch Intern Med 153:2033–2040. Erratum in: Arch Intern Med 1993, 153:2412

Laurence DR, Bennett PN (1992) Clinical pharmacology, 7th edn. Churchill Livingstone, Edinburgh, pp 416–423

Massee DR, Smith DC, Westengard JC, Bull BS (1991) Heparin supplementation of nonionic contrast agents. J Vasc Interv Radiol 2:209–213

Morcos SK (1998) Contrast media-induced nephrotoxicity-questions and answers. Br J Radiol 71:357–365

Morcos SK, El Nahas AM, Brown P, Haylor J (1992) Effect of iodinated water soluble contrast media on urinary protein assays. BMJ 305:29

Morcos SK, Dawson P, Pearson JD et al (1998) The hemodynamic effects of iodinated water soluble radiographic contrast media: a review. Eur J Radiol 29:31–46

Morcos SK, Thomsen HS, Webb JAW and ESUR Contrast Media Safety Committee (1999) Contrast media-induced nephrotoxicity: a consensus report. Eur Radiol 9:1602–1613

Morris DL, Wisneski JA, Gertz EW, Wexman M, Axelrod R, Langberg JJ (1985) Potentiation by nifedipine and diltiazem of the hypotensive response after contrast angiography. J Am Coll Cardiol 6:785–791

Normann PT, Frøysa A, Svaland M (1995) Interference of gadodiamide injection (OMNISCAN®) on the colorimetric determination of serum calcium. Scand J Clin Lab Invest 55:421–426

Parvez Z, Moncada R, Messmore HL, Fareed J (1982) Ionic and nonionic contrast media interaction with anticoagulant drugs. Acta Radiol Diagn (Stockh) 23:401–404

Pislaru S, Pislaru C, Szilard M, Arnout J, van de Werf F (1998) In vivo effects of contrast media on coronary thrombolysis. J Am Coll Cardiol 32:1102–1108

Prince MR, Erel HE, Lent RW et al (2003) Gadodiamide administration causes spurious hypocalcemia. Radiology 227:639–646

Proctor KAS, Rao LV, Roberts WL (2004) Gadolinium magnetic resonance contrast agents produce analytic interference in multiple serum assays. Am J Clin Pathol 121:282–292

Reynolds N, Wallington TB, Burton JL (1993) Hydralazine predisposes to acute cutaneous vasculitis following urography with iopamidol. Br J Dermatol 129:82–85

Swanson DP, Chilton HM, Thrall JH (eds) (1990) Pharmaceuticals in medical imaging: radiopaque contrast media, radiopharmaceuticals, enhancement agents for magnetic resonance imaging and ultrasound. Macmillan, New York, p 42

Tatum JL, Burke TS, Hirsch JI, Miller WW, Fratkin MJ (1983) Pitfall to modified in vivo method of technetium-99m red blood cell labeling. Iodinated contrast media. Clin Nucl Med 8:585–587

Thomsen HS, Bush WH (1998) Adverse effects of contrast media: incidence, prevention and management. Drug Safety 19:313–324

Thomsen HS, Morcos SK (2003) Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. Br J Radiol 76:513–518

Thomsen HS, Morcos SK and ESUR Contrast Media Safety Committee (1999) Contrast media and metformin. Guidelines to distinguish the risk of lactic acidosis in non-insulin dependent diabetics after administration of contrast media. Eur Radiol 9:738–740

Van der Molen AJ, Thomsen HS, Morcos SK, and ESUR Contrast Media Safety Committee (2004) Effect of iodinated contrast media on thyroid function in adults. Eur Radiol 14:902–907

15 Contrast Medium Extravasation Injury

Jarl Å. Jakobsen

CONTENTS

15.1 Introduction

The incidence of extravasation injuries due to contrast media seems to be increasing and there is little or no consensus among radiologists about treatment. Subcutaneous extravasation is a well-recognized complication of intravenous administration of iodinated and MR contrast media (Cohan et al. 1996; Federle et al. 1998; Cochran et al. 2001; Pond and Dorr 1993; Runge et al. 2002). Its incidence after mechanical bolus injection is higher than that reported for hand-injection or drip-infusion techniques but there seems to be no relation between injection rate and extravasation frequency (Pond and Dorr 1993; Jacobs et al. 1998). The clinical presentation is highly variable. Most extravasations involve small volumes of contrast material and induce minimal swelling or localized erythema, which rapidly diminish. Extensive tissue necrosis and severe skin and subcutaneous ulceration are rare and usually follow high volume extravasations (Cohan et al. 1996; Ayre-Smith 1982).

J. Å. Jakobsen, MD
Professor, Department of Radiology, Rikshospitalet, 0017 Oslo, Norway

15.2 Risk Factors

15.2.1 Patient Factors

Infants, small children and unconscious patients are more likely to develop extravasation (Cohan et al. 1996) because they are unable to complain of pain at the injection site. Patients receiving chemotherapy are also at a higher risk of extravasation because chemotherapy may cause fragility of the vein wall. Extravasation injuries are more severe in patients with low muscular mass and atrophic subcutaneous tissue. In addition, patients with arterial insufficiency (e.g. atherosclerosis, diabetes mellitus or connective tissue diseases) or compromised venous drainage (e.g. thrombosis) or lymphatic drainage (e.g. radiation therapy, surgery or regional node dissection) are less able to tolerate extravasation than those with normal circulation.

15.2.2 Contrast Media Type and Volume

Extravasation of low-osmolar contrast media is better tolerated than extravasation of high-osmolar media. The osmolality threshold for significant tissue injury is estimated to be 1.025–1.420 mOsm/kg water (Cohan et al. 1990a,b; Elam et al. 1991; Sistran et al. 1991). However, four severe injuries have been reported with nonionic contrast media, none of which required reconstructive surgery (Pond et al. 1992; Young 1994; Memolo et al. 1993;

Benson et al. 1996). Runge et al. (2002) showed after extravascular injection of 0.3 ml of a MR contrast medium in the hind limbs of rats that in particular the higher osmolar agents like gadopentetate dimeglumine and gadoversetamide have more harmful consequences than agents with a lower osmolality such as gadodiamide and gadoteridol.

The vast majority of extravasations involve small volumes of contrast material and symptoms resolve completely within 24 h (Cohan et al. 1996, 1997; Federle et al. 1998; Jacobs et al. 1998; Sistran et al. 1991). Rarely severe skin ulceration and necrosis can follow extravasation of volumes as small as 10 ml (Ayre-Smith 1982). Large-volume extravasation may lead to severe damage to extravascular tissue and is most likely to occur when contrast medium is injected with an automated power injector and the injection site is not closely monitored (Cohan et al. 1996, 1997).

15.2.3 Factors Due to Injection Technique

The type of venous access affects the frequency of extravasation. In 40% of one series of patients with contrast medium extravasation, indwelling intravenous lines were used (Sistrom et al. 1991). Extravasations are more frequent with metal needles than with plastic cannulae (Gothlin 1972).

The injection site also appears to be important with 78% of 36 patients who had contrast medium injected through a dorsal vein of the great toe for lower limb venography developing extravasation (Gothlin 1972). The use of tourniquets and the presence of edema increase the risk of extravasation with lower limb venography (Cohan et al. 1996). Injections into the dorsum of the hand are frequently associated with extravasation injury (Gault 1993).

Mechanical power injection for CT studies is responsible for many extravasation injuries. The frequency of extravasation with power injection rates between 1 and 2 ml/s varies from 0.2% to 0.4% (Federle et al. 1998; Cohan et al. 1990a; Sistrom et al. 1991; Miles et al. 1990; Kaste and Young 1996). With the development of CT angiography, multiphasic organ imaging and faster delivery of intravenous contrast media, it is important to assess critically whether extravasation and reaction rates increase proportionally with injection rates. However, in a study by Jacobs et al. (1998) the extravasation rate (0.6%) did not differ significantly between groups of patients receiving different injection rates of contrast media. In addition no correlation was noted between the extravasation rate and catheter location, catheter size or catheter type. High-volume extravasation may occur if the extravasation is deep or if the patient remains asymptomatic.

15.3 Mechanisms and Toxicity

Multiple factors are involved in the pathogenesis of extravasation injuries. The first factor is osmolality above 1.025–1.420 mOsm/kg water. Both iodinated radiographic and gadolinium contrast agents of low osmolality are better tolerated than high-osmolar iodinated contrast agents. With MR imaging contrast agents, the osmotic loads and the volumes that are administered are markedly lower than with iodinated agents. However, in rats, extravasation of dimeglumine gadopentetate (1960 mmol/kg water) was associated with a higher incidence of necrosis, hemorrhage and edema than occurred with gadoteridol (789 mmol/kg water) (Cohan et al. 1991; Runge et al. 2002). Gadoteridol at a concentration of 0.5 mol/l was no more toxic than 0.9% saline.

The second factor is the cytotoxicity of contrast media with conflicting results in the literature when ionic and non-ionic contrast media are compared. In a laboratory study (McAlister and Palmer 1971) extravasated ionic contrast media produced acute inflammation followed by a chronic inflammatory process, with fibrosis and adjacent muscle atrophy detected at the injection site by 8 weeks. Early detection is important to avoid the acute inflammatory response which peaks at 24–48 h after extravasation (Cohan et al. 1990b). While Cohan et al. (1990b) found that ionic contrast media were more toxic than non-ionic agents, no difference was found by Jacobs et al. (1998). The presence of meglumine as a cation may also play a role in the cytotoxicity of ionic contrast media (Kim et al. 1990).

The third factor is the volume of extravasated contrast medium. Although severe skin lesions have been described following an extravasation of less than 15 ml, the majority occurred with large-volume extravasations (Upton et al. 1979).

The fourth factor is the mechanical compression caused by large-volume extravasations that may lead to compartment syndromes (Pond et al. 1992; Young 1994; Memolo et al. 1993; Benson et al. 1996). Infection of the extravasated site may increase the severity of the injury.

Extravasation from indwelling intravenous lines is often due to phlebitis that develops in the veins that have been cannulated (Cohan et al. 1996). Thrombosis increases vascular resistance in the same way as an injection does. Other mechanisms include the inadequate placement of the catheter in the vein, multiple punctures of the same vein, and high injection pressure, which can break the vessel wall.

15.4 Clinical Picture

The presentation of extravasation of iodinated and gadolinium contrast media varies from minor erythema and swelling to tissue necrosis associated with progressive edema and skin ulceration. The injuries may heal and only rarely lead to long-term sequelae including hypoesthesia, marked weakness and pain (Federle et al. 1998). Symptoms of extravasation are very variable. Many patients complain of stinging or burning pain, while others do not experience any discomfort and remain asymptomatic. On physical examination, the extravasation site appears swollen, red and tender. Most extravasation injuries resolve spontaneously within 2–4 days. At the initial examination it is not possible to predict whether the extravasation injury will resolve or will result in ulceration, necrosis and soft tissue damage. A number of clinical findings suggest severe injury and justify seeking the advice of a surgeon. These include skin blistering, altered tissue perfusion, paresthesia, and increasing or persistent pain after 4 h (Cohan et al. 1996). Extravasation may also result in acute compartmental syndromes producing tense and dusky forearms, with swelling and diminished arterial pulses. Compartmental syndromes may necessitate emergency fasciotomy to relieve neurovascular compromise (Pond et al. 1992; Young 1994; Memolo et al. 1993; Benson et al. 1996).

Extravasation injuries must be distinguished from other local reactions to injected fluid including hypersensitivity reactions and local irritative effects of iodinated contrast agents on the vessel wall. In these reactions edema and erythema are absent and the catheter is well positioned in the vein. Transient, local pain has been reported in 2%–5% of patients following intravenous administration of ionic contrast material while delayed arm pain at or above the injection site has been reported in 0.1%–14.0% of patients who received iodinated contrast material (Shehadi 1975; McCullogh et al. 1989). Pain may last for several days (mean, 3 days, range, 1–30 days) and may progress to phlebitis in rare cases (Panto and Davies 1986). Similar features may also be observed with extravasation of high-osmolar contrast agents.

Extravasated gadolinium is better tolerated than conventional ionic radiographic contrast media and produces a zone of signal void on short relaxation time MR images because of its high local concentration (Carrier et al. 1993).

The presence of a trained nurse or physician beside the patient during contrast medium injection would be ideal for early detection, but exposure to ionizing radiation makes such close observation impossible. New devices for detection of extravasation are currently under evaluation. In a study (Birnbaum et al. 1999) of 500 patients an extravasation detection accessory (EDA) had a sensitivity of 100% and a specificity of 98% for detecting clinically relevant extravasation (>10 ml). The device was easy to use, safe and accurate in the monitoring of intravenous injections for extravasation, and could prove especially useful in high flow rate CT applications.

15.5 Treatment

There is no consensus about the best approach for the management of extravasation (Cohan et al. 1996; Federle et al. 1998; Park et al. 1993; Katayama et al. 1990; Yucha et al. 1994). The methods described in the following sections have been used:

15.5.1 Elevation of the Affected Limb

Elevation is often useful to reduce edema by decreasing the hydrostatic pressure in capillaries.

15.5.2 Topical Application of Heat or Cold

Heat produces vasodilatation and thus resorption of extravasated fluid and edema, while cold produces vasoconstriction and limits inflammation. The immediate application of warm compresses reduced the volume of extravasated fluid in healthy volunteers (Hastings-Tolsma et al. 1993). In an experi-

mental study application of cold was associated with a decrease in the size of skin ulcers produced by extravasation of iothalamate and diatrizoate (Elam et al. 1991). In untreated rats, rats treated with warmth, and rats treated with cooling no significant difference was found at the injection site (Cohan et al. 1990a). In patients, who have suffered from extravasation, cooling can be produced with ice packs placed at the injection site for 15–60 min three times a day for 1–3 days or until symptoms resolve.

15.5.3 Prevention of Secondary Infection

Applications of silver sulfadiazine ointment are recommended by many plastic surgeons whenever blistering is evident (Heckler 1989).

15.5.4 Hyaluronidase and DMSO (Dimethylsulfoxide)

Hyaluronidase is an enzyme that breaks down connective tissue and facilitates absorption of extravasated drugs into the vascular and lymphatic systems. Local subcutaneous injection of hyaluronidase has been used in patients with large extravasation of high or low osmolality contrast medium and of chemotherapeutic agents (Laurie et al. 1984). It should be administered within 1 h of extravasation to obtain quick dissipation of the skin swelling. Doses recommended in the literature range from 15 U to 250 U diluted in 1.5–6 ml of fluid (Cohan et al. 1996; Federle et al. 1998; Flemmer and Chan 1993). It is well tolerated, with the only known side effect being urticaria. Conflicting results have been published about its efficacy. Most animal and clinical studies suggest a beneficial effect (Cohan et al. 1996; Heckler 1989; Laurie et al. 1984), while McAlister and Palmer (1971) reported a harmful effect.

DMSO is a free-radical scavenger and an effective solvent. It may also have antibacterial, anti-inflammatory, and vasodilatory properties (Fiend and Freedman 1978; Rospond and Engel 1993). It is effective in preventing ulceration caused by extravasated doxorubicin, but its efficacy has not been proven for treating extravasation of contrast media.

Corticosteroids, vasodilators, and a variety of other agents have been proposed for treating extravasation, but most studies failed to demonstrate any value of these agents or did not evaluate extravasation of contrast media.

15.5.5 Surgery

Most plastic surgeons believe that the majority of extravasation injuries heal without surgery and recommend a conservative policy (Cohan et al. 1990a). Surgical drainage or emergency suction applied within 6 h can be effective (Loth and Jones 1988) and the use of emergency suction alone or combined with saline flushing have also been helpful (Gault 1993; Vandeweyer et al. 2000). However, the efficacy of surgery has not been compared to conservative treatment in a randomized trial.

15.5.6 Aspiration of Fluid from the Extravasation Site

Aspiration of fluid from the injection site is controversial, as it usually removes only a small amount of extravasated fluid and carries a risk of infection.

15.6 Conclusion

Extravasation of contrast material is a not infrequent complication of enhanced imaging studies and large volume extravasation may result in severe damage. Early identification is important and conservative management is effective in most cases (see Appendix).

References

Ayre-Smith G (1982) Tissue necrosis following extravasation of contrast media. J Can Assoc Radiol 33:104

Benson LS, Sathy MJ, Port RB (1996) Forearm compartment syndrome due to automated injection of computed tomography contrast material. J Orthop Trauma 10:433–436

Birnbaum BA, Nelson RC, Chezmar JL, Glick SN (1999) Extravasation detection accessory: clinical evaluation in 500 patients. Radiology 212:431–438

Carrier DA, Ford JJ, Hayman LA (1993) MR appearance of extravasated gadolinium contrast medium. Am J Neuro Radiol 14:363–364

Cochran ST, Bomyea K, Sayre JW (2001) Trends in adverse events after IV administration of contrast media. Am J Roentgenol 176:1385–1388

Cohan RH, Dunnick NR, Leder RA, Baker ME (1990a) Extravasation of nonionic contrast media: efficacy of conservative treatment. Radiology 174:65–67

Cohan RH, Leder RA, Bolick D et al (1990b) Extravascular extravasation of radiographic contrast media: effects of conventional and low-osmolar contrast agents in the rat thigh. Invest Radiol 25:504–510

Cohan RH, Leder RA, Herzberg AJ et al (1991) Extravascular toxicity of two magnetic resonance contrast agents: preliminary experience in the rat. Invest Radiol 26:224–226

Cohan RH, Ellis JH, Garner WL (1996) Extravasation of radiographic contrast material: recognition, prevention, and treatment. Radiology 200:593–604

Cohan RH, Bullard MA, Ellis JH, Jan SC et al (1997) Local reactions after injection of iodinated contrast material: detection, management, and outcome. Acad Radiol 4:711–718

Elam EA, Dorr RT, Lagel KE, Pond GD (1991) Cutaneous ulceration due to contrast extravasation: experimental assessment of injury and potential antidotes. Invest Radiol 26:13–16

Federle MP, Chang PJ, Confer S, Ozgun B (1998) Frequency and effects of extravasation of ionic and nonionic CT contrast media during rapid bolus injection. Radiology 206:637–640

Fiend C, Freedman HA (1978) Effects and possible mechanism of action of dimethyl sulfoxide on Friend cell differentiation. Biochem Pharmacol 27:1309–1313

Flemmer L, Chan JSL (1993) A pediatric protocol for management of extravasation injuries. Pediatr Nurs 19:355–358

Gault DT (1993) Extravasation injuries. Br J Plast Surg 46:91–96

Gothlin J (1972) The comparative frequency of extravasal injection at phlebography with steel and plastic cannulas. Clin Radiol 23:183–184

Hastings-Tolsma TM, Yucha CB, Tompkins J, Robson L, Szeverenyi N (1993) Effect of warm and cold applications on the resolution of IV infiltrations. Res Nurs Health 16:171–178

Heckler FR (1989) Current thoughts on extravasation injuries. Clin Plast Surg 16:557–563

Jacobs JE, Birnbaum BA, Langlotz CP (1998) Contrast media reactions and extravasation: relationship to intravenous injection rates. Radiology 209:411–416

Kaste SC, Young CW (1996) Safe use of power injectors with central and peripheral venous access devices for pediatric CT. Pediatr Radiol 26:499–501

Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Mattsuura K (1990) Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. Radiology 175:621–628

Kim SH, Park JH, Kim YI, Kim CW, Han MC (1990) Experimental tissue damage after subcutaneous injection of water-soluble contrast media. Invest Radiol 25:678–685

Laurie WS, Wilson L, Kernahan A, Bauer S, Vistnes DLM (1984) Intravenous extravasation injuries: the effectiveness of hyaluronidase in their treatment. Ann Plast Surg 13:191–194

Loth TS, Jones DEC (1988) Extravasations of radiographic contrast material in the upper extremity. J Hand Surg 13:395–398

McAlister WH, Palmer K (1971) The histologic effects of four commonly used contrast media for excretory urography and an attempt to modify the responses. Radiology 99:511–516

McCullogh M, Davies P, Richardson R (1989) A large trial of intravenous Conray 325 and Niopam 300 to assess immediate and delayed reactions. Br J Radiol 62:260–265

Memolo M Dyer R, Zagoria RJ (1993) Extravasation injury with nonionic contrast material. Am J Roentgenol 160:203

Miles SG, Rasmussen JF, Litwiller T (1990) Safe use of an intravenous power injector for CT: experience and protocol. Radiology 176:69–70

Panto PN, Davies P (1986) Delayed reactions to urographic contrast media. Br J Radiol 59:41–44

Park KS, Kim SH, Park JH, Han MC, Kim DY, Kim SJ (1993) Methods for mitigating soft-tissue injury after subcutaneous injection of water-soluble contrast media. Invest Radiol 28:332–334

Pond GD, Dorr RT (1993) Extravasation injury with non-ionic contrast material. Am J Roentgenol 160:203–204

Pond GD, Dorr RT, McAleese KA (1992) Skin ulceration from extravasation of low-osmolar contrast medium: a complication of automation. Am J Roentgenol 158:915–916

Rospond RM, Engel LM (1993) Dimethyl sulfoxide for treating anthracycline extravasation. Clin Pharm 12:560–561

Runge VM, Dickey KM, Williams NM, Peng X (2002) Local tissue toxicity in response to extravascular extravasation of magnetic resonance contrast media. Invest Radiol 37:393–398

Shedadi WH (1975) Adverse reactions to intra-vascularly administered contrast media: a comprehensive study based on a prospective survey. Radiology 124:145–152

Sistrom CL, Gay SB, Peffley L (1991) Extravasation of iopamidol and iohexol during contrast-enhanced CT: report of 28 cases. Radiology 176:65–67

Upton J, Mulliken JB, Murray JE (1979) Major intravenous extravasation injuries. Am J Surg 137:497–506

Vandeweyer E, Heymans O, Deraemaecker R (2000) Extravasation injuries and emergency suction as treatment. Plast Reconstr Surg 105:109–110

Yucha CB, Hastings-Tolsma TM, Szeverenyi N (1994) Effect of elevation on intravenous extravasations. J Intraven Nurs 17:231–234

Young RA (1994) Injury due to extravasation of nonionic contrast material (letter). Am J Roentgenol 162:1499

Section IV:
MR Contrast Media

16 Non-tissue Specific Extracellular MR Contrast Media

Remy W. F. Geenen and Gabriel P. Krestin

CONTENTS

16.1 Introduction

In the early days of magnetic resonance imaging, it was thought that the excellent soft tissue contrast would obviate the need for any type of contrast agent, making the procedure completely non-invasive. However, things turned out differently and nowadays 30%–40% of all MRI examinations worldwide are performed with contrast agents (Shellock and Kanal 1999).

The MRI contrast agents are paramagnetic because they contain a paramagnetic ion, which is encapsulated by a chelate to detoxify it. They have a net positive magnetic susceptibility and become magnetic in an external magnetic field (Nelson and Runge 1995). The presence of a paramagnetic substance strongly affects the relaxation properties of water protons leading to changes in tissue contrast (Nelson and Runge 1995). Paramagnetic contrast agents are predominantly used as positive T1 relaxation contrast agents, with little effect on T2 relaxation, and then only in high concentrations. The paramagnetic ion has unpaired electrons, creating a magnetic dipole moment. This accelerates the relaxation rates of water protons, either by direct interaction of the paramagnetic ion with them or by local magnetic field influence (Nelson and Runge 1995). As knowledge about paramagnetic ions increased in the early 1980s, copper (Cu^{2+}), manganese (Mn^{2+}) and gadolinium (Gd^{3+}) were recognized as being capable of shortening the T1 of water (de Haën 2001). After extensive testing of many paramagnetic chelates, the gadolinium diethylene triamine pentaacetic acid salt (Gd-DTPA) was singled out both because of its high tolerability in animals and preserved good relaxation properties. Gd has atomic number 64 and is one of a series of 17 chemically similar metals, the lanthanides (Wastie and Latief 2004). It is present in the earth's crust in five parts per million and is obtained primarily from monazite, a phosphate mineral. Gd is named after the Finnish chemist Johan Gadolin, who lived from 1760–1852 (Wastie and Latief 2004). On November 10th 1983, Gd-DTPA was first tested in man, and in early 1988, the pharmaceutical product gadopentetate dimeglumine 0.5 mmol/l was launched as the first MR contrast medium (de Haën 2001).

Today, 7-Gd based non-tissue specific, extracellular chelates are available commercially (Table 16.1). One of them, gadobenate dimeglumine, behaves like a conventional extracellular Gd-chelate in the first minutes after administration and as a liver specific agent in the delayed phase (Chap. 18). The other six agents, are non-tissue specific. Depending on the net charge and the molecular structure of the chelate, they can be divided into ionic or non-ionic and linear or macro cyclic. In clinical practice, these differences seem to be of little significance (Bellin et al. 2003). The osmotic load of all Gd-based contrast media is low, compared to iodinated contrast media. For example the osmotic load of gadopentetate dimeglumine and gadobenate dimeglumine, the Gd che-

R. W. F. Geenen, MD
Department of Radiology, Erasmus MC – University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
G. P. Krestin, MD
Professor, Department of Radiology, Erasmus MC – University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

Table 16.1. Characteristics of commercially available non-tissue specific, extracellular gadolinium-based MR contrast agents

Molecule name	Gadopentetate dimeglumine Gd-DTPA	Gadoterate meglumine Gd-DOTA	Gadodiamide Gd-DTPA-BMA	Gadoteridol Gd-HP-DO3A	Gadobenate dimeglumine Gd-BOPTA	Gadobutrol Gd-BT-DO3A	Gadoversetamide Gd-DTPA-BMEA
Year of Introduction	1988	1989	1993	1994	1998	1998	2000
Molecular Structure	Linear, ionic	Cyclic, ionic	Linear, non-ionic	Cyclic, non-ionic	Linear, ionic	Cyclic, non-ionic	Linear, non-ionic
Thermodynamic Stability (log K_{eq})	22.1	25.8	16.9	23.8	22.6	21.8	16.6
Conditional Stability Constant at PH 7.4	18.1	18.8	14.9	17.1	18.4		15.0
Osmolality (Osm/kg)	1.96	1.35	0.65	0.63	1.97	1.6	1.11
Viscosity (mPas at 37°C)	2.9	2.0	1.4	1.3	5.3	4.96	2.0
T1 relaxivity ($L/mmols^{-1}$)	4.9	4.3	4.8	4.6	9.7	5.6	
Metal chelate (mg/ml)	469	278.3	287	279.3	334	604.7	330.9
Excess chelate (mg/ml)	0.4	-	12	0.23	-		28.4

lates with the highest osmolality, in a 70-kg patient at a standard dose of 0.1 mmol/kg is 27.4 mOsm. In the same patient, the osmotic load of the non-ionic agent iohexol in a dose sufficient for CT is 105 mOsm (Shellock and Kanal 1999). This is because of the relatively low amounts of Gd-based contrast media given compared to the amount of iodinated contrast medium given for CT (Chap. 17). However, the osmolality of gadolinium agents is of importance if the contrast medium is injected accidentally into the extravascular tissues (Chap. 15).

The stability of the molecule depends on its thermodynamic and conditional stability. These parameters are not directly related to the molecular structure, although as a rule of thumb macro cyclic contrast media have a higher stability than linear (Table 16.1). After injection, they are distributed in the intravascular space and then they start to diffuse freely into and out of the extracellular space. They do not enter tissues with specialized vascular barriers and are excreted unchanged by passive glomerular filtration with >95% excreted by 1 day if kidney function is normal; <0.1% is eliminated via faeces (Bellin et al. 2003). Their biological elimination half-lives are approximately 1.5 h (Kendal and Halls 1993).

16.2 Safety Issues

16.2.1 Phase I–III Studies

Several recent reviews all cite the same articles about phase I–III trials of one single agent (Kirchin and Runge 2003; Runge 2000; Shellock and Kanal 1999). A problem with these trials is the different study design and the different definition of adverse events. Therefore, it is difficult to compare results and it is even more difficult to draw definite conclusions on the incidence of adverse events with individual agents and the safety of individual agents. In European and Japanese studies gadopentetate dimeglumine was shown to have low incidence rates of adverse events (0.63%), whereas in the USA, with legally imposed differences in registration and documentation of adverse events, the incidence was 7.6% (Niendorf et al. 1991).

Nonetheless, it seems that the safety profiles of gadopentetate dimeglumine, gadoterate meglumine, gadoteridol, gadodiamide, gadobenate dimeglumine and gadoversetamide are comparable (Kirchin and Runge 2003; Shellock and Kanal 1999). In general, the total incidence rate of adverse events appears to be less than 5% and the incidence of a single adverse event is approximately 1% (Shellock and Kanal 1999). The newer gadobutrol produced adverse reactions considered to be possibly drug related in 4.6% of patients (Balzer et al. 2003). Gadobutrol is contra-indicated in patients with uncorrected hypokalemia. Furthermore, special care is needed in patients with (family) history of congenital long QT syndrome, previous arrhythmias after taking drugs that prolong cardiac repolarisation or who are taking class III antiarrhythmic drugs. The recommendations are based on the assumption that gadobutrol in a high dose (≥4 times maximal dose) can block potassium channels, resulting in a prolonged QT interval and accelerated ventricular rhythm.

The most common reported adverse events with gadolinium agents are headache, nausea, vomiting, hives and altered taste (Kirchin and Runge 2003; Runge 2000; Shellock and Kanal 1999). Treatment for adverse reactions is the same as for iodinated contrast media (Chap. 4). Anaphylactoid reactions to

Gd chelates do occur, but their incidence is very low. Thus the first documented anaphylactoid reaction to gadopentetate dimeglumine was observed some time after approval and not in clinical trials (Runge 2000). The true incidence of such reactions for Gd chelates is not known, but appears to be between 1:100,000 and 1:500,000 (Shellock and Kanal 1999). One fatal reaction to a Gd chelate (gadopentetate dimeglumine) has been reported (Jordan and Mintz 1995). Witte and Anzai (1994) reported one patient who had a life-threatening anaphylactoid reaction after gadoteridol but had not previously reacted after gadopentetate dimeglumine.

16.2.2 Randomized Double-Blind Trials

Fourteen randomized double-blind studies have been published (Table 16.2) and in 11 of these the agent used for comparison was gadopentetate dimeglumine (Åkeson et al. 1995; Brugières et al. 1994; Greco et al. 2001; Grossman et al. 2000; Knopp et al. 2003, 2004; Myhr et al. 1992; Oudkerk et al. 1995; Rubin et al. 1999; Sadni et al. 1997; Valk et al. 1993). In a further study of 60 patients, gadodiamide was compared to gadoterate meglumine (Balériaux et al. 1993). In the two remaining studies, gadobenate dimeglumine was compared to either gadodiamide or gadoterate meglumine (Runge et al. 2001; Colosimo et al. 2004). The total number of patients studied differs considerably between the different agents (see Table 16.2 for details). There were large differences in the incidence of adverse events in the different studies. For gadopentetate dimeglumine the incidence of doubtful to highly probable related adverse events varied between 0.77%–18%. The figures were 0%–18,8% for gadodiamide, 0.97%–14.1% for gadoterate meglumine and 0%–22% for gadobenate dimeglumine. Interestingly, the study with the largest patient population (n=1038) showed the lowest incidence rate of adverse events (Oudkerk et al. 1995). Furthermore, in two studies no adverse events occurred with gadodiamide and no adverse events occurred with gadobenate dimeglumine in one study, suggesting that too few patients were assessed (Balériaux et al. 1993; Sadni et al. 1997; Knopp et al. 2004). In none of the studies was there a significant difference in adverse events between agents. Thus, all agents have a similar safety profile and to show a significant difference between two agents, a double blind randomized study would probably need to consist of between 10,000s and 100,000s of patients. Because of the high costs and the low impact for individual patients, such a study will very likely never be performed.

16.2.3 Other Studies

In a survey of American Society of Neuroradiology fellowship directors, to which just over 50% responded (Murphy et al. 1999), the adverse effects of approximately 835,535 doses of gadolinium were studied (687,255 doses of gadopentetate dimeglumine, 74,275 doses of gadodiamide and 64,005 doses of gadoteridol). Overall, 454 (0.066%) patients had adverse reactions to gadopentetate dimeglumine, 23 (0.031%) patients to gadodiamide and 260 (0.406%) patients to gadoteridol. The number of reactions to gadoteridol was significantly greater.

In a descriptive study of moderate to severe reactions after either gadopentetate dimeglumine or gadoterate meglumine in approximately 30,000 patients over a 10-year time period, three moderate to severe reactions occurred, all after gadoterate meglumine (de Ridder et al. 2001).

In a drug-use evaluation study, 3558 patients who received gadoteridol were assessed for adverse reactions. The data were compared to earlier obtained retrospective data from the same hospital on gadopentetate dimeglumine, which included 4892 patients. With gadoteridol, 2.1% of the patients had adverse reactions, compared to 1.3% of the patients receiving gadopentetate dimeglumine. With both agents, the most frequent symptom was nausea (Hieronim et al. 1995).

In a study of 56 patients with multiple sclerosis, who received monthly MRI examinations with gadopentetate dimeglumine 0.1 mmol/kg for research purposes, no significant effects on routine haematology, serum chemistry, renal and liver function and serum iron profiles were found. The patients had received between three and 53 doses of gadopentetate dimeglumine. It was concluded that repeated monthly administration of gadopentetate dimeglumine at the standard dose is safe (Tresley et al. 1997).

16.2.4 Double and Triple Dosage

During the phase I–III studies with gadoversetamide, no significant difference in adverse event rates for doses between 0.1 mmol/kg and 0.4 mmol/kg was noted (Brown et al. 2002). In another study with

Table 16.2. Results of randomised double-blind studies.

Authors (year)	Agents	Study design	No. of patients	Percentage of adverse events per patient	Percentage of adverse effects related to agent per patienta
Myhr et al. (1992)	Gadodiamide	Randomised	59		
	Gadopentetate dimeglumine	Double-blind	Gadodiamide 30	Gadodiamide 23%	Gadodiamide 10%
		Parallel	Gadopentetate dimeglumine 29	Gadopentetate dimeglumine 17%	Gadopentetate dimeglumine 10.3%
Valk et al. (1993)	Gadodiamide	Randomised	79		
		Double-blind	Gadodiamide 39	Gadodiamide 5%	Gadodiamide 5%
	Gadopentetate dimeglumine	Parallel	Gadopentetate dimeglumine 40	Gadopentetate dimeglumine 2.5%	Gadopentetate dimeglumine 2.5%
Balériaux et al. (1993)	Gadodiamide	Randomised	60		
		Double-blind	Gadodiamide 30	Gadodiamide 0%	Gadodiamide 0%
	Gadoterate meglumine	Parallel	Gadoterate meglumine 30	Gadoterate meglumine 6.7%	Gadoterate meglumine 3.3%
Brugières et al. (1994)	Gadoterate meglumine	Randomised	299		
		Double-blind	Gadoterate meglumine 149	Gadoterate meglumine 17.3%	Gadoterate meglumine 14.1%
		Parallel			Gadopentetate dimeglumine 18%
	Gadopentetate dimeglumine		Gadopentetate dimeglumine 150	Gadopentetate dimeglumine 19.3%	
Oudkerk et al. (1995)	Gadoterate meglumine	Randomised	1038		
		Double-blind	Gadoterate meglumine 518	Gadoterate meglumine 2.2%	Gadoterate meglumine 0.97%
		Parallel			Gadopentetate dimeglumine 0.77%
	Gadopentetate dimeglumine		Gadopentetate dimeglumine 520	Gadopentetate dimeglumine 1.5%	
Åkeson et al. (1995)	Gadodiamide	Randomised	60		
		Double-blind	Gadodiamide 30	Gadodiamide 13.3%	Gadodiamide 10%
	Gadopentetate dimeglumine	Parallel	Gadopentetate dimeglumine 30	Gadopentetate dimeglumine 6.7%	Gadopentetate dimeglumine 3.3%
Sadni et al. (1997)	Gadodiamide	Randomised	99		
		Double-blind	Gadodiamide 49	Gadodiamide 0%	Gadodiamide 0%
	Gadopentetate dimeglumine	Parallel	Gadopentetate dimeglumine 50	Gadopentetate dimeglumine 6%	Gadopentetate dimeglumine 4%
Rubin et al. (1999)	Gadoversetamide	Randomised	193		
		Double-blind	Gadoversetamide 99	Gadoversetamide 37.4%	Gadoversetamide 9.1%
		Parallel	Gadopentetate dimeglumine 94		Gadopentetate dimeglumine 13.8%
	Gadopentetate dimeglumine			Gadopentetate dimeglumine 47.9%	
Grossman et al. (2000)	Gadoversetamide	Randomised	395		
		Double-blind	Gadoversetamide 262	Gadoversetamide 27.1%	?
		Parallel	Gadopentetate dimeglumine 133		
	Gadopentetate dimeglumine			Gadopentetate dimeglumine 26.3%	
Greco et al. (2001)	Gadoteridol	Randomised	92		
		Double-blind	Gadoteridol 89	Gadoteridol 2.2%	Gadoteridol 2.2%
	Gadopentetate dimeglumine	Cross-over	Gadopentetate dimeglumine 92	Gadopentetate dimeglumine 4.3%	Gadopentetate dimeglumine 4.3%
Runge et al. (2001)	Gadobenate dimeglumine	Randomised Double-blind Parallel	205		
			Gadogenate dimeglumine 136	Gadobenate dimeglumine 25.7%	Gadobenate dimeglumine 22.0%
	Gadodiamide		Gadodiamide 69	Gadodiamide 31.9%	Gadodiamide 18.8%

Authors (year)	Agents	Study design	No. of patients	Percentage of adverse events per patient	Percentage of adverse effects related to agent per patienta
Knopp et al. (2003)	Gadobenate dimeglumine	Randomised Double-blind Parallel	189 Gadobenate dimeglumine 142	adobenate dimeglumine 12.7%	Gadobenate dimeglumine 11.3%
	Gadopentetate dimeglumine		Gadopentetate dimeglumine 47	Gadopentetate dimeglumine 14.4%	Gadopentetate dimeglumine 10.6%
Knopp et al. (2004)	Gadobenate dimeglumine	Randomised Double-blind Cross-over	27 Gadobenate dimeglumine 27	Gadobenate dimeglumine 0%	Gadobenate dimeglumine 0% Gadopentetate dimeglumine 3.7%
	Gadopentetate dimeglumine		Gadopentetate dimeglumine 27	Gadopentetate dimeglumine 7.4%	
Colosimo et al. (2004)	Gadobenate dimeglumine	Randomised Double-blind Cross-over	31 Gadobenate dimeglumine 26	Gadobenate dimeglumine 11,5%	Gadobenate dimeglumine 7.7%
	Gadoterate meglumine		Gadoterate meglumine 28	Gadoterate meglumine 7.1%	Gadoterate meglumine 3.6%

[a]Judged doubtful/highly probable by principal investigator.

gadoversetamide, patients received 0.1 mmol/kg, 0.3 mmol/kg or 0.5 mmol/kg. The incidence of adverse events increased statistically significantly with increasing dose (Swan et al. 1999a). In a phase III clinical trial, 38 patients received the standard gadodiamide dose and 40 received a triple dose. Five patients from the standard dose group and two from the triple dose group reported adverse events, none of which were judged to be related to the contrast medium (Demaerel et al. 1994). In a double blind multicenter study with single versus triple dose gadodiamide no adverse events possibly related to gadodiamide administration were recorded (Thurnher et al. 2001). In a phase III study in 199 patients with suspected CNS pathology, patients either received 0.1 or 0.3 mmol/kg gadopentetate dimeglumine (Haustein et al. 1993). A total of 15 adverse events in 12 patients were encountered, eight in the 0.1 mmol/kg group and seven in the 0.3 mmol/kg group.

16.2.5 Renal Safety

In most patients with moderate to severe impaired renal function, gadopentetate dimeglumine, gadoterate meglumine, gadodiamide, gadobenate dimeglumine, gadoteridol, gadobutrol and gadoversetamide do not significantly affect serum creatinine levels (Bellin et al. 1992; Haustein et al. 1992; Joffe et al. 1998; Swan et al. 1999a,b; Tombach et al. 2001; Yoshikawa and Davies 1997). However, contrast medium induced nephropathy may occur after gadolinium based contrast media just as after iodinated contrast media (Chap. 17).

In 3.5% of 195 patients with abnormal pre-examination creatinine clearance levels, acute renal failure (anuria) developed after gadolinium-based contrast medium administration. For MR angiography the incidence was 1.9% and for digital subtraction angiography it was 9.5% (Sam et al. 2003). Dialysis was required in three of the seven patients who developed acute renal failure. The doses of gadolinium-DTPA ranged from 0.31 to 0.41 mmol/kg for MR angiography and 0.27 to 0.42 mmol/kg for digital subtraction angiography. Several other reports have shown the nephrotoxic potential of gadolinium based contrast media (Thomsen al. 2002). It has even been reported after an intravenous injection of 0.14 mmol/l of a gadolinium based contrast medium (Thomsen 2004). An experimental study in pigs has indicated the gadolinium based contrast media are more nephrotoxic than iodinated contrast media in equimolar doses (Elmståhl et al. 2004).

16.2.6 Pregnancy and Lactation

Gadolinium contrast media may be used in pregnant women. Lactating women can safely continue to breast feed after receiving gadolinium contrast media. A detailed account of both these topics is given in Chap. 9.

16.2.7 Transmetallation

Free Gd^{3+} is extremely toxic. The term transmetallation describes the extent to which Gd^{3+} can be replaced by other endogenous metals, such as zinc or copper, resulting in the release of free Gd^{3+} (Bellin et al. 2003; Gibby et al. 2004). This is dependent on the thermodynamic and conditional stability constants (Gibby et al. 2004). The higher these constants, the more energy is needed to break open the structure in which Gd^{3+} is held (Kirchin and Runge 2003). An indirect measure of the stability of the Gd chelate is the amount of excess chelate in the formulation (Kirchin and Runge 2003). The excess chelate is considered necessary because of the possibility of transmetallation with endogenous ions. In fact, the agents with the weakest thermodynamic and conditional stability constant have the largest amount of excess chelate (Table 16.1). Transmetallation may also occur when the Gd-chelate remains inside the body for longer, as is the case in patients with renal failure (Shellock and Kanal 1999).

The clinical importance of transmetallation still has to be shown. To date, no harmful effects of free Gd^{3+} in humans have been reported (Runge 2000; Kirchin and Runge 2003). Normann et al. (2000) did not find free Gd^{3+} in blood or dialysate for up to 5 days after injection of gadodiamide in patients with end-stage renal failure.

16.3 Infants and Children

In infants less than 6 months of age, gadodiamide was safe and well tolerated (Marti-Bonmati et al. 2000). In a group of 50 children between 6 months and 13 years of age, two adverse events occurred that were considered of uncertain relationship to the administration of gadodiamide (Hanquinet et al. 1996). In pediatric patients in phase I–III clinical trials with gadopentetate dimeglumine and gadoteridol, the number of adverse events was comparable to adults (Niendorf et al. 1991; Yoshikawa and Davies 1997). For gadoteridol, three adverse events were reported in a multicenter study with 103 children between 0.3–17.5 years (Ball et al. 1993). In two studies using gadopentetate dimeglumine, one with 156 children younger than 2 years and the other with 91 children younger than 1 year, no immediate or delayed adverse events were noted (Eldevik and Brunberg 1994; Tsai-Goodman et al. 2004). In a study with 17 healthy children between 1.2–16.6 years of age, no adverse events were recorded after intravenous injection of 0.1 mmol/kg gadoversetamide (Baker et al. 2004).

16.4 Sickle Cell Anaemia and Other Haemoglobinopathies

To date, there is no evidence suggesting that Gd-based contrast media are potentially dangerous to patients with sickle cell disease or other haemoglobinopathies (Bellin et al. 2003; Shellock and Kanal 1999).

References

Åkeson P, Jonsson E, Haugen I et al (1995) Contrast-enhanced MRI of the central nervous system: comparison between gadodiamide injection and gadolinium-DTPA. Neuroradiology 37:229–233

Baker JF, Kratz LC, Stevens GR et al (2004) Pharmacokinetics and safety of the MRI contrast agent gadoversetamide injection (OptiMARK) in healthy paediatric subjects. Invest Radiol 39:334–339

Balériaux D, Matos C, de Greef D (1993) Gadodiamide injection as a contrast medium for MRI of the central nervous system: a comparison with gadolinium-DOTA. Neuroradiology 35:490–494

Ball WS, Nadel SN, Zimmerman RA et al (1993) Phase III multicenter clinical investigation to determine the safety and efficacy of gadoteridol in children suspected of having neurologic disease. Radiology 186:769–774

Balzer JO, Loewe C, Davis K et al (2003) Safety of contrast-enhanced MR angiography employing gadobutrol 1.0 M as contrast material. Eur Radiol 13:2067–2074

Bellin MF, Deray G, Assogba U et al (1992) Gd-DOTA: evaluation of its renal tolerance in patients with chronic renal failure. Magn Reson Imaging 10:115–118

Bellin MF, Vasile M, Morel-Precetti S (2003) Currently used non-specific extracellular MR contrast media. Eur Radiol 13:2688–2698

Brown JJ, Kristy RM, Stevens GR et al (2002) The OptiMARK clinical development program: summary of safety data. J Magn Reson Imaging 15:446–455

Brugières P, Gaston A, Degryse HR et al (1994) Randomised double blind trial of the safety and efficacy of two gadolinium complexes (Gd-DTPA and Gd-DOTA). Neuroradiology 36:27–30

Colosimo C, Knopp MV, Barreau X et al (2004) A comparison of Gd-BOPTA and Gd-DOTA for contrast-enhanced MRI of intracranial tumours. Neuroradiology 46:655–665

De Haën C (2001) Conception of the first magnetic resonance imaging contrast agents; a brief history. Top Magn Reson Imaging 12:221–230

Demaerel P, Marchal G, Wilms G et al (1994) Gadodiamide injection at 0.1 and 0.3 mmol/kg body weight: a phase III double-blind, parallel, randomised clinical investigation of known or suspected central nervous system lesions at 1.5T. Neuroradiology 36:355–359

De Ridder F, de Maeseneer M, Stadnik T et al (2001) Severe adverse reactions with contrast agents for magnetic resonance: clinical experience in 30000 MR examinations. JBR-BTR 84:150–152

Eldevik PO, Brunberg JA (1994) Gadopentetate dimeglumine-enhanced MR of the brain: clinical utility and safety in patients younger than two years of age. Am J Neuroradiol 15:1001–1008

Elmståhl B, Nyman U, Leander P et al (2004) Gadolinium contrast media are more nephrotoxic than a low osmolar iodine medium employing doses with equal X-ray attenuation in renal arteriography: an experimental study in pigs. Acta Radiol 11:1219–1228

Gibby WA, Gibby KA, Gibby WA (2004) Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (Prohance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy. Invest Radiol 39:138–142

Greco A, Parker JR, Ratcliffe CG et al (2001) Phase III, randomized, double-blind, cross-over comparison of gadoteridol and gadopentetate dimeglumine in magnetic resonance imaging of patients with intracranial lesions. Australas Radiol 45:457–463

Grossman RI, Rubin DL, Hunter G et al (2000) Magnetic resonance imaging in patients with central nervous system pathology: a comparison of OptiMARK (Gd-DTPA-BMEA) and Magnevist (Gd-DTPA). Invest Radiol 35:412–419

Hanquinet S, Christophe C, de Greef D et al (1996) Clinical evaluation of gadodiamide injection in paediatric MR imaging. Pediatr Radiol 26:806–810

Haustein J, Niendorf HP, Krestin GP et al (1992) Renal tolerance of gadolinium-DTPA/dimeglumine in patients with chronic renal failure. Invest Radiol 27:153–156

Haustein J, Laniado M, Niendorf HP et al (1993) Triple-dose versus standard-dose gadopentetate dimeglumine: a randomized study in 199 patients. Radiology 186:855–860

Hieronim DE, Kanal E, Swanson DP (1995) Dosage of gadoteridol and adverse reactions relative to gadopentetate. Am J Health Syst Pharm 52:2556–2559

Joffe P, Thomsen HS, Meusel M (1998) Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. Acad Radiol 5:491–502

Jordan RM, Mintz RD (1995) Fatal reaction to gadopentetate dimeglumine. AJR 164:743–744

Kirchin MA, Runge VM (2003) Contrast agents for magnetic resonance imaging. Safety update. Top Magn Reson Imaging 14:426–435

Knopp VM, Bourne MW, Sardanelli F et al (2003) Gadobenate dimeglumine-enhanced MRI of the breast: analysis of dose response and comparison with gadopentetate dimeglumine. AJR 181:663–676

Knopp VM, Esser M, Paul P et al (2003) Utilization and adverse event reporting of gadopentetate dimeglumine (Gd-DTPA) as a MR contrast agent after 45 million administrations and 15 years of use. Radiology 229 [Suppl]:724

Knopp MV, Runge VM, Essig M et al (2004) Primary and secondary brain tumors at MR imgaging: bicentric intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. Radiology 230:55–64

Marti-Bonmati L, Vega T, Benito C et al (2000) Safety and efficacy of Omniscan (gadodiamide injection) at 0.1 mmol/kg for MRI in infants younger than 6 months of age: phase III open multicenter study. Invest Radiol 35:141–147

Murphy KPJ, Szopinski KT, Cohan RH et al (1999) Occurrence of adverse reactions to gadolinium-based contrast material and management of patients at risk: a survey of the American Society of Neuroradiology fellowship directors. Acad Radiol 6:656–664

Myhr G, Rinck PA, Børseth A (1992) Gadodiamide injection and gadopentetate dimeglumine. A double-blind study in MR imaging of the CNS. Acta Radiol 33:405–409

Nelson KL, Runge VM (1995) Basic principles of MR contrast. Top Magn Reson Imaging 7:124–136

Niendorf HP, Dinger JC, Haustein J et al (1991) Tolerance data of Gd-DTPA: a review. Eur J Radiol 13:15–20

Normann PT, Joffe P, Martinsen I, Thomsen HS (2000) Identification and quantification of gadodiamide in serum, peritoneal dialysate and faeces from end-stage renal patients dosed with gadodiamide injection by inductively coupled plasma-atomic emission spectroscopy and comparative analysis by high-performance liquid chromatography. J Pharm Biomed Anal 22:939–947

Oksendal A, Hals P (1993) Biodistribution and toxicity of MR imaging contrast media. J Magn Reson Imaging 3:157–165

Oudkerk M, Sijens PE, van Beek EJR et al (1995) Safety and efficacy of Gadoterate meglumine (Gd-DOTA) versus Magnevist (Gd-DTPA) in magnetic resonance imaging of the central nervous system. Invest Radiol 30:75–78

Rubin DL, Desser TS, Semelka R et al (1999) A multicenter, randomized, double-blind study to evaluate safety, tolerability, and efficacy of OptiMARK (gadoversetamide injection) compared with Magnevist (gadopentetate dimeglumine) in patients with liver pathology: Results of a phase III clinical trial. J Magn Reson Imaging 9:240–250

Runge VM (2000) Safety of approved MR contrast media for intravenous injection. J Magn Reson Imaging 12:205–213

Runge VM, Armstrong MR, Barr RG et al (2001) A clinical comparison of the safety and efficacy of Multihance (gadobenate dimeglumine) and Omniscan (gadodiamide) in magnetic resonance imaging in patients with central nervous system pathology. Invest Radiol 36:65–71

Sadni M, Collignon J, Dondelinger RF et al (1997) Safety and efficacy of contrast-enhanced MRI in the brain, head and neck: gadodiamide injection versus gadopentetate dimeglumine. JBR-BTR 80:225–228

Sam AD II, Morasch MD, Collins J et al (2003) Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. J Vasc Surg 38:313–318

Shellock FG, Kanal E (1999) Safety of magnetic resonance imaging contrast agents. J Magn Reson Imaging 10:477–484

Swan SK, Baker JF, Free R, Tucker RM et al (1999a) Pharmacokinetics, safety, and tolerability of gadoversetamide injection (OptiMARK) in subjects with central nervous system or liver pathology and varying degrees of renal function. J Magn Reson Imaging 9:317–321

Swan SK, Lambrecht LJ, Townsend R, Davies et al (1999b)

Safety and pharmacokinetic profile of gadobenate dimeglumine in subjects with renal impairment. Invest Radiol 34:443–448

Thomsen HS (2004) Gadolinium-based contrast media may be nephrotoxic even at approved doses (case report). Eur Radiol 14:1654–1656

Thomsen HS, Almén T, Morcos SK, members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2002) Gadolinium-containing contrast media for radiographic examinations: a position paper. Eur Radiol 12:2600–2605

Thurnher SA, Capelastagui A, del Olmo FH et al (2001) Safety and effectiveness of single- versus triple-dose gadodiamide injection-enhanced MR angiography of the abdomen: a phase III double-blind multicenter study. Radiology 219:137–146

Tombach B, Bremer C, Reimer P et al (2000) Pharmacokinetics of 1 M gadobutrol in patients with chronic renal failure. Invest Radiol 35:35–40

Tombach B, Bremer C, Reimer P et al (2001) Renal tolerance of a neutral gadolinium chelate (gadobutrol) in patients with chronic renal failure: results of a randomized study. Radiology 218:651–657

Tombach B, Bremer C, Reimer P et al (2002) Using highly concentrated gadobutrol as an MR contrast agent in patients also requiring hemodialysis: safety and dialysability. AJR 178:105–109

Tresley RM, Stone LA, Fields N et al (1997) Clinical safety of serial monthly administrations of gadopentetate dimeglumine in patients with multiple sclerosis: implications for natural history and early-phase treatment trials. Neurology 48:832–835

Tsai-Goodman B, Geva T, Odegard KC et al (2004) Clinical role, accuracy, and technical aspects of cardiovascular magnetic resonance imaging in infants. Am J Cardiol 94:69–74

Valk J, Algra PR, Hazenberg CJ et al (1993) A double-blind, comparative study of gadodiamide injection and gadopentetate dimeglumine in MRI of the central nervous system. Neuroradiology 35:173–177

Wastie ML, Latief KH (2004) Gadolinium: named after Finland's most famous chemist. Br J Radiol 77:146–147

Witte RJ, Anzai LL (1994) Life-threatening anaphylactoid reaction after intravenous gadoteridol administration in a patient who had previously received gadopentetate dimeglumine. Am J Neuroradiol 15:523–524

Yoshikawa K, Davies A (1997) Safety of ProHance in special populations. Eur Radiol 7 [Suppl 5]:S246–S250

17 Gadolinium Contrast Media for Radiographic Examinations

Henrik S. Thomsen

CONTENTS

17.1 Introduction

It has been suggested that patients with significant renal impairment and/or previous severe reactions to iodinated contrast media should receive gadolinium-based MRI contrast agents instead of the traditional iodinated radiographic contrast agents (Albrecht and Dawson 2000; Bittner et al. 1997; Engelbrecht et al. 1996). Another possible indication could be before thyroid treatment with radioactive iodine to avoid interference with iodine uptake.

At the kV (~70) used for digital angiography, the attenuation of X-rays by gadolinium is approximately the same as for iodine. At the kV (~120) used for CT, the attenuation of X-rays by gadolinium is approximately double that of iodine. Therefore theoretically gadolinium could therefore replace iodine as a radiographic contrast agent.

H. S. Thomsen, MD
Professor, Department of Diagnostic Radiology 542E, Copenhagen University Hospital at Herlev, Herlev Ringvej 75, 2730 Herlev, Denmark

Gadolinium based contrast agents are in general known be safe and not nephrotoxic in the usual MRI doses up to 0.3 mmol/kg body weight (BW) However, the dose requirement for a satisfactory diagnostic study differs between MR and X-ray examination because different properties of the gadolinium are being used in the two modalities. The use of gadolinium-based contrast agents in radiographic examinations is contentious and the risks poorly understood (Thomsen et al. 2002; Thomsen 2003).

17.2 Gadolinium Preparations

The first four marketed gadolinium contrast media (gadopentate dimeglumine, gadoterate, gadodiamide, gadoteridol) are available in a concentration of 0.5 mmol/ml. The same applies to gadobenate dimeglumine which unlike the other four agents is also excreted via the liver (1%) (Chap. 17). Recently, gadobutrol has been introduced in a concentration of 1 mmol/ml (see also Chaps. 9 and 16 for non-renal safety aspects). For all six agents there is one Gd-atom in each molecule, so the molar concentration of the agent and of gadolinium is the same. Traditionally, iodine radiographic contrast media are marketed based on the mg of iodine per ml. The concentration of 300 mg I/ml is equal to 2.38 mmol I/ml. Since there are three iodine atoms per molecule, the molar concentration of the agent is only 0.8 mmol/ml.

The commonly used dose for body CT is 150 ml of a 300 mg I/ml (2.38 mmol I/ml) solution. The standard dose for contrast-enhanced MR examination is 0.2 ml/kg BW of a 0.5 mmol/ml gadolinium-based contrast agent. For body CT, a patient weighing 70 kg would receive 120 mmol of the iodinated agent molecule (0.8 mmol/ml × 150 ml) and 360 mmol of iodine (2.38 mmol/ml × 150 ml). For MR examination, this same 70 kg patient would receive 7 mmol of the gadolinium based agent molecule and 7 mmol

of gadolinium [0.5 mmol/ml × 14 ml (0.2 ml/kg BW × 70 kg BW)]. Thus, the number of iodinated contrast agent molecules administered would be almost 17 times that of gadolinium containing molecules, and the number of iodine atoms administered would be 51 times that of gadolinium. For a patient weighing 50 kg, the difference is even larger [~24 times (molecule) and ~72 times (atom)], whereas for a patient weighing 100 kg it is less [~12 times (molecule) and ~36 times (atom)].

17.3 Pharmacokinetics

The gadolinium chelates have pharmacokinetics similar to those of iodinated radiographic contrast agents with the exception of gadobenate dimeglumine which is also excreted by the liver in small amounts (Chap. 17), but is mainly used for non liver specific indications with the five other "extracellular" gadolinium chelates (Chap. 16). Both types of agent are distributed in the extracellular space and excreted by glomerular filtration. Thus, the T½ is almost the same, and both types of agents can be used to measure the glomerular filtration rate. In patients with normal kidney function about 98% of these agents is excreted within 24 h of injection. However, in patients with severe renal impairment, excretion of gadolinium and iodinated agents differs. Nearly no gadolinium is found in the feces in patients with renal insufficiency, whereas up to 6% of the injected iodine has been recovered in the feces of such patients (Joffe et al. 1998). No free gadolinium is found in the blood several days after injection of gadolinium chelates in patients with end-stage renal failure despite the slow excretion (Joffe et al. 1998; Normann et al. 2000).

17.4 Toxicity (LD_{50})

Acute intravenous LD_{50} of contrast media in mice is expressed as mmol iodine or gadolinium atoms per kg BW. For the five gadolinium-based contrast agents, dimeglumine gadopentate, gadobenate dimeglumine, gadoterate, gadoteridol, gadodiamide, the figures are 6, 8, 8, 18 and 20 mmol gadolinium/kg, respectively. The LD_{50} for the conventional high osmolality iodinated contrast agent diatrizoate is about 50 mmol iodine/kg. The LD_{50} of low osmolality nonionic monomers, e.g. iopromide, is much higher, about 150 mmol iodine per kg) (Weinmann et al. 1990; Weinmann 1999). These LD_{50} values suggest that comparing attenuating atoms the acute intravenous toxicity of the gadolinium-based contrast media is 6 to 25 times that of the nonionic iodinated monomers.

17.5 Incidence of General Reactions to Gadolinium Based Contrast Agents

General adverse reactions similar to those observed with iodinated contrast media may be seen following injection of gadolinium based contrast agents, but the frequency is lower with the incidence of moderate and severe reactions well below 1% (Niendorf et al. 1991; Thomsen 1997). However, the number of patients exposed to unapproved dosages (above 0.3 mmol/kg BW) is still too small to draw any conclusion about the safety of these higher doses. In the few published studies, varying doses of gadolinium-based agents (20–440 ml) have been used and the number of patients has been small. Equally, the prevalence of generalized reactions to very low doses of iodinated contrast agents (e.g. 10 ml of a 300 mgI/ml solution) is not documented in a large number of patients.

17.6 Attenuation of X-Rays by Iodine and Gadolinium

Iodine has the atomic number 53 and an atomic weight of 127, whereas gadolinium has the atomic number 64 and an atomic weight of 157. Attenuation increases with the atomic number of the atom but decreases with the energy (keV) of the X-ray photons, except at the K-edges. At photon energies between the K-edge of iodine [33 kilo electron Volt (keV)] and that of gadolinium (52 keV), iodine attenuates approximately twice as many X-ray photons as does gadolinium. At all other photon energies, the opposite prevails (Nyman et al. 2002). For CT, the maximal X-ray photon energy is between 120–140 keV and the most common photon energies in the spectrum are between 60–70 keV. This is above the K-edge of gadolinium, so the attenuation by gadolin-

ium in this situation is about twice that of iodine; but since there are three iodine atoms per contrast medium molecule, the iodine molecule attenuates 1.5 times more radiation than does a gadolinium-based contrast molecule. For common radiographic examinations, the maximal X-ray photon energy is between 70–90 keV and the most common photon energies in the spectrum are above and below the K-edge of gadolinium (50 keV). Because of the range of photon energies, attenuation is approximately the same for iodine and gadolinium atoms. Hence, the attenuation by the iodinated contrast agent molecule is three times that of the gadolinium molecule (Nyman et al. 2002). Below 33 keV only very few photons will pass through the body.

It should theoretically be possible to obtain radiographic images of diagnostic quality with gadolinium-based contrast agents, but the image quality will generally be inferior to that achieved with iodinated contrast agents. This can be explained by the difference in molar concentrations between gadolinium- and iodine-based contrast agents. A 0.5 mmol/ml concentration of iodine atoms contains 63 mgI/ml. Assuming that a 0.5 mmol/ml concentration of gadolinium attenuates to the same extent as a 0.5 mmol/ml concentration of iodine, a patient receiving these equi-attenuating concentrations will receive only 1/3 of the iodine contrast medium molecules compared to the situation with gadolinium contrast medium molecules. Considering the molar concentration of an iodinated contrast agent at 300 mgI/ml, the attenuation of this preparation is almost five times that of gadolinium preparations at equi-volume. Thus, the volume of gadolinium preparation required to obtain "comparable" attenuation is five times that of the iodine preparation.

17.7 Clinical Studies

Prince et al. (1996) studied 64 patients undergoing MR examination with a gadolinium-based agent and a radiographic examination with an iodinated contrast medium. They concluded that high-dose gadolinium chelates are significantly less nephrotoxic than iodinated agents, since eleven of the 64 patients had a significant increase in serum creatinine after intravenous or intraarterial administration of iodine-based contrast media whereas none had increased serum creatinine levels after intravenous administration of a gadolinium-based contrast agent. However, the molar doses and concentrations of the iodine and gadolinium atoms were not comparable. Although the exact dose of the iodinated contrast used for each patient could not be verified, between 30 and 60 g I was administered. For the MR examinations between 0.2 and 0.4 mmol/kg BW were used. Assuming that all patients were standard (~70 kg), the dose of iodine atoms was approximately 17 times higher than that of gadolinium atoms. Thus, the doses were not comparable and had equi-attenuating doses been used, the results might have been different.

Over recent years, gadolinium-based contrast agents have been used for examinations such as CT, intravenous urography and digital subtraction angiography of various parts of the body (e.g. liver, renal and peripheral arteries). Albrecht and Dawson (2000) studied 15 patients receiving 0.3 mmol/kg BW gadopentate dimeglumine; five had abdominal CT, five abdominal DSA and five intravenous urography. No side-effects were reported, but generally the image quality was inferior to that obtained subsequently with standard doses of iodinated contrast media (50--150 ml of a 300 or 350 mgI/ml solution). The authors suggested that higher doses including more concentrated solutions of gadolinium-based contrast media might be useful (Albrecht and Dawson 2000).

Gadolinium-based contrast media have also been used for endoscopic retrograde cholangiography, cystography, urethrocystography, and retrograde pyelography and during percutaneous nephrostomy and biliary tract drainage with resultant adequate image quality and no side-effects (Velmas and Markkola 1998). Coche et al. (2001) reported successful detection of pulmonary embolism using gadolinium-enhanced helical CT (0.4 mmol/kg gadodiamide) in a 77-year-old woman with previous allergy-like reaction to iodinated contrast medium and renal insufficiency (serum creatinine of 200 μmol/ml) without any problems. A total of 14 patients with abnormal S-creatinine levels underwent digital subtraction vena cavography with a gadolinium-based contrast agent (maximum 0.4 mmol/kg BW) for filter placement, thrombolysis or diagnosis. Three of the 14 patients had a significant increase in serum creatinine (> 44 μmol/ml), but there were other concurrent causes, which might account for the deterioration of renal function (Kaufmann et al. 1999). It was concluded that gadolinium-based contrast agents were suitable for digital subtraction venography in patients with renal insufficiency.

In an azotemic patient with suspected renal artery stenosis, a total of 40 ml (0.5 mmol/ml) undi-

luted dimeglumine gadopentate was injected arterially (Matchett et al. 1996). The serum creatinine increased from 290 μmol/l to 390 μmol/l, but this might have been attributable to a myocardial infarction which the patient developed 3 days after the procedure. Acute renal failure was described following lower extremity arteriography with 80 ml of 0.5 mmol/ml (0.44 mmol/kg BW) of gadoteridol in an insulin-dependent diabetic patient with nephropathy (Gemery et al. 1998). S-creatinine transiently increased from 350 to 820 μmol/ml and the deterioration was considered most likely due to the contrast agent.

A total of 31 patients with azotemia or previous severe adverse reaction to iodinated contrast media underwent digital subtraction angiography with between 20 and 60 ml of 0.5 mmol/ml gadopentate (Hammer et al. 1999). In nine cases, CO_2 was also used and in eight cases between 6 and 40 ml of iohexol 350 mgI/ml (mean 17.8 ml) were used. In no patient did S-creatinine increase more than 44 μmol/l within 48 h. Spinosa et al. (1998) studied 13 renal transplant patients with suspected vascular causes of renal insufficiency and/or accelerated hypertension with both CO_2 and a gadolinium-based contrast agent (16–60 ml gadodiamide). Digital subtraction angiography was considered adequate in all patients. In two patients renal failure progressed (> 44 μmol/l within 48 h), but concurrent causes of the renal dysfunction were also present; one had received 20 and the other received 60 ml of gadodiamide. During peripheral arteriography Spinosa et al. (1999) found that gadodiamide with an osmolality of 789 mOsm per kilogram of water was less painful than gadopentate dimeglumine with an osmolality of greater than 1800 mOsm per kilogram of water. No effects on renal function were found. Later Spinosa et al. (2000) reported one of 18 azotemic patients (6%) whose renal function deteriorated after undergoing CO_2 angiography supplemented with 0.5 mmol/ml gadodiamide (20–100 ml; mean volume 55 ml; 0.13–.04 mmol/kg). The affected patient received 70 ml gadodiamide (0.3 mmol/kg BW)

Injections of 80–440 ml of gadodiamide during arteriography have also been reported (Gemette et al. 2001). A S-creatinine increase of 53 μmol/ml or more occurred in eight of 20 patients (40 %) with a preprocedural S-Cr of 115–548 μmol/ml. In three of the eight patients, the creatinine values did not return to baseline value. Following peripheral gadolinium arteriography, angioplasty and stent placement, a patient with renal insufficiency (340 ìmol/l) developed acute renal failure and acute pancreatitis (Schenker et al. 2001). Acute pancreatitis has been seen both after intraarterial (Gemery et al. 1998) and intravenous (Terzi and Sokman 1999) injection of a gadolinium-based contrast agent.

17.8 Experimental Nephrotoxicity

Intravenous injection (9 ml/kg) of gadopentate (0.1 mol/ml), iohexol (300 mgI/ml), metrizoate (300 mgI/ml) and normal saline in rabbits showed nephrotoxicity of the same order for all three contrast agents (Leander et al. 1992). The molar concentration and dose of iodine atoms was 24 times higher than the molar concentration and dose of gadolinium atoms. Thus, the iodinated agents might have had a lower nephrotoxic effect than the gadolinium media if the two agents had been compared in equi-attenuating doses and concentrations. Rat studies where high equimolar doses (4.59 mmol/kg BW) of gadolinium (gadopentate and gadodiamide) and iodinated (diatrizoate and iohexol) contrast agents were injected intravenously showed no significant deterioration in the function of normal and diseased kidneys (Thomsen et al. 1994, 1995). There was a significant correlation between albuminuria and the osmolality of the contrast medium; gadopentate caused the highest excretion and gadiodiamide and iohexol the least. However, the degree of albuminuria does not correlate with nephrotoxic potential of a contrast medium. In these studies the dose of iodine atoms was three times the dose of gadolinium atoms.

In an ischemic rat model, intra-aortic injections of 1.5 ml (0.5 mmol/ml) gadopentate (0.75 mmol Gd atoms) and 2.6 ml 370 mgI/ml diatrizoate (7.6 mmol iodine atoms) caused a significant decrease in creatinine clearance of similar magnitude, 50% and 67%, respectively (Deray et al. 1990; Brillet et al. 1994). Gadoterate [1.5 ml (0.5 mmol/l)] alone caused no decrease in renal function in this model. The dose of iodine was ten times higher than the dose of gadolinium and the two different doses produced a similar significant decrease in creatinine clearance. Whether the iodinated contrast medium would produce less decrease in creatinine clearance than the gadolinium medium if equimolar doses had been given remains speculative.

In an experimental model of renal ischemia in pigs, 0.5 molar gadopentate dimeglumine (3 ml/kg BW) caused severe impairment of renal function; the low-

osmolar gadodiamide caused less deterioration in renal function, and the low-osmolar iohexol (3 ml of 190 mgI/ml per kg BW) caused even less (Elmståhl et al. 2004). Three ml per kg BW of iohexol (70 mg iodine/ml), which for angiography is equi-attenuating with 0.4 molar gadopentate dimeglumine, caused no change in renal function. An in vitro study using the isolated perfused rat kidney showed that a large dose of gadopentate dimeglumine (0.3 mmol/kg BW) did not cause significant reduction in renal function (Brown et al. 1993). However, an equimolar dose per kg BW of iodine atoms in a 70 kg man would be 10 ml at concentration of 265 mg iodine/ml.

17.9 MR Examinations and Nephrotoxicity

Sam et al. (2003) reported that in 3.5% of 195 patients with abnormal pre-examination creatinine clearance levels, acute renal failure (anuria) developed after gadolinium-based contrast medium administration. For MR angiography the incidence was 1.9% and for digital subtraction angiography 9.5%. Dialysis was required in three of the seven patients who developed acute renal failure. The average creatinine clearance in the whole group was 38.2±1.6 ml/min/1.73 m^2 and in the seven patients who developed contrast medium induced nephropathy it was 32.5±7.8 ml/min/1.73 m^2. The doses of gadolinium-DTPA ranged from 0.31 to 0.41 mmol/kg for MR angiography and 0.27 to 0.42 mmol/kg for digital subtraction angiography. Contrast medium induced nephropathy occurred after a moderate (0.14 mmol/kg) – approved – dose of a gadolinium-based contrast medium in a patient with moderate to severe diabetic nephropathy and chronic heart failure (Thomsen 2004). In diabetic patients with multiple risk factors it may be appropriate to take the same precautions before enhanced MR examinations as before enhanced radiographic examinations.

17.10 Conclusion

Nephrotoxicity of the gadolinium-based contrast agents when used for radiographic studies, CT and MRI has now been described in both man and animals. Use of high doses (> 0.3 mmol/kg BW) of the gadolinium agents in patients with impaired renal function is contraindicated.

Several reports have shown the usefulness of gadolinium-based agent in radiographic examinations including CT when iodinated contrast agents were contraindicated for a variety of reasons. The major drawback when using gadolinium-based contrast agents for CT or radiography is that commercially available contrast media have only one gadolinium atom per molecule and a low molar concentration. In comparison, iodinated monomers for radiographic examinations contain three iodine atoms per molecule and have molar concentration five times that of gadolinium in the four gadolinium-based contrast agents (dimeglumine gadopentate, gadobenate dimeglumine, gadoteridol, gadodiamide, gadoterate). Hence, image quality is generally inferior when gadolinium-based contrast media are used for radiography. Gadolinium-based contrast media should not be used for radiographic examinations (see Appendix).

References

Albrecht T, Dawson P (2000) Gadolinium-DTPA as X-ray contrast medium in clinical studies. Br J Radiol 73:878–882

Bittner CA, Goodwin SC, Lu D, McNamara TO, Joseph T (1997) Gadolinium-based contrast agents for angiographic use as a safe radiocontrast in patients with impaired renal function. J Vasc Interv Radiol [Suppl] 8:178

Brillet G, Dubois M, Beaufils H, Bourboze R, Deray G (1994) Renal tolerance of gadolinium-DOTA and gadolinium-DTPA in rats. Invest Radiol 29:352–354

Brown PWG, Haylor JL, Morcos SK, El Nahas AM (1993) The functional effects of gadolinium-DTPA on the isolated perfused rat kidney. Eur J Radiol 16:85–89

Coche EE, Hammer FD, Gofette PP (2001) Demonstration of pulmonary embolism with dynamic gadolinium-enhanced spiral CT. Eur Radiol 11:2306–2309

Deray G, Dubois M, Martinez F, Baumelou B, Beaufils H, Bourboze R, Baumelou A, Jacobs C (1990) Renal effects of radiocontrast agents in rats: A new model of acute renal failure. Am J Nephrol 10:507–513

Elmståhl B, Nyman U, Leander P et al (2004) Gadolinium contrast media are more nephrotoxic than low dose iodine medium employing doses with equal X-ray attenuation in renal arteriography: an experimental study in pigs. Acad Radiol 11:1219–1228

Engelbrecht V, Koch JA, Rassek M, Mödder U (1996) Gadodiamide and gadolinium-DTPA as intravenous media in computed tomography. Röfo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 165:24–28

Gemery J, Idelson B, Reid S et al (1998) Acute renal failure after arteriography with a gadolinium-based contrast agent. AJR Am J Roentgenol 171:1277–1278

Gemmete JJ, Forauer AR, Kazanjian S, Dasika N, Williams DM, Cho K (2001) Safety of large volume gadolinium angiography. J Vasc Interv Radiol 12 (part 2):S28

Hammer FD, Gofette PP, Maliase J, Mathurin P (1999) Gadolinium dimeglumine: an alternative contrast agent for digital subtraction angiography. Eur Radiol 9:128–136

Joffe P, Thomsen HS, Meusel M (1998) The pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency treated conservatively or undergoing hemodialysis or continuous ambulatory peritoneal dialysis. Acad Radiol 5:491–502

Kaufmann JA, Geller SC, Bazari H, Waltman AC (1999) Gadolinium-based contrast agents as an alternative at vena cavography in patients with renal insufficiency – early experiences. Radiology 212:280–284

Leander P, Allard P, Caillé JM, Golman K (1992) Early effect of gadopentate and iodinated contrast media on rabbit kidneys. Invest Radiol 27:922–926

Matchett WJ, McFarland DR, Rusell DK, Sailors DM, Moursi MM (1996) Azotemia: gadopentate dimeglumine as contrast agent at digital subtraction angiography. Radiology 201:569–571

Niendorf HP, Gifford LM, Haustein J, Cornelius I, Alhassan A, Clauss W (1991) Tolerance data of Gd-DTPA: a review. Eur J Radiol 13:15–20

Normann PT, Joffe P, Martinsen I, Thomsen HS (2000) Identification and quantification of gadodiamide in serum, peritoneal dialysate and faeces from end-stage renal patients dosed with gadodiamide injection by inductively coupled plasma-atomic emission spectroscopy and comparative analysis by high-performance liquid chromatography. J Pharmaceut Biomed Anal 22:939–947

Nyman U, Elmståhl B, Leander P, Nilsson M, Golman K, Almén T (2002) Are gadolinium-based contrast media really safer than iodinated media for digital subtraction angiography in patients with azotemia? Radiology 223:311–318

Prince MR, Arnoldus C, Frisoli JK (1996) Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. JMRI 1:162–166

Sam AD II, Morasch MD, Collins J, Song G, Chen R, Pereles FS (2003) Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. J Vasc Surg 38:313–318

Schenker MP, Solomon JA, Roberts DA (2001) Gadolinium arteriography complicated by acute pancreatitis and acute renal failure. J Vasc Interv Radiol 12:393

Spinosa DJ, Matsumo AH, Angle JF, Hagspiel KD, Iassacs R (1998) Gadolinium based contrast and carbon dioxide angiography to evaluate transplants for vascular causes of renal insufficiency and accelerated hypertension. J Vasc Interv Radiol 9:909–916

Spinosa DJ, Matsumoto AH, Hagspiel KD, Angle JF, Hartwell GD (1999) Gadolinium-based contrast agents in angiography and interventional radiology. AJR Am J Roentgenol 173:1403–1409

Spinosa DJ, Angle JF, Hagspiel KD, Kern JA, Hartwell GD, Matsumoto AH (2000) Lower extremity arteriography with use of iodinated contrast material or gadodiamide to supplement CO2 angiography in patients with renal insufficiency. JVIR 11:35–43

Terzi C, Sokmen S (1999) Acute pancreatitis induced by magnetic-resonance-imaging contrast agent. Lancet 354:1789–1790

Thomsen HS (1997) Frequency of acute adverse events to a non-ionic low-osmolar contrast medium: the effect of verbal interview. Pharmacol Toxicol 80:108–110

Thomsen HS (2003) ESUR Guidelines in contrast media. AJR Am J Roentgenol 181:1461–1471

Thomsen HS (2004) Gadolinium-based contrast media may be nephrotoxic even at approved doses. Eur Radiol 14:1654–1656

Thomsen HS, Almén T, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (2002) Gadolinium-containing contrast media for radiographic examinations: a position paper. Eur Radiol 12:2600–2605

Thomsen HS, Dorph S, Larsen S et al (1994) Urine profiles and kidney histology after intravenous injection of ionic and nonionic radiologic and magnetic resonance contrast media in normal rats. Acad Radiol 1:128–135

Thomsen HS, Dorph S, Larsen S et al (1995) Urine profiles and kidney histology after intravenous injection of ionic and nonionic radiologic and magnetic resonance contrast media in rats with cisplatin nephropathy. Acad Radiol 2:675–682

Velmas T, Markkola T (1998) Gd-DTPA as an alternative contrast agent in conventional and interventional radiology. Acta Radiol 39:223–226

Weinmann HJ (1999) Gadolinium chelates: physico-chemical properties, formulation and toxicology. In: Dawson P, Cosgrove DO, Grainger RG (eds) Textbook of contrast media. Isis Medical Media, Oxford, p 228

Weinmann JH, Press WR, Gries H (1990) Tolerance of extracellular contrast agents for magnetic resonance imaging. Invest Radiol 25:S49–S50

18 Safety of MR Liver Specific Contrast Media

Marie-France Bellin

CONTENTS

18.1 Introduction

Although non-specific gadolinium (Gd) chelates dominate MR imaging of the liver, liver specific contrast agents are increasingly used in order to better detect and characterize liver lesions (Bluemke et al. 2003; Kirchin and Runge 2003; Kopp et al. 1997; Marti-Bonmati et al. 2003; Ros et al. 1995; Spinazzi et al. 1999). They offer the additional advantages of longer retention by the liver and thus a longer window of time for imaging and liver specific uptake. Liver specific agents include superparamagnetic iron oxide particles, manganese based preparations (manganese chelate (mangafodipir trisodium) and free manganese for oral intake), and gadolinium based contrast agents (gadobenate dimeglumine, Gd-BOPTA and gadoxetate, Gd-EOB-DTPA) that combines the properties of a conventional extracellular fluid contrast agent with those of a liver specific agent (Table 18.1). An oral agent containing manganese is still awaiting approval. Manganese based agents also have a high hepatobiliary excretion. The superparamagnetic iron oxide particles differ from the gadolinium- and manganese based products by being mainly T2-agents (associated with a decrease in signal intensity and accumulation in the reticuloendothelial cells) whereas the latter are mainly T1-agents (associated with an increase in signal intensity and accumulation in hepatocytes).

Although theoretical safety concerns exist, MR contrast agents have been shown to be safe and well tolerated in clinical use. The rate of adverse events seems higher with liver specific contrast agents than with extracellular gadolinium chelates (Bellin et al. 1994, 2003; Kirchin and Runge 2003). However, the incidence of adverse events has not been studied in randomized clinical trials. In addition, the mode of administration of superparamagnetic iron oxide particles, either infusion or intravenous bolus administration, has been discussed as a factor influencing their tolerance (Bluemke et al. 1994; Kehagias et al. 2001; Kopp et al. 1997; Reimer and Balzer 2003). The same applies to oral versus intravenous administration of manganese based agents. The literature about tolerance and safety of liver specific agents is limited.

18.2 Superparamagnetic Iron Oxides (SPIO)

Superparamagnetic iron oxides (SPIO) are extremely effective T_2 relaxation agents that produce a long-range disturbance in magnetic field homogeneity and thus reduce the T_2 relaxation time, producing signal loss on T_2 and T_2*-weighted images (Bellin et al. 1994; Bluemke et al. 2003; Ros et al. 1995). The strong T_2 effect (susceptibility effect) is particularly apparent when SPIO particles are distributed inhomogeneously after uptake by Kupffer cells. After intravenous injection, SPIO particles are specifically taken up within minutes by the reticuloendothelial

M-F. Bellin, MD
Professor, Université Paris 11, AP-HP, Service de Radiologie, Hôpital Paul Brousse, 12–14 avenue Paul Vaillant Couturier, 94804 Villejuif Cedex, France

Table 18.1. Overview of the various liver specific MR contrast agents

Liver specific MR agents	Target cell	Main effect on signal intensity		Generic names	Main route of elimination
		T1	T2		
Superparamagnetic iron oxides	Reticuloendothelial cells	↑[a]	↓	Ferucarbotran Ferumoxides	Metabolized
Manganese based contrast agents	Hepatocytes	↑	↓[a]	Mangafodipir trisodium CMC-001	Biliary
Hepatobiliary gadolinium chelates	Hepatocytes	↑	~	Gd-BOPTA[b] Gd-EOB-DTPA	Biliary and renal

[a]Slight effect.

[b]Also extracellular agent.

system (RES), mostly in the liver (approximately 80% of the injected dose) and spleen (5%–10% of the injected dose) (Breuer et al. 2003; Federle et al. 2000; Gallez et al. 1996; Wang et al. 2001). In the liver they are taken up by normal RES Kupffer cells and decrease the signal intensity of the normal liver parenchyma on T_2 and T_2*-weighted images. Since most liver lesions (including metastases and the vast majority of hepatocellular carcinomas) do not have an intact RES, they retain their signal intensity, so that the contrast between normal and abnormal liver tissue is increased. Some uptake of SPIO particles has been observed in focal nodular hyperplasia (Precetti-Morel et al. 1999) and very rare cases of well differentiated hepatocellular adenomas and carcinomas. SPIO particles also have a T_1 effect, which is substantially less than their T_2 effect and can be used for lesion characterization when the agent is given as a bolus injection and for the characterization of hemangiomas (Montet et al. 2004).

Two different preparations are available: ferumoxides and ferucarbotran. The commercial preparation of ferumoxides sold in USA contains 11.2 mg of iron/ml whereas in Europe the concentration of the agent is 22.4 mg of iron/ml. The approved dose is 0.8 mg of iron/kg body weight for ferumoxides and for ferucarbotran 0.56 mg iron/kg body weight.

SPIO particles are composed of an iron oxide core, 3-5 nm in diameter, covered by low molecular weight dextran for ferumoxides and by carbodextran for ferucarbotran. The overall size of the particles, the coating of the iron core and the electrical charge of the surfaces influence their pharmacodynamic and clinical properties. In principle, smaller particles circulate longer in the blood space and may accumulate in the macrophages of the lymph nodes, liver and spleen while large particles have a shorter half life and target the liver more specifically (Stark et al. 1988). Ferumoxides have a mean diameter of 160 nm, a blood half life of 8 min, and a high T_2 relaxivity of 0.95×10^{-5} L mol^{-1} s^{-1}at 0.47 T while ferucarbotran has a smaller mean diameter of 60 nm, a blood half life similar to that of ferumoxides, and a 1.9×10^{-5} L mol^{-1} s^{-1} T_2 relaxivity. The package inserts indicate that these agents are approved for adult patients and liver imaging. Safety and efficacy studies in patients under 18 years old have not been carried out. The recommended dose for ferumoxides is 15 µmol Fe/kg (i.e. 0.075 ml/kg) and 10 µmol Fe/kg for ferucarbotran for T_2-weighted imaging at retention phase. Dosage remains the same in subjects with liver or renal insufficiency.

For ferumoxides, the dose of contrast agent should be diluted in 100 ml of 5% isotonic glucose solution and slowly infused intravenously for a period of at least 30 min. The imaging window is large: 0.5–6 h after administration for T_2- to T_2*-weighted imaging (Bellin et al. 1994). Because of the smaller size of the particles of ferucarbotran and since this agent can be injected as a bolus, it has stronger T_1 relaxivity properties and can also be used for T_1-weighted imaging and MR angiography following a bolus injection. A recently published study (Bluemke et al. 2003) has shown that direct undiluted injection of ferumoxides administered at 2 ml/min had safety and effectiveness profiles similar to those of slow infusion. Ferucarbotran is approved for bolus injection at a dose of 10 µmol Fe/kg.

SPIO particles are metabolized into a soluble, nonsuperparamagnetic form of iron. Dextrans follow the metabolism cycle while iron is incorporated into the body iron pool (e.g., ferritin, hemosiderin and hemoglobin) within a few days. Iron is progressively cleared from the liver (half life, 3 days) and spleen (half life, 4 days). The total additional iron load per single dose

does not exceed 2% of the total iron content of the human body (Ros et al. 1995; Stark et al. 1988).

18.2.1 Ferumoxides

In the original clinical trial performed with ferumoxides at a dose of 40 μmol Fe/kg (Stark et al. 1988) two adverse reactions were seen in two of 15 patients, including one rash and one case of transient hypotension. Subsequent trials were performed with new formulations (a sodium citrate solvent was replaced by a mannitol solution), lower doses and slower injection rates. In a phase II clinical trial that included 30 adult patients with liver metastases (Bellin et al. 1994), no adverse events were seen and there were no significant changes in heart rate, blood pressure, or urine analyses. There were significant changes in the following parameters: protein level, serum iron, transferrin and ferritin levels, and transferrin saturation coefficient.

Regarding safety, the largest series included 208 patients in a phase III clinical trial conducted in the US (Ros et al. 1995). The patients received 213 doses of 10 μmol Fe/kg given as a slow IV infusion. A total of 8% experienced adverse reactions classified as possibly or probably related to drug administration. No serious adverse reactions to ferumoxides were reported. The intensity of adverse events reported was mild to moderate except for severe back pain in two patients and severe flushing in one. Back pain and flushing were reported in 4% and 2% of the patients, respectively, and were the most frequently reported adverse events. The exact mechanism of back pain is unknown but has been associated with a variety of colloids, emulsions and other particulate agents. The package insert indicates that in the event of lumbar pain, chest pain, hypotension, or dyspnea, the infusion must be stopped and the patient kept under medical surveillance until the symptoms disappear. The administration of ferumoxides can be then continued under medical supervision by reducing the infusion rate and extending the infusion over at least 60 min. In Ros et al.'s (1995) series, none of the changes in clinical laboratory, vital signs and electrocardiographic findings were reported to be clinically significant. Ferumoxides are contraindicated in patients with known allergy or hypersensitivity to dextran or to any of the other components and should be used with caution in patients with hemosiderosis or hemochromatosis.

18.2.2 Ferucarbotran

Three main papers have addressed the safety of ferucarbotran in clinical trials (Kehagias et al. 2001; Kopp et al. 1997; Reimer and Balzer 2003), including a recently published review (Reimer and Balzer 2003). The phase II clinical trial (Kehagias et al. 2001) included 36 patients who received a bolus injection of ferucarbotran at a dose of 4, 8, or 16 μmol Fe/kg BW. No drug related adverse event occurred and there were no significant changes in heart rate following bolus administration of ferucarbotran. Serum iron and ferritin levels were increased at all doses. The serum iron level reached a maximum 24 h after injection. A statistically significant but transient decrease in the serum level of factor XI was observed with the highest dose level. In the last published series (Kopp et al. 1997), which included 19 patients as part of a phase III clinical trial, only one patient experienced moderate adverse events that were probably related to the injection of ferucarbotran. They consisted in a diffuse erythematous rash associated with a feeling of pressure at the thorax which lasted for 30 min. Changes in vital signs and laboratory tests were minimal and did not affect the patients' clinical condition. In their review, Reimer and Balzer (2003) summarized the safety data obtained during the whole clinical development. A total of 162 adverse reactions was documented in 1053 patients, of whom 75 were classified as possibly, probably, or definitely related to the injection of ferucarbotran. In all, 73 of 75 adverse events occurred within the first 3 h and were of mild intensity, and one anaphylactoid reaction was observed.

18.3 Manganese Based Contrast Agents

Mangafodipir trisodium is a chelate comprising a manganese ion (Mn^{2+}) bound to a large linear ligand (fodipir; DPDP), that reduces the intravenous acute toxicity of free Mn^{2+} (Elizondo et al. 1991; Federle et al. 2000). The metal chelate has a net electric charge of –3 (resulting from the +2 charge of the manganese ion and the –5 charge of DPDP) which is counterbalanced by the presence in the solution of three sodium ions, each having a charge of +1. The agent is available in two preparations: one for a 1- to 2-min injection (US) of a concentration 0.05 mol/l

and one for 10- to 15-min infusion (Europe) with a concentration of 0.01 mol/l. Manganese is a paramagnetic ion that causes increased signal intensity on T_1-weighted images, but it has also a minor T_2 effect causing reduction in the signal intensity.

An initial study (Lim et al. 1991) in healthy male volunteers showed that liver enhancement begins early, within 1–2 min of injection, with steady-state enhancement reached in 5–10 min. Liver enhancement persists for several hours allowing greater flexibility of scanning protocols and patient scheduling when compared to Gd chelates.

The degree of liver enhancement depends on the physiological status of the liver parenchyma.

The Mn^{2+} ion has five unpaired electrons and is a powerful T_1 relaxation contrast agent that produces positive enhancement of normal hepatic tissue (increased signal intensity). The approved dose is 5 μmol/kg (0.1 ml/kg) with the injection given over 1 min. Manganese (as manganese chloride ($MnCl_2$)) can also be administrated orally (Thomsen et al. 2004a,b). Through gastrointestinal uptake the manganese reaches to the liver via the portal system and circulation of free manganese is almost avoided. Between 0.8 and 1.6 g manganese chloride is given per patient.

Following intravenous injection, the manganese ion accumulates in the liver, bile, pancreas, kidneys, and cardiac muscle (Gallez et al. 1996; Hustvedt et al. 1997). Following oral intake, manganese accumulates only in the liver and bile (Thomsen et al. 2004a). Cirrhosis may cause heterogeneous enhancement, while fibrosis may account for decreased enhancement. A meta-analysis comparing safety and efficacy of mangafodipir trisodium in patients with liver lesions and cirrhosis showed that significantly higher numbers of lesions were found on the postcontrast images than in precontrast images, both in the groups of cirrhotic (n=137 patients) and non-cirrhotic patients (n=480 patients) (Marti-Bonmati et al. 2003). This increase was not influenced by the presence of liver cirrhosis. Lesion characterization was significantly improved in cirrhotic patients after administration of mangafodipir trisodium but not in non-cirrhotic patients. The number and intensity of the adverse events did not differ significantly between the two groups of patients. They were recorded in 6.7% of patients in the cirrhotic group and 7.0% in the non-cirrhotic group. Most adverse events were mild or moderate, with only one patient per group having a severe adverse event.

Mangafodipir trisodium has been shown to be a safe contrast agent at the approved dose of 5 μmol/kg (0.1 ml/kg), as a slow infusion of 2–3 ml/min (Torres et al. 1997) or with higher injection rates (Marti-Bonmati et al. 2001). The first large series conducted with this agent was reported in 1991. It was a phase II trial that included 141 patients among which 38 (27%) exhibited minor side effects (Rummeny et al. 1991). Flushing and warmth were reported in 21/141 patients (14%), and nausea in three (2.1%). In 1993, Aicher et al. (1993) reported side effects in six of 20 (30%) patients, including flushing, warmth and/or metallic taste. The results of a small European phase III trial that included 82 patients reported mild or moderate adverse events in 17% while 4% experienced infusion related discomfort (Wang et al. 1997).

The rate of adverse events observed in a large European phase III clinical trial was 7% in 624 patients (Torres et al. 1997). The largest reported series that has been reported on efficacy and safety is a multicenter phase III clinical trial which included 404 adult patients in 18 institutions in the US (Federle et al. 2000; Wang et al. 1997). The study design included an initial contrast-enhanced CT examination followed by unenhanced MRI, injection of Mn-DPDP (5 μmol/kg IV), and enhanced MRI at 15 min post-injection. Mangafodipir-enhanced MRI provided additional diagnostic information in 48% of the patients and altered patient management in 6%. A total of 23% of the patients reported experiencing at least one adverse reaction, and 146 adverse events in all were reported (Wang et al. 1997). The most frequent adverse reactions associated with the administration of mangafodipir trisodium are nausea, headache, and pruritus (Federle et al. 2000; Torres et al. 1997). Sensations of heat and flushing are most common with high injection rates and are probably related to peripheral vasodilatation (Federle et al. 2000; Torres et al. 1997). Transient decrease in alkaline phosphatase levels have also been reported with the use of mangafodipir trisodium.

The exact mechanism of adverse events is unknown but may be due, at last partly, to in vivo dechelation of the contrast agent, with rapid incorporation of the manganese ion into hepatocytes. The dechelation of mangafodipir trisodium may induce flushing, as well as uptake by the intestinal mucosa and pancreas (Blume et al. 1994; Mayo-Smith et al. 1998; Wang et al. 1997). After dechelation, the manganese ions bind to human serum proteins. Cardiovascular effects may be seen due to circulating increased concentrations of manganese. Mn^{2+} given intravenously interferes with myocardial processing of Ca^{2+} and can act as a Ca^{2+} blocker affecting

cardiac contractility and muscle physiology. Manganese also uncouples myocardial as well as smooth muscle excitation and contraction, leading to further decrease in cardiac contractility and hypotension and in the brain it may also interfere with the electrochemical potential of cell membranes. Approximately 15% of the manganese ion contained in the initial injection is eliminated in the urine by 24 h and 59% in the feces by 5 days (data from package insert).

18.4 Hepatobiliary Gadolinium Chelates

Hepatobiliary gadolinium chelates include gadobenate dimeglumine (Gd-BOPTA) that is currently approved in Europe for MRI of the central nervous system (CNS) and liver, and gadoxetic acid disodium (Gd-EOB-DTPA) which is approved for hepatic MRI in some European countries.

18.4.1 Gadobenate Dimeglumine

Unlike other available gadolinium based agents that are excreted exclusively by glomerular filtration through the kidneys, Gd-BOPTA is eliminated through both the renal and hepatobiliary pathways (Kirchin et al. 1998, 2001; Spinazzi et al. 1999). Hepatic uptake represents 2%–4% of the injected dose. In addition, this agent has a capacity for weak and transient protein binding (Cavagna et al. 1997), making it potentially suitable for MR angiography with an in vivo T_1 relaxivity approaching twice that of the conventional gadolinium chelates. The approved dose for hepatic imaging is 0.05 mmol/kg (0.1 ml/kg of a 0.5 M solution) and for CNS imaging 0.1 mmol/kg (0.2 ml/kg of a 0.5 M solution). Gadobenate dimeglumine should be administered undiluted followed by a bolus of 0.9% sodium chlorate solution.

Gadobenate dimeglumine behaves as a conventional extracellular contrast agent in the first minutes following administration and can be used for dynamic bolus imaging. It behaves as a liver-specific agent in a later, delayed phase (40–120 min after administration). As it is taken up specifically by normally functioning hepatocytes through a complex interplay of various carrier systems, it produces a marked and long-lasting enhancement of the normal liver parenchyma. As most tumor nodules are devoid of functional hepatocytes they do not take up the agent and thus appear hypointense on enhanced MR images (Hamm et al. 1999; Kirchin et al. 2001). Numerous clinical trials have shown that Gd-BOPTA increases sensitivity and specificity and thus increases detection and characterization of liver tumors (Caudana et al. 1996; Grazioli et al. 2000; Hamm et al. 1999; Kirchin et al. 1998; Manfredi et al. 1998, 1999; Peterstein et al. 2000; Rosati et al. 1994; Vogl et al. 1997).

Three exhaustive reviews have been published (Hamm et al. 1999; Kirchin et al. 2001; Rosati et al. 1994), including extended clinical experience from phase I studies to post-marketing surveillance. They reported a low incidence of serious events and confirmed the excellent safety profile of Gd-BOPTA. Between July 1990 and September 2000, 2891 subjects participated in 65 clinical trials, including 2540 subjects (2430 adults and 110 children) who received Gd-BOPTA. 1986 (78.2%) subjects received a single injection and 554 subjects received two or more injections. For adult patients and volunteers, the overall incidence of adverse events was 19.8% and events potentially related to Gd-BOPTA administration were reported for 15.1% of adult patients. Headache, injection site reaction, nausea, abnormal taste, and flushing were the most common adverse events, with a reported frequency of between 1.0% and 2.6%. Serious adverse events potentially related to Gd-BOPTA were reported in five (0.2%) patients. An apparent tendency towards a greater incidence of both total and study agent related events were noted in patients younger than 65 years and in studies conducted in the US compared to Europe.

A study comparing gadobenate dimeglumine and gadopentetate dimeglumine for MR imaging of liver tumors reported an incidence of adverse events of 4.7% (6/128) for gadobenate versus 1.6% (2/127) for gadopentetate, but the difference was not significant (Kuwatsuru et al. 2001). Results of controlled studies were available in 410 patients and revealed no differences between Gd-BOPTA and Gd-DTPA or placebo in the incidence and type of adverse events. For the controlled liver study and for patients with renal impairment, end-stage renal disease or hepatic impairment, the incidence of adverse events following Gd-BOPTA administration was similar to that following placebo administration. Regarding vital signs and evaluation of clinical laboratory data and ECG findings, no clinically meaningful trends were noted. The most frequently reported adverse event among the hematology parameters was hypochro-

mic anemia (0.6%). In the pediatric population (n=110 subjects), the incidence of adverse events was 12.7% ; one event was classified as severe but not related to the study agent, and two events were classified as serious (one report of worsening of vomiting that was considered to be possibly related, and one report of hypoxia that was considered to be not related).

Safety and efficacy of gadobenate dimeglumine have not been established in patients under 18 and thus gadobenate dimeglumine is not approved in patients less than 18 years old. The package insert indicates that patients should be observed during the 15 min following injection as the majority of severe adverse events occurs within 15 min after injection.

18.4.2 Gadoxetic Acid

Gadoxetic acid disodium (Gd-EOB-DTPA) is a paramagnetic hepatobiliary contrast medium with a molecular weight of 726 D. In human plasma, it has a higher T1-relaxivity compared to Gd-DTPA (R1 8.2 mM^{-1} s^{-1}) due to a greater degree of protein binding (~10%). At body temperature, the aqueous formulation of 0.25 mol/l has an osmolality of 890 mOsmol/kg water. In animals it is excreted almost equally by the kidneys and biliary system, while about 2% enters the enterohepatic circulation (Schuhmann-Giampieri et al. 1992).

Like other gadolinium agents, gadoxetic acid disodium behaves as a conventional extracellular contrast agent in the first minutes following administration and can be administered as a fast intravenous bolus. The liver-specific, delayed phase commences earlier than Gd-BOPTA and delayed imaging can be started as early as 15–20 min after administration, which is a logistic benefit compared to other liver-specific media (Giovagnoni and Paci 1996; Reimer et al. 2004). The excretion by the biliary system is significantly larger than Gd-BOPTA (2%–4%), making contrast-enhanced MR cholangiography also feasible (Bollow et al. 1997).

For gadoxetic acid disodium only pre-marketing safety data in humans are available from registration clinical trials. In phase I trials with tested doses between 0.01–0.1 mmol/kg body weight, no serious side effects or changes in laboratory values were seen in 44 healthy volunteers (Hamm et al. 1995). The phase II trials were conducted in two parts. As a result of these trials, 0.025 mmol/kg body weight (or 7 ml for a 70 kg adult) was considered to be the optimum dose for clinical use. While no adverse events in any patient were reported in 33 patients in the first part (Reimer et al. 1996), in the second part eight minor adverse events were reported in six of 171 patients, all of them mild. No adverse effects were graded as serious. Also, there were no significant changes in vital parameters or laboratory values (Stern et al. 2000). In the recent phase III multicenter trial (Huppertz et al. 2004), 162 patients received Gd-EOB-DTPA and showed improved liver lesion detection. A total of 21 adverse events were recorded in 11 patients (6.8%). Of these, 13 were definitely, possibly or probably related to the contrast medium, and most frequent symptoms included nausea, headache, altered taste, vasodilatation, and injection site pain (Bollow et al. 1997; Huppertz et al. 2004). In a recent review summarizing the safety data on Gd-EOB-DTPA from phase II and phase III clinical studies conducted in Europe, Japan and USA (Breuer et al. 1997), a total of 120 (8.5%) of the 1404 patients experienced one or more adverse effects, which in 3.4% of the patients the adverse effects were considered to be definitely, possibly or probably related to the drug by the investigator. None of the eight serious adverse events that occurred in five patients were considered to be drug related.

Interactions of Gd-EOB-DTPA with commercially available drugs were only tested in animal models. Results in a rat model showed that only rifampicin significantly decreased hepatic enhancement, while prednisolone, doxorubicin, cisplatin and propanolol led to a slight increase in enhancement (Kato et al. 2002).

18.5 Conclusions

Liver specific contrast agents were developed after conventional extracellular gadolinium chelates and fewer data exist about their safety. They belong to different classes of agent and therefore exhibit different physicochemical properties, modes of action and metabolic pathways. In each category, at least one agent has been approved for clinical use to improve lesion detection and characterization on MR examinations. Liver specific contrast agents appear in general to be safe and well tolerated. No safety information from comparative trials has been published as to whether the overall incidence of adverse reactions between the liver-

specific iron oxides and gadolinium based agents differ. This topic needs to be evaluated with further clinical trials. Guidelines on the safety aspects are presented in the Appendix.

References

Aicher KP, Laniado M, Kopp AF et al (1993) Mn-DPDP-enhanced MR imaging of malignant liver lesions: efficacy and safety in 20 patients. J Magn Reson Imaging 3:731–737

Bellin MF, Zaim S, Auberton E et al (1994) Liver metastases: safety and efficacy of detection with superparamagnetic iron oxide in MR imaging. Radiology 193:657–663

Bellin MF, Vasile M, Morel-Precetti S (2003) Currently used non-specific extracellular MR contrast media. Eur Radiol 13:2688–2698

Bluemke DA, Weber TM, Rubin D et al (2003) Hepatic MR imaging with ferumoxides: multicenter study of safety and effectiveness of direct injection protocol. Radiology 228:457–464

Blume J, Palmie S, Aue B et al (1994) Pancreatic contrast enhancement with Mn-bis pyridoxal ethylene diamine diacetic acid and the influence of a hormonal stimulation of the pancreas in pigs. Acad Radiol 1:253–260

Bollow M, Taupitz M, Hamm B et al (1997) Gadolinium-ethoxybenzyl-DTPA as a hepatobiliary contrast agent for use in MR cholangiography: results of an in vivo phase-I clinical evaluation. Eur Radiol 7:126–132

Breuer J, Balzer T, Shamsi K et al (2003) Clinical experience from phase II and phase III studies for Gd-EOB-DTPA: a new liver specific MR contrast agent. Eur Radiol 13 [Suppl 2]:S109

Caudana R, Morana G, Pirovano GP et al (1996) Focal malignant hepatic lesions: MR imaging enhanced with gadolinium benzyloxypropionictetra-acetate (BOPTA) – preliminary results of phase II clinical application. Radiology 199:513–520

Cavagna FM, Maggioni F, Castelli PM et al (1997) Gadolinium chelates with weak binding to serum proteins: a new class of high-efficiency, general purpose contrast agents for magnetic resonance imaging. Invest Radiol 32:780–796

Elizondo G, Fretz CJ, Stark DD et al (1991) Preclinical evaluation of Mn-DPDP: new paramagnetic hepatobiliary contrast agent for MR imaging. Radiology 178:73–78

Federle M, Chezmar J, Rubin DL et al (2000) Efficacy and safety of mangafodipir trisodium (MnDPDP) Injection for hepatic MRI in adults: results of the US multicenter phase III clinical trials. Efficacy of early imaging. J Magn Reson Imaging 12:689–701

Gallez B, Bacic G, Swartz HM (1996) Evidence for the dissociation of the hepatobiliary MRI contrast agent Mn-DPDP. Magn Reson Med 35:14–19

Giovagnoni A, Paci E (1996) Liver III: Gadolinium-based hepatobiliary contrast agents (Gd-EOB-DTPA and Gd-BOPTA/Dimeg). Magn Reson Imaging Clin North Am 4:61–72

Grazioli L, Morana G, Caudana R et al (2000) Hepatocellular carcinoma: correlation between gadobenate dimeglumine-enhanced MRI and pathological findings. Invest Radiol 35:25–34

Hamm B, Staks T, Mühler A et al (1995) Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. Radiology 195:785–792

Hamm B, Kirchin M, Pirovano G et al (1999) Clinical utility and safety of MultiHance in magnetic resonance imaging of liver cancer: results of multicenter studies in Europe and the USA. J Comput Assist Tomogr 23 [Suppl 1]:S53–S60

Huppertz A, Balzer T, Blakeborough A et al for the European EOB Study Group (2004) Improved detection of focal liver lesions at MR imaging: multicenter comparison of gadoxetic acid-enhanced MR images with intraoperative findings. Radiology 230:266–275

Hustvedt SO, Grant D, Southon TE et al (1997) Plasma pharmacokinetics, tissue distribution and excretion of MnDPDP in the rat and dog after intravenous administration. Acta Radiol 38:690–699

Kato N, Yokawa T, Tamura A et al (2002) Gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid interaction with clinical drugs in rats. Invest Radiol 37:680–684

Kehagias DT, Gouliamos AD, Smyrniotis V et al (2001) Diagnostic efficacy and safety of MRI of the liver with superparamgnetic iron oxide particles (SHU 555 A). J Magn Reson Imaging 14:595–601

Kirchin MA, Runge VM (2003) Contrast agents for magnetic resonance imaging: safety update. Top Magn Reson Imaging 14:426–435

Kirchin MA, Pirovano G, Spinazzi A (1998) Gadobenate dimeglumine (Gd-BOPTA): an overview. Invest Radiol 33:798–809

Kirchin MA, Pirovano G, Venetianer C et al (2001) Safety assessment of gadobenate dimeglumine (MultiHance): extended clinical experience from phase I studies to post-marketing surveillance. J Magn Reson Imaging 14:281–294

Kopp AF, Laniado M, Dammann F et al (1997) MR imaging of the liver with Resovist: safety, efficacy, and pharmacodynamic properties. Radiology 204:749–756

Kuwatsuru R, Kadoya M, Ohtomo K et al (2001) Comparison of gadobenate dimeglumine with gadopentetate dimeglumine for magnetic resonance imaging of liver tumors. Invest Radiol 36:632–641

Lim KO, Stark DD, Leese PT et al (1991) Hepatobiliary MR imaging: first human experience with MnDPDP. Radiology 178:79–82

Manfredi R, Maresca G, Baron RL et al (1998) Gadobenate dimeglumine (BOPTA)-enhanced MR imaging: patterns of enhancement in normal liver and cirrhosis. J Magn Reson Imaging 8:862–867

Manfredi R, Maresca G, Baron RL et al (1999) Delayed MR imaging of hepatocellular carcinoma enhanced by gadobenate dimeglumine (Gd-BOPTA). J Magn Reson Imaging 9:704–710

Marti-Bonmati L, Torregrosa A, Miguel A et al (2001) Safety and efficacy of a bolus administration of mangafodipir trisodium in MR studies. (Poster) Ninth scientific meeting ISMRM and 14th annual meeting ESMRMB, Glasgow. Proc ISMRM 2036

Marti-Bonmati L, Fog AF, Op de Beeck B et al (2003) Safety and efficacy of mangafodipir trisodium in patients with liver lesions and cirrhosis. Eur Radiol 13:1685–1692

Mayo-Smith WW, Schima W, Saini S et al (1998) Pancreatic enhancement and pulse sequence analysis using low-dose mangafodipir trisodium. AJR Am J Roentgenol 170:649–652

Montet X, Lazeyras F, Howarth N et al (2004) Specificity of SPIO particles for characterization of liver hemangiomas using MRI. Abdom Imaging 29:60–70

Peterstein J, Spinazzi A, Giovagnoni A et al (2000) Evaluation of the efficacy of gadobenate dimeglumine in magnetic resonance imaging of focal liver lesions: a multicenter phase III clinical study. Radiology 215:727–736

Precetti-Morel S, Bellin MF, Ghebontni L et al (1999) Focal nodular hyperplasia of the liver on ferumoxides-enhanced MR imaging: features on conventional spin-echo, fast spin-echo and gradient-echo pulse sequences. Eur Radiol 9:1535–1542

Reimer P, Balzer T (2003) Ferucarbotran (Resovist), a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications. Eur Radiol 13:1266–1276

Reimer P, Rummeny EJ, Shamsi K et al (1996) Phase II clinical evaluation of Gd-EOB-DTPA: dose, safety aspects, and pulse sequence. Radiology 199:177–183

Reimer P, Schneider G, Schima W (2004) Hepatobiliary contrast agents for contrast-enhanced MRI of the liver: properties, clinical development and applications. Eur Radiol 14:559–578

Ros PR, Freeny PC, Harms SE et al (1995) Hepatic MR imaging with ferumoxides: a multicenter clinical trial of the safety and efficacy in the detection of focal hepatic lesions. Radiology 196:481–488

Rosati G, Pirovano G, Spinazzi A (1994) Interim results of phase II clinical testing of gadobenate dimeglumine. Invest Radiol 29:S183–S185

Rummeny E, Ehrenheim C, Gehl HB et al (1991) Manganese-DPDP as a hepatobiliary contrast agent in the magnetic resonance imaging of liver tumors. Results of clinical phase II trials in Germany including 141 patients. Invest Radiol 26 [Suppl 1]:S142-S145 Discussion S150–S155

Schuhmann-Giampieri G, Schmitt-Willich H, Press WR et al (1992) Preclinical evaluation of Gd-EOB-DTPA as a contrast agent in MR imaging of the hepatobiliary system. Radiology 183:59–64

Spinazzi A, Lorusso V, Pirovano G et al (1999) Safety, tolerance, biodistribution and MR imaging enhancement of the liver with Gd-BOPTA: results of clinical pharmacologic and pilot imaging studies in non-patient and patient volunteers. Acad Radiol 6:282–291

Stark DD, Weissleder R, Elizondo G et al (1988) Superparamagnetic iron oxide: clinical application as a contrast agent for MR imaging of the liver. Radiology 168:297–301

Stern W, Schick F, Kopp AF et al (2000) Dynamic MR imaging of liver metastases with Gd-EOB-DTPA. Acta Radiol 41:255–262

Thomsen HS, Loegager V, Noergaard H et al (2004a) Oral manganese for liver imaging at three different field strengths. Acad Radiol 11:630–636

Thomsen HS, Svendsen O, Klastrup S (2004b) Increased manganese concentration in the liver after oral intake. Acad Radiol 11:38–44

Torres CG, Lundby B, Sterud AT et al (1997) MnDPDP for MR imaging of the liver. Results from the European phase III studies. Acta Radiol 38:631–637

Vogl TJ, Stupavsky A, Pegios W et al (1997) Hepatocellular carcinoma: evaluation with dynamic and static gadobenate dimeglumine-enhanced MR imaging and histopathologic correlation. Radiology 205:721–728

Wang C, Ahlstrom H, Ekholm S et al (1997) Diagnostic efficacy of MnDPDP in MR imaging of the liver. A phase III multicenter study. Acta Radiol 38:643–649

Wang YXJ, Hussain SM, Krestin GP (2001) Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. Eur Radiol 11:2319–2331

Section V:
Ultrasonographic Contrast Media

19 Safety of Ultrasound Contrast Agents

R. Oyen

CONTENTS

19.1 Introduction

The use of ultrasound contrast agents has increased over recent years. It is generally considered that ultrasound contrast agents approved for clinical use are well tolerated and serious adverse reactions are rarely observed. In this chapter the evidence supporting this impression is reviewed.

19.2 General Considerations on the Acoustic Properties of Microbubble Based Ultrasound Contrast Media

Ultrasound contrast media for intravenous injections are usually gas-filled microbubbles with a mean diameter less than a red blood cell. The contrast agents can be described according to the concentration of particles, size of particles or microbubbles, volume of gas, kind of gas, kind of shell, additives, etc. There are only a few products approved for clinical use, and they are all based on microbubbles (Table 19.1).

The effect of ultrasound contrast media is mainly produced by increased backscattering intensity as compared to that from blood, other fluids, and most tissues (Jakobsen 1996). The spectral Doppler intensity is also increased, with a brighter spectral waveform displayed, and a stronger sound is produced. When color Doppler technique is applied, ultrasound contrast media enhance the frequency or the power intensity and thus give rise to stronger color encodings. The effect of ultrasound contrast media is most efficient when various contrast specific nonlinear techniques are used. Typically, the microbubbles oscillate as a response to the external sound field during scanning, both in a linear and in a nonlinear way. This is the basis for nonlinear techniques such as second harmonic imaging (Burns 1996), pulse or phase inversion, or pulse cancellation, which improves the detection of microbubbles specifically (Burns et al. 2000). The effect on microbubble behavior is dependent on the acoustic pressure created by the ultrasound probe. Usually, with increasing wave pressure, the effect on imaging comes from reflection, then asymmetrical vibration, and finally disruption of microbubbles, respectively (Correas et al. 2001). These changes in microbubble behavior may induce unwanted effects. Therefore, the effect of insonation on microbubble behavior is dependent on the level of the mechanical index (MI), as well as the properties of the contrast agent and the imaging mode chosen.

19.3 Experimental Findings on Microbubble Based Ultrasound Contrast Media

The cavitation phenomenon refers to formation, growth and collapse by implosion of microbubbles. The "cavitation threshold" is the level at which the amount of acoustic energy introduced into the fluid

R. Oyen, MD
Department of Radiology, Katholieke Universiteit Leuven, Herestraat 49, 3000 Leuven, Belgium

Table 19.1. Ultrasound contrast agents. Not all are commercially available. Generic names are given in parentheses

Product name	Clinical nature
Imavist (AF0150)	Perfluorohexane and nitrogen gas in stabilized microbubbles
SonoVue (BR1)	Sulphur hexafluoride gas in polymer with phospholipids
Definity (DMP 115)	Fluorocarbon gas in liposomes
Albunex	Air-filled protein shell
Optison (FS069)	Octafluropropane-filled albumin microspheres
Echovist	Galactose-based gas bubbles
Levovist (SHU 508A)	Galactose-based, palmitic acid stabilized air-bubbles

initiates cavitation. The implosion causes large changes in pressure and temperature in the close vicinity. This cavitation phenomenon has caused concern in relation to the safety of microbubble enhancing agents.

In vitro studies have shown that ultrasound contrast agents may cause hemolysis and platelet aggregation (Miller and Gies 1998; Poliachick et al. 1999; Carstensen et al. 1993; Everbach et al. 1998). The amount of hemolysis seems to correlate with the amount of microbubbles present, the acoustic pressure exerted on the blood, and also depends on the type of ultrasound contrast medium. The phenomenon of cavitation is considered to be the cause of most of the observed side effects.

In vivo studies of pigs and dogs with pulmonary hypertension have shown that pulmonary function can be affected by high doses of ultrasound contrast media (Walday et al. 1994; Ostensen et al. 1992; Yamaya et al. 2002). The interaction between ultrasound contrast media and pulsed ultrasound waves seems not to cause pulmonary damage (Raeman et al. 1997).

Animal studies showed no significant effect of ultrasound contrast media on left ventricular (LV) function or myocardial blood flow (Main et al. 1997; Meza et al. 1996). However, Chen et al. (2002), reported an increase in troponin T (a marker of myocardial ischemia) when a high mechanical index for bubble destruction was transmitted. This was not associated with LV dysfunction or histopathological evidence of myocardial damage. Furthermore, in one study on rats, several types of arrhythmia were observed when ultrasound contrast media and ultrasound were combined (Zachary et al. 2002).

Disruption of the blood–brain barrier may occur in rats after intravenous injection of ultrasound contrast media (Mychaskiw et al. 2000).

The combination of ultrasound exposure and ultrasound contrast media may cause damage to the endothelial cells and venules and capillaries in rat mesentery (Kobayashi et al. 2002, 2003; Rasmussen et al. 2003).

19.4 Clinical Safety of Ultrasound Contrast Media

The side effects observed in animal studies have not been observed in clinical practice despite extensive investigation (Nanda and Carstensen 1997; Morel et al. 2000; Myreng et al. 1999; Robbin et al. 1998; Borgers et al. 2002). The microbubbles are so small that obstruction or trapping in the capillaries does not seem to be a problem. Adverse reactions caused by cavitation have not been shown in humans. The galactose content of some agents, and human protein content of others have been considered to be the potential causes of adverse reactions, but clinical investigations have shown no major problems so far.

The most common general adverse reactions reported are the same as those seen with other types of contrast media, i.e. headache, warm sensation and flushing. More unusual events are nausea and vomiting, dizziness, chills and fever, altered taste, dyspnea, chest pain, etc. (0%–5%) (Correas et al. 2001; Myreng et al. 1999; Bokor et al. 2001; Claudon et al. 2000; Rott 1999; ter Haar 2002; Goldberg 1997; Cohen et al. 1998; Kaps et al. 1999; Fritsch and Schlief 1995). Similar findings were however observed in placebo groups. Such adverse reactions are rare, usually transient, mild and common to many agents (Correas et al. 2001). Allergy-like reactions occur rarely; general flush with erythema and papules has been reported (Correas et al. 2001). Three anaphylactic reactions have been reported, two in women aged 59 and 70 years respectively, and one in a man of 70 years (de Groot et al. 2004). Asymptomatic premature ventricular contractions have been observed during triggered imaging with ultrasound contrast (van der Vouw et al. 2000).

It has been recommended that therapeutic ultrasound and lithotripsy should be avoided in the day following the use of ultrasound contrast agents

(Brayman and Miller 1997; Dalecki et al. 1997; Delius 1994). Decisions about the use of contrast materials in the maternal circulation depend on the clinical condition of the mother (Rott 1999, Ecmus (2004).

European Medicine Agency (EMMA) recently took precautionary measures to limit the use of the ultrasonographic contrast agent sulphur hexafluoride in patients with cardiac disease. Throughout Europe a number of serious allergic reactions with probable secondary cardiovascular problems have been reported. In addition to this, there have been three reports of fatal outcome soon after the administration of this agent. All of these patients were however at risk of serious cardiac complications because of underlying cardiac problems (de Groot et al. 2004) (Table 19.2).

Table 19.2. Frequency of adverse reactions during intravenous administration ultrasound contrast agents (for manufacturer details, see Table 19.1)

Product name	Adverse reaction Reported 0.5%–5%	Adverse reaction <1% Reported <1%
Levovist, Optison, SonoVue	**Body as a whole** Headache Hypersensitivity at injection site	**Body as a whole** Abdominal pain Weakness Pain Back pain Chest pain Fatigue
	Cardiovascular system Hypertension	**Cardiovascular system** Atrial fibrillation Palpitation Tachycardia
	Digestive system Nausea	**Digestive system** Anorexia Diarrhea Dyspepsia Musculoskeletal system Leg cramps
	Nervous system Dizziness Dry mouth Vasodilatation	**Nervous system** Paresthesia
	Special senses Abnormal smell or taste	**Respiratory system** Dyspnoea
		Skin and appendages Sweating Rash Pruritus

19.5 Recommendation on the Use of Ultrasound Contrast Media

The European Committee for Medical Ultrasound Safety (ECMUS) recommends that ultrasound contrast media should only be used if there is a good clinical indication, and the risk/benefit ratio should be carefully assessed (ECMUS 2004). In addition this Committee emphasized that high values of Mechanical Index should be used only when essential for a particular clinical study (ECMUS 2003).

It is important to acknowledge that ultrasound contrast media are fairly new products and it may take several years of accurate surveillance to document possible adverse reactions to them. It is also not clear whether there are important differences in safety among the products currently available.

19.6 Conclusion

In vitro and animal studies have shown adverse effects of ultrasound contrast media related to the properties of the particles and the interaction between microbubbles and ultrasound beam energy causing bubble destruction. However, clinical studies have not shown such adverse events and indicate that ultrasound contrast media are generally safe. Most adverse events seen clinically are non-specific and unrelated to the constituents of the various products. Adverse reactions are usually minor (e.g., headache, nausea, altered taste, sensation of heat) and self resolving. These symptoms may not be related to the ultrasound contrast materials as they have also been observed in placebo-controlled groups. Intolerance to some components may occur. Generalized allergy-like or hypersensitivity reactions occur only rarely. Any rare adverse reactions should be treated symptomatically.

The use of ultrasound contrast media should always be clinically justified. It is important that the exposure time to ultrasound and the acoustic output shown be kept to lowest level consistent with obtaining diagnostic information. A guideline on the safety of ultrasound contrast media can been found in the Appendix.

References

Bokor D, Chambers JB, Rees PJ, Mant TGK, Luzzani F, Spinazzi A (2001) Clinical safety of SonoVue, a new contrast agent for ultrasound imaging, in healthy volunteers and in patients with chronic obstructive pulmonary disease. Invest Radiol 36:104–109

Borges AC, Walde T, Reibis RK et al (2002) Does contrast echocardiography with Optison induce myocardial necrosis in humans? J Am Soc Echocardiogr 15:1080–1086

Brayman AA, Miller MW (1997) Acoustic cavitation nuclei survive the apparent ultrasonic destruction of Albunex microspheres. Ultrasound Med Biol 23:793–796

Burns PN (1996) Harmonic imaging with ultrasound contrast agents (1996) Clin Radiol 51:S50–S55

Burns PN, Wilson SR, Simpson DH (2000) Pulse inversion imaging of liver blood flow: improved method for characterizing focal masses with microbubble contrast. Invest Radiol 35:58–71

Carstensen EL, Kelly P, Church CC et al (1993) Lysis of erythrocytes by exposure to CW ultrasound. Ultrasound Med Biol 19:147–165

Chen S, Kroll MH, Shohet RV, Frenkel P, Mayer SA, Grayburn PA (2002) Bioeffects of myocardial contrast microbubble destruction by echocardiography. Echocardiography 19:495–500

Claudon M, Pouin PF, Baxter G, Ohban T, Maniez Devos D (2000) Renal arteries in patients at risk of renal arterial stenosis: multicenter evaluation of the echo-enhancer SH U 508A at color and spectral Doppler US. Levovist Renal Artery Stenosis Study Group. Radiology 214:739–746

Cohen JL, Cheirif J, Segar DS, Gillam LD, Gottdiener JS, Hausnerova E (1998) Improved left ventricular endocardial border delineation and opacification with Optison (FS069), a new echocardiographic contrast agent. Results of a phase III Multicenter Trial. J Am Coll Cardiol 32:746–752

Correas J-M, Bridal L, Lesavre A, Méjean A, Claudon M, Hélénon O (2001) Ultrasound contrast agents: properties, principles of action, tolerance, and artifacts. Eur Radiol 11; 1316–1328

Dalecki D, Raeman CH, Child SZ, Penney DP, Carstensen EL (1997) Remnants of Albunex nucleate acoustic cavitation. Ultrasound Med Biol 23:1405–1412

De Groot MC, van Zwieten-Boot BJ, van Grootheest AC (2004) Severe adverse reactions after the use of sulphur hexafluroide (SonoVue) as an ultrasonographic contrast agent. Ned Tijdschr Geneesk 48:1887–1888

Delius M (1994) Medical applications and bioeffects of extracorporeal shcok waves. Shock Waves 4:55–72

European Committee of Medical Ultrasound Safety (ECMUS) (2003) Clinical safety statement for diagnostic ultrasound. EFSUMB Newsletter 2003, 17:15 or www.efsumb.org/safstat2003.htm, accessed 2004–12–14

European Committee of Medical Ultrasound Safety (ECMUS) (2004) ECMUS Safety Committee tutorial paper. Safety of ultrasonic contrast agents. www.efsumb.org/tutpap11.htm, accessed 2004–12–14

Everbach EC, Makin IR, Francis CW, Meltzer RS (1998) Effect of acoustic cavitation on platelets in the presence of an echo-contrast agent. Ultrasound Med Biol 24:129–136

Fritsch T, Schlief R (1995) Levovist. Drugs of the future 20:1224–1227

Goldberg BB (1997) Ultrasound contrast agents. Martin Dunitz, London

Haggag KJ, Russell D, Walday P, Skiphamn A, Torvik A (1998) Air-filled ultrasound contrast agents do not damage the cerebral microvasculature or brain tissue in rats. Invest Radiol 33:129–135

Jakobsen J (1996) Echo-enhancing agents in the renal tract Clin Radiol 51:S40–S43

Kaps M, Seidel G, Bokor D, Modrau B, Algermissen C (1999) Safety and ultrasound enhancing potentials of a new sulfur hexafluoride-containing agent in the cerebral circulation. J Neuroimaging 9:150–154

Kobayashi N, Yasu T, Yamada S et al (2002) Endothelial cell injury in venule and capillary induced by contrast ultrasonography. Ultrasound Med Biol 28:949–956

Kobayashi N, Yasu T, Yamada S et al (2003) Influence of contrast ultrasonography with perflutren lipid microspheres on microvessel injury. Circ J 67:630–636

Main ML, Escobar JF, Hall SA, Grayburn PA (1997) Safety and efficacy of QW7437, a new fluorocarbon-based echocardiographic contrast agent. J Am Soc Echocardiogr 10:798–804

Meza M, Greener Y, Hunt R et al (1996) Myocardial contrast echocardiography: reliable, safe, and efficacious myocardial perfusion assessment after intravenous injections of a new echocardiographic contrast agent. Am Heart J 132:871–881

Miller DL, Gies RA (1998) Enhancement of ultrasonically-induced hemolysis by perfluorocarbon-based compared to air-based echo-contrast agents. Ultrasound Med Biol 24:285–292

Morel DR, Schwieger I, Hohn L (2000) Human pharmacokinetics and safety evaluation of SonoVue, a new contrast agent for ultrasound imaging. Invest Radiol 35:80–85

Mychaskiw G 2nd, Badr AE, Tibbs R, Clower BR, Zhang JH (2000) Optison (FS069) disrupts the blood--brain barrier in rats. Anesth Analg 91:798–803

Myreng Y, Molstad P, Ytre-Arne K et al (1999) Safety of the transpulmonary ultrasound contrast agent NC100100: a clinical and hemodynamic evaluation in patients with suspected or proven coronary artery disease. Heart 82:333–335

Nanda NC, Carstensen EL (1997) Echo-enhancing agents: safety. In: Nanda NC, Schlief R, Goldberg BB (eds) Advances in Echo imaging using contrast enhancement. Kluwer Academic, Dordrecht, pp 115–131

Ostensen J, Hede R, Myreng Y, Ege T, Holtz E (1992) Intravenous injection of Albunex microspheres causes thromboxane mediated pulmonary hypertension in pigs, but not in monkeys or rabbits. Acta Physiol Scand 144:307–315

Poliachik SL, Chandler WL, Mourad PD et al (1999) Effect of high-intensity focused ultrasound on whole blood with and without microbubble contrast agent. Ultrasound Med Biol 25:991–998

Raeman CH, Dalecki D, Child SZ, Meltzer RS, Carstensen EL (1997) Albunex does not increase the sensitivity of the lung to pulsed ultrasound. Echocardiography 14:553–558

Rasmussen H, Dirven HA, Grant D, Johnsen H, Midtvedt T (2003) Etiology of cecal and hepatic lesions in mice after administration of gas-carrier contrast agents used in ultrasound imaging. Toxicol Appl Pharmacol 188:176–184

Robbin ML, Eisenfeld AJ (for the EchoGen Contrast Ultrasound Study Group) (1998) Perflenapent emulsion: a US contrast

agent for diagnostic radiology – multicenter, double-blind comparison with a placebo. Radiology 207:717–722
Rott HD (1999) Safety of ultrasonic contrast agents. European Committee for Medical Ultrasound Safety (EFSUMB). Eur J Ultrasound 9:195–197
Ter Haar GR (2002) Ultrasonic contrast agents: safety considerations reviewed. Eur J Radiol 41:217–221
Van der Wouw PA, Brauns AC, Bailey SE, Powers JE, Wilde AA (2000) Premature ventricular contractions during triggered imaging with ultrasound contrast. J Am Soc Echocardiogr 13:288–294
Walday P, Tolleshaug H, Gjoen T et al (1994) Biodistributions of air-filled albumin microspheres in rats and pigs. Biochem J 299:437–443
Yamaya Y, Niizeki K, Kim J, Entin PL, Wagner H, Wagner PD (2002) Effects of optison on pulmonary gas exchange and hemodynamics. Ultrasound Med Biol 28:1005–1013
Zachary JF, Hartleben SA, Frizzell LA, O'Brien WD Jr (2002) Arrhythmias in rat hearts exposed to pulsed ultrasound after intravenous injection of a contrast agent. J Ultrasound Med 21:1347–1356

Section VI:
Barium Preparations

20 Barium Preparations: Safety Issues

Sameh K. Morcos

CONTENTS

20.1 Introduction

The use of barium sulphate to image the gastrointestinal tract (GIT) was first proposed in 1910 by Bechem and Gunther. Since those early days barium sulphate preparations have improved markedly and now they are used routinely in radiology departments worldwide. Adverse effects directly related to the oral or rectal administration of barium preparations will be discussed in this chapter. Technique related complications of barium examinations are beyond the scope of this account.

20.2 Barium Sulphate

All barium preparations are based on barium sulphate, which is a heavy insoluble material produced from barite. Pure barium sulphate suspension is not suitable for imaging the GIT as it flocculates easily and produces very poor mucosal coating. Therefore, additives (e.g. pectin, sorbitol, agar-agar, carboxymethyl-cellulose) are used in the commercial barium preparations to enhance the mucosal coating properties of the suspension, prevent flocculation and improve the taste for oral use (Almen and Aspelin 1995). More than 90 different additives have been described in the literature. However, the manufacturers of the barium suspensions very often keep the exact type and proportions of additives in each barium preparation secret for commercial reasons.

20.3 Adverse Effects of Barium Sulphate Preparations

Barium sulphate is insoluble in water and theoretically non-toxic (Morcos 2000). The particles of barium sulphate suspension remain in the intestinal lumen and are not absorbed. Barium ions are toxic, but the extremely small amounts of barium ions that are present in the suspension and available for intestinal absorption are regarded as being of no practical importance (Almen and Aspelin 1995).

Oral or rectal administration of barium sulphate is usually safe but constipation and abdominal pain may occur after barium meals or enemas (Smith et al. 1988). The main risk is that barium may remain in the colon for 6 weeks or longer in elderly patients or patients with partial colonic obstruction. Prolonged stasis of barium may occur following a barium enema into the distal loop of a colostomy (Morcos 2000). Baroliths (barium fecoliths) are rare complications of barium contrast examinations and usually seen in diverticula of the colon. Baroliths are often asymptomatic but may be associated with abdominal pain, appendicitis, bowel obstruction or perforation. They may even have to be removed surgically (Smith et al. 1988; Morcos and Brown 2001). Baroliths of the small bowel are rare. A case of small bowel obstruction secondary to barolith which developed at the site of narrowing of a loop of ileum secondary to a carcinoid tumour has been reported (Regan et al. 1999). Interference with the flow of barium at this segment precipitated the development of the barolith.

S. K. Morcos, FRCS, FFRRCSI, FRCR
Department of Diagnostic Imaging, Northern General Hospital NHS Trust, Sheffield S5 7AU, UK

Table 20.1. Adverse effects of barium preparations

Adverse effect	Result
Retention of barium in colon	• Abdominal discomfort • Constipation
Formation of barolith	• Bowel obstruction • Appendicitis
Aggravation of toxic dilatation of the colon	• Colonic perforation may be precipitated
Leakage of barium into peritoneal cavity	• Peritonitis • Peritoneal adhesions and bowel obstruction
Extraperitoneal leakage of barium	• Granulomatous inflammatory reaction • Fibrosis
Aspiration of barium into bronchial tree	• Respiratory failure • Chemical pneumonia
Intravasation of barium suspension	• Barium pulmonary emboli • Disseminated intravascular coagulation • Septicaemia • Hypotension
Allergic reactions to barium preparations	• Severe anaphylactic reactions may develop to the additives of the barium preparations • Bronchospasm • Angioedema • Urticaria

Toxic dilatation of the colon may be aggravated by barium enema (Morcos 2000; Williams and Harned 1991).

Barium sulphate even when sterile can cause marked peritoneal irritation with considerable fluid loss into the peritoneal cavity (Morcos 2000). Perforation into the peritoneal cavity following barium enema occurs rarely. Those at risk are children, debilitated adults or patients in whom the colon is already weakened by inflammatory, malignant or parasitic disease. The perforation may be triggered by manipulations involved in giving the barium enema or result from hydrostatic pressure (Morcos 2000). Perforation of the colon by barium enema may result in death (Morcos 2000). The incidence of perforation is approximately one in 6000 examinations. The mixture of barium and faeces produces severe peritonitis and dense adhesions. The mortality has been reported to be 58% with conservative treatment, and still as high as 47% with surgical intervention (Zheutlin et al. 1952). Early surgery is indicated and large volumes of intravenous fluids improve the prognosis. Patients who recover may develop fibrogranulomatous reactions and adhesions which can lead to bowel obstruction or ureteric occlusion (Morcos 2000). Perforation of the duodenum and barium leakage into the peritoneal cavity may also occur rarely in patients with duodenal ulcer (Morcos 2000).

Extraperitoneal perforation and leakage of barium into the retroperitoneum or mediastinum may cause few immediate symptoms, but delayed endotoxic shock can develop 12 h later and is frequently fatal. Inflammatory reaction leading to formation of barium granulomata and fibrosis may occur. Painful masses, rectal strictures and ulcers have been described following extraperitoneal leakage (Morcos 2000).

Intravenous barium intravasation after enema examination has also been reported and may be associated with mortality of up to 55%. Barium emboli in the lungs, disseminated intravascular coagulation, septicaemia and severe hypotension have been documented following barium intravasation. Most cases have been attributed to trauma from the tip of the enema tube or retention balloon, mucosal inflammation, or misplacement of the tube in the vagina. The amount and speed of intravasation of the barium, as well as the site of the intravasation and the general health of the patient determine the outcome of this complication (Morcos 2000; Williams and Harned 1991).

Disseminated intravascular coagulation, septicaemia and severe hypotension have also been documented following venous intravasation of Gastrografin (a high osmolar water soluble contrast medium preparation containing sodium and meglumine diatrizoate used for imaging of the GIT and suitable only for oral or rectal administration) (Glauser et al. 1999).

Low osmolar water soluble contrast media should be used in preference to Gastrografin or barium preparations in patients with suspected compromise of bowel wall integrity. Barium leaking into a sigmoid abscess during a barium enema examination and intravasating into the portal venous system has been reported (Wheatley and Eckhauser 1991).

Accidental administration of a barium enema into the vagina instead of the rectum may occur and can be very hazardous: in a number of these patients there has been rupture of the vagina with fatal venous intravasation of barium (Morcos 2000).

Aspiration of barium sulphate preparation into the lungs during barium meal examination can cause significant respiratory embarrassment particularly in patients with poor respiratory function and general condition. If thick barium paste is inhaled, it occludes small bronchi and may cause

fatal asphyxiation. Aspiration of barium may also cause fatal pneumonia (Morcos and Brown 2001; Tamm and Kortsik 1999; Lareau and Berta 1976; Gray et al. 1980). Persistent alveolar deposition of barium sulphate on the chest radiograph which only decreases slightly compared to the initial X-ray will be observed (Tamm and Kortsik 1999). It has been recommended that bronchoscopy should be performed early following barium aspiration to extract barium from the bronchial tree and prophylactic antibiotic therapy is important to prevent lung infection (Tamm and Kortsik 1999). Water soluble low osmolar contrast media, which are better tolerated, should be used instead of barium preparations if there is a possibility of aspiration during an upper GIT examination (Ginai et al. 1994).

Hypersensitivity reactions to products used during barium meal examinations are extremely rare (Morcos 2000). Barium sulphate is generally regarded as an inert and insoluble compound that is neither absorbed nor metabolized and is eliminated unchanged from the body. However, some studies have demonstrated that very small amounts of barium ions can be absorbed from the GIT. Isolated cases of barium encephalopathy have been attributed to absorption of barium following the use of barium sulphate (Morcos 2000). Plasma and urine barium levels can be elevated after oral barium sulphate administration. In addition, many additives are present in commercial barium products and are essentially the same as the additives used in food products. Some of these agents are capable of inducing an immune response. A patient with a history of a severe reaction to barium agents should not receive barium products again (Morcos and Brown 1999; Seymour and Kesack 1997; Stringer et al. 1993).

Reactions to other constituents of barium sulphate enemas are now being recognized with increasing frequency and could be as common as one in 1000 (Morcos 2000). They vary from urticarial rashes to severe anaphylactic collapse, and can be particularly severe in patients with asthma (Morcos 2000). Hypersensitivity to the latex balloon catheter used in double contrast barium enemas appears to be a common mechanism (Ownby et al. 1991), but hypersensitivity to glucagon, to the preservative methylparaben or to other additives seems to be responsible in some cases (Morcos 2000).

A fatal case of poisoning resulted from the use of barium sulfide which had been mistaken for barium sulphate has been reported (Morcos 2000). A guideline on the safe use of barium preparations can be found in the Appendix.

References

Almen T, Aspelin P (1995) Contrast media in diagnostic radiology. In: Pettersson H (ed) The NICER centennial book 1995. A global textbook of radiology, chap 7. NICER Institute, Lund, p 131

Bechem C, Gunther H (1910) Barium sulphate as a shadow-forming contrast medium in radiological investigations. Z Rontgenk Radiumfortschr 12:369–376

Ginai AZ, Ten Kate FJW, Ten Berg RGM, Hoornstra K (1994) Experimental evaluation of various available contrast agents for use in the upper gastrointestinal tract in case of suspected leakage. Effects on lungs. Br J Radiol 57:895–901

Glauser T, Savioz D, Grossholz M et al (1999) Venous intravasation of Gastrografin: a serious but underestimated complication. Eur J Surg 165:274–277

Gray C, Sivaloganathan S, Simkins KC (1980) Aspiration of high-density barium contrast medium causing acute pulmonary inflammation – report of two fatal cases in elderly women with disordered swallowing. Clin Radiol 40:397

Lareau DG, Berta JW (1976) Fatal aspiration of thick barium. Radiology 120:317

Morcos SK (2000) Radiological contrast media. In: Dukes MNG, Aronson JKS (eds) Side effects of drugs, 14 edn, chap 46.1. Elsevier Science, Amsterdam, pp 1603–1605

Morcos SK, Brown P (1999) Radiological contrast agents. In. Aronson JK (ed) Side effects of drugs, annual 24, chap 46. Elsevier Science, Amsterdam, p 503

Morcos SK, Brown P (2001) Radiological contrast agents. In: Aronson JK (ed) Side effects of drugs, annual 24, chap 46. Elsevier Science, Amsterdam, pp 524–525

Ownby DR, Tomlanovich M, Sammons N et al (1991) Anaphylaxis associated with latex allergy during barium enema examinations. AJR Am J Roentgenol 156:903–908

Regan JK, O'Neil HK, Aizenstein RI (1999) Small Bowel carcinoid presenting as a barolith. Clin Imaging 23:22–25

Seymour PC, Kesack CD (1997) Anaphylactic shock during a routine upper gastrointestinal series. AJR Am J Roentgenol 168:957–958

Smith HJ, Jones K, Hunter TB (1988) What happens to patients after upper and lower gastrointestinal studies? Invest Radiol 23:822

Stringer DA, Hassal E, Ferguson AC et al (1993) Hypersensitivity reaction to single contrast barium meal studies in children. Paediatr Radiol 23:587–588

Tamm I, Kortsik C (1999) Severe barium sulfate aspiration into the lung: clinical presentation, prognosis and therapy. Respiration 66:81–84

Wheatley MJ, Eckhauser FE (1991) Portal venous barium intravasation complicating barium enema examination. Surgery 109:788–791

Williams SM, Harned RK (1991) Recognition and prevention of barium enema complications. Curr Probl Diagn Radiol 20:123–151

Zheutlin N, Lasser EC, Rigler LG (1952) Clinical studies on the effect of barium in the peritoneal cavity following rupture of the colon. Surgery 32:967

Appendix

21 ESUR Guidelines on Contrast Media

Henrik S. Thomsen, Sameh K. Morcos, Torsten Almén, Peter Aspelin, Marie-France Bellin, Hugo Flaten, Jean-Marc Idée, Jarl Å. Jakobsen, Andrea Löwe, Raymond Oyen, Alberto Spinazzi, Fulvio Stacul, Aart J. van der Molen, and Judith A. W. Webb

CONTENTS

The Contrast Media Safety Committee of the European Society of Urogenital Radiology c/o Henrik S. Thomsen, MD, Professor, Department of Diagnostic Radiology, Copenhagen University Hospital at Herlev, 2730 Herlev, Denmark

21.1 Renal Adverse Reactions

ESUR Guidelines

21.1.1 To Avoid Contrast Medium-Induced Nephrotoxicity

Definition		Contrast medium nephrotoxicity is a condition in which an impairment in renal function [an increase in serum creatinine by more than 25% or 44 μmol/l (0.5 mg/dl)] occurs within 3 days following the intravascular administration of a contrast medium (CM) in the absence of an alternative etiology
Risk factors	**Look for:**	• Raised S-creatinine levels, particularly secondary to diabetic nephropathy • Dehydration • Congestive heart failure • Age over 70 years old • Concurrent administration of nephrotoxic drugs, e.g. non-steroid anti-inflammatory drugs
In patients with risk factor(s)	**Do:**	• Make sure that the patient is well hydrated; give at least 100 ml oral (e.g. soft drinks) or intravenous (normal saline) fluids, depending on the clinical situation, per hour starting 4 h before to 24 h after contrast administration – in warm areas increase the fluid volume • Use low- or iso-osmolar contrast media • Stop administration of nephrotoxic drugs for at least 24 h • Consider alternative imaging techniques, which do not require the administration of iodinated contrast media
	Do not:	• Give high osmolar contrast media • Administer large doses of contrast media • Administer mannitol and diuretics, particularly loop-diuretics • Perform multiple studies with contrast media within a short period of time

21.1.2 Determination of Serum Creatinine

At time of referral for a contrast enhanced imaging examination identify patients with increased probability of abnormal S-creatinine levels		The referring clinician should ask the patient for a history of: • Renal disease • Renal surgery • Proteinuria • Diabetes mellitus • Hypertension • Gout • Recent nephrotoxic drugs The answers should be provided to the department of Radiology with the imaging request Serum creatinine not older than 6 months should be provided with the imaging request, if available
Non-emergency examinations	**Look for:**	• Positive answer to one or more of the above questions • Known abnormal S-creatinine level at time of referral • Procedures requiring intraarterial contrast medium administration
	Action:	• S-creatinine level must be measured within 7 days of the examination • The Department of Radiology must be informed if the S-creatinine level is increased at least 24 h before the scheduled examination time in order to make the necessary arrangements
Emergency examinations		1. In emergency situations S-creatinine measurement can be waived 2. If the procedure can be deferred without harm to the patient, S-creatinine should be measured
In patients with abnormal S-creatinine levels		• Consider alternative imaging techniques, which do not require the administration of iodinated contrast media • Stop administration of nephrotoxic drugs for at least 24 h • Make sure that the patient is well hydrated • Use low- or iso-osmolar contrast media

21.1.3 Dialysis and Contrast Media Administration

Patients	Recommendations
On hemodialysis (all contrast media can be removed by hemodialysis)	• Avoid osmotic and fluid overload • Correlation of the time of contrast medium injection with the hemodialysis session is unnecessary • Extra hemodialysis session for removal of contrast medium is unnecessary
With severely reduced renal function	• Please refer to ESUR guidelines to avoid contrast medium-induced nephrotoxicity (hydration, use small doses of low osmolar contrast media) • Hemodialysis is unnecessary • In MRI examinations avoid doses more than 0.3 mmol/kg BW of gadolinium-based contrast agents
On continuous ambulatory peritoneal dialysis (CAPD) [all contrast media can be removed by peritoneal dialysis]	*Examinations using iodinated agents:* • To protect residual renal function please refer to ESUR guidelines to avoid contrast medium-induced nephrotoxicity • Hydration should be considered only after careful evaluation of fluid balance state of the patient • Hemodialysis is not recommended *Examinations using gadolinium agents:* • To protect residual renal function use doses up to 0.3 mmol/kg BW of gadolinium-based contrast agents • Hemodialysis is not recommended

21.1.4 Administration of Contrast Media to Diabetics Taking Metformin

S-creatinine level should be measured in every diabetic patient treated with biguanides prior to intravascular administration of contrast media. Low-osmolar contrast media should always be used in these patients.

Elective studies

a) If the serum creatinine is normal, the radiological examination should be performed and intake of metformin stopped from the time of the study. The use of metformin should not be resumed for 48 h and should only be restarted if renal function/serum creatinine remains within the normal range.

b) If renal function is abnormal, the metformin should be stopped and the contrast study should be delayed for 48 h. Metformin should only be restarted 48 h after contrast medium, if renal function/serum creatinine is unchanged.

Emergency cases

a) If the serum creatinine is normal, the study may proceed as suggested for elective patients.

b) If the renal function is abnormal (or unknown), the physician should weigh the risks and benefits of contrast administration. Alternative imaging techniques should be considered. If contrast media administration is deemed necessary and the following precautions should be implemented:

- Metformin therapy should be stopped.
- The patient should be hydrated (e.g. at least 100 ml per hour of soft drinks or intravenous saline up to 24 h after contrast medium administration – in warm areas more fluid should be given).
- Monitor renal function (S-creatinine), serum lactic acid and pH of blood.
- Look for symptoms of lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnea, lethargy, diarrhea and thirst). Blood test results indicative of lactic acidosis: pH < 7.25 and lactic acid > 5 mmol.

ESUR Position Statement

21.1.5 The Use of Gadolinium-Based Contrast Media for Radiographic Examinations

Legal position	Gadolinium-based contrast media are not approved for X-ray examinations
Uses of gadolinium-based contrast media for X-ray examinations reported in the literature	• Significant renal impairment • Prior severe generalized adverse reaction to iodinated contrast media • Imminent thyroid treatment with radioactive iodine
ESUR position	1. The use of gadolinium-based contrast media for radiographic examinations is not recommended to avoid nephrotoxicity in patients with renal impairment since they are more nephrotoxic than iodinated contrast media in equivalent X-ray attenuating doses 2. The use of gadolinium-based contrast medium in approved intravenous doses up to 0.3 mmol/kg BW will not give diagnostic radiographic information in most cases

21.2 Non-renal Adverse Reactions

ESUR Guidelines

21.2.1 Prevention of Generalized Contrast Medium Reactions

A. Risk Factors for Reactions

- Previous generalized contrast medium reaction, either moderate (e.g. urticaria, bronchospasm, moderate hypotension) or severe (e.g. convulsions, severe bronchospasm, pulmonary edema, cardiovascular collapse).
- Asthma.
- Allergy requiring medical treatment.

B. To Reduce the Risk of Generalized Contrast Medium Reactions

- Use nonionic agents.

C. Premedication is Recommended in High Risk Patients (Defined in A)

- When ionic agents are used.
- When nonionic agents are used, opinion is divided about the value of premedication.

D. Recommended Premedication

- Corticosteroids
  Prednisolone 30 mg orally or methylprednisolone 32 mg orally 12 and 2 h before contrast medium.
  Corticosteroids are not effective if given less than 6 h before contrast medium.
- Antihistamines H1 and H2 may be used in addition to corticosteroids, but opinion is divided.

E. Remember for All Patients

- Have a trolley with resuscitation drugs in the examination room.
- Observe patients for 20–30 min after contrast medium injection.

F. Extravascular Administration

- When absorption or leakage into the circulation is possible, take the same precautions as for intravascular administration.

21.2.2 Management of Acute Adverse Reactions to Contrast Media

21.2.2.1 Drugs/Instruments

- Oxygen
- Adrenaline 1:1,000
- Antihistamine H1 – suitable for injection
- Atropine
- β2-agonist metered dose inhaler
- IV Fluids – normal saline or Ringers solution
- Anti-convulsive drugs (diazepam)
- Sphygmomanometer
- One-way mouth “breather” apparatus

First line emergency drugs and instruments should be in the examination room

21.2.2.2 First Line Treatment of Acute Reactions to Contrast Media

Nausea/Vomiting

Transient: Supportive treatment.
Severe, protracted: Appropriate antiemetic drugs should be considered.

Urticaria

Scattered, transient: Supportive treatment including observation.
Scattered, protracted: Appropriate H1-antihistamine intramuscularly or intravenously should be considered. Drowsiness and/or hypotension may occur.
Profound: Consider adrenaline 1:1,000, 0.1–0.3 ml (0.1–0.3 mg) intramuscularly in adults, 0.01 mg/kg intramuscularly up to 0.3 maximum in children. Repeat as needed.

Bronchospasm

1. Oxygen by mask (6–10 l/min)
2. β-2-agonist metered dose inhaler (2–3 deep inhalations)
3. Adrenaline
   a) Normal blood pressure
      Intramuscular: 1:1,000, 0.1–0.3 ml (0.1–0.3 mg) [use smaller dose in a patient with coronary artery disease or elderly patient]
      In pediatric patients: 0.01 mg/kg up to 0.3 mg maximum
   b) Decreased blood pressure
      Intramuscular: 1:1,000, 0.5 ml (0.5 mg), (in pediatric patients: 0.01 mg/kg intramuscularly)

Laryngeal Edema

1. Oxygen by mask (6–10 l/min)
2. Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) for adults, repeat as needed.

Hypotension

Isolated hypotension

1. Elevate patient's legs
2. Oxygen by mask (6–10 l/min)
3. Intravenous fluid: rapidly, normal saline or lactated Ringer's solution
4. If unresponsive: adrenaline (1:1,000), 0.5 ml (0.5 mg) intramuscularly, repeat as needed

Vagal reaction (hypotension and bradycardia)

1. Elevate patient's legs
2. Oxygen by mask (6–10 l/min)
3. Atropine 0.6–1.0 mg intravenously, repeat if necessary after 3–5 min, to 3 mg total (0.04 mg/kg) in adults. In pediatric patients give 0.02 mg/kg intravenously (maximum 0.6 mg per dose) repeat if necessary to 2 mg total
4. Intravenous fluids: rapidly, normal saline or lactated Ringer's solution

Generalized anaphylactoid reaction

1. Call for resuscitation team
2. Suction airway as needed
3. Elevate patient's legs if hypotensive
4. Oxygen by mask (6–10 l/min)
5. Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) in adults. Repeat as needed. In pediatric patients 0.01 mg/kg to 0.3 mg (maximum dose)
6. Intravenous fluids (e.g. normal saline, lactated Ringer's)
7. H1-blocker e.g. diphenhydramine 25–50 mg intravenously

21.2.3 Late Adverse Reactions to Intravascular Iodinated Contrast Media

Definition:	A late adverse reaction to intravascular iodinated contrast medium is defined as a reaction which occurs between 1 h and 1 week after contrast medium injection
Reactions:	A variety of late symptoms (e.g. nausea, vomiting, headache, musculoskeletal pains, fever) have been described following contrast medium, but many are not related to contrast medium Skin reactions of similar type to other drug eruptions are true late adverse reactions. They are usually mild to moderate and self-limiting
Risk factors for skin reactions:	• Previous contrast medium reaction • Interleukin-2 treatment
Management:	Symptomatic and similar to the management of other drug-induced skin reactions
Prophylaxis:	• Generally not recommended • Patients who have had a previous serious late adverse reaction, can be given oral steroids (see ESUR guidelines on prevention of generalized adverse reactions)
Recommendations:	Tell patients who have had a previous contrast medium reaction or who are on interleukin-2 treatment that a late skin reaction is possible and that they should contact a doctor if they have a problem

21.3 Other Adverse Effects of Contrast Media

ESUR Guidelines

21.3.1 Prevention and Management of Extravasation of Contrast Media

Risk factors relate to:	*The technique:* • Use of a power injector • Less optimal injection sites including lower limb and small distal veins • Large volume of contrast medium • High osmolar contrast medium *The patient:* • Unable to communicate • With fragile or damaged veins • With arterial insufficiency • With compromised lymphatic and/or venous drainage
To reduce the risk:	• Intravenous technique should always be careful, preferably using plastic catheters for power injection • Use low osmolar contrast medium
Type of injuries	• Most injuries are minor • Severe injuries include skin ulceration, soft tissue necrosis, and compartment syndrome
Treatment	• Conservative management is adequate in most cases: o Limb elevation o Apply ice packs o Careful monitoring • If a serious injury is suspected, seek the advice of a surgeon

21.3.2 Effect of Iodinated Contrast Media on Thyroid Function in Adults

Absolute contraindication	
	• Iodinated contrast media should not be given to patients with manifest hyperthyroidism
Development of thyrotoxicosis after iodinated contrast media	
No risk	• Patients with normal thyroid function
At risk	• Patients with Graves' disease • Patients with multinodular goiter and thyroid autonomy, especially if they are elderly and/or live in areas of dietary iodine deficiency
Recommendations	• Prophylaxis is generally not necessary • Patients at risk should be closely monitored by endocrinologists after iodinated contrast medium injection • In selected high-risk patients, prophylactic treatment may be given by an endocrinologist; this is more relevant in areas of dietary iodine deficiency • Intravenous cholangiographic contrast media should not be given to patients at risk
Radioactive iodine treatment	
Recommendation	• Patients undergoing therapy with radioactive iodine should not have received iodinated contrast media for at least 2 months before treatment
Isotope imaging of the thyroid	
Recommendation	• Isotope imaging of the thyroid should be avoided for 2 months after iodinated contrast medium injection

21.3.3 Pulmonary Effects of Contrast Media

High risk patients	**Action**
History of pulmonary hypertension History of bronchial asthma Incipient cardiac failure	• Use low or iso-osmolar contrast media • Avoid large doses of contrast media

21.3.4 Contrast Media and Catecholamine-Producing Tumours (Phaeochromocytoma and Paraganglioma)

	Tumour localisation when catecholamine-producing tumour detected biochemically	Characterisation of incidentally detected adrenal mass
Preparation		
(a) Before intravenous contrast medium (iodinated or gadolinium)	α and β-Adrenergic blockade with orally administered drugs under the supervision of the referring physician is advised. Further α-blockade with intravenous phenoxy-benzamine is not necessary	No special preparation
(b) Before intra-arterial iodinated contrast medium	α and β-Adrenergic blockade with orally administered drugs and α-blockade with intravenous phenoxybenzamine under the supervision of the referring physician are recommended	
Type of contrast medium which should be used		
Iodinated agent	Nonionic agent	Nonionic agent
Gadolinium agent	Any agent (ionic or nonionic)	Any agent (ionic or nonionic)

21.3.5 The Use of Iodinated and Gadolinium Contrast Media During Pregnancy and Lactation

	Iodinated agents	Gadolinium agents
Pregnancy	a) In exceptional circumstances, when radiographic examination is essential, iodinated contrast media may be given to the pregnant female b) Following administration of iodinated agents to the mother during pregnancy, thyroid function should be checked in the neonate during the first week	a) When MR examination is necessary, gadolinium media may be given to the pregnant female b) Following administration of gadolinium agents to the mother during pregnancy, no neonatal tests are necessary
Lactation	Breast feeding may be continued normally when iodinated agents are given to the mother	Breast feeding may be continued normally when gadolinium agents are given to the mother
Pregnant or lactating mother with renal impairment	No additional precautions are necessary for the fetus or neonate. Follow ESUR guidelines for contrast media administration when renal function is impaired	No additional precautions are necessary for the fetus or neonate. Follow ESUR guidelines for contrast media administration when renal function is impaired

21.3.6 Avoiding Interaction Between Contrast Media and Other Drugs

Do	Be aware of the patient's drug history Keep proper records of the contrast medium injection (time, dose, name)	
Drugs needing special attention	Metformin	Refer to ESUR guidelines on Metformin
	Cyclosporine Cisplatin Aminoglycosides Non-steroid anti-inflammatory drugs	Refer to ESUR guidelines on nephrotoxicity
	β–blocker	Refer to ESUR guidelines on prevention and management of adverse reactions
	Interleukin-2	Refer to ESUR guidelines on delayed reactions
	Hydralazine	Avoid contrast medium injection if possible
Do not	Mix contrast media with other drugs in tubes or syringes Make non emergency biochemical analysis on blood or urine collected within 24 h of contrast medium injection	
Isotope studies	Thyroid	Refer to ESUR guidelines on thyroid function in adults
	Bone, red blood cell labeling	Avoid contrast medium injection for at least 24 h before the isotope study

21.3.7 Safety of Ultrasound Contrast Media

Statement:	• Ultrasound contrast media are generally safe
Type and severity of reactions:	• The majority of reactions are minor (e.g. headache, nausea, sensation of heat, altered taste) and self-resolving • Allergy-like reactions occur rarely
To reduce the risk:	• Check for intolerance of any of the components of the contrast agent • Use the lowest level of acoustic output and shortest scanning time to allow a diagnostic examination
Treatment:	• If a serious event occurs – refer to ESUR guidelines on management of adverse reactions to contrast media

21.3.8 Safety of MR Extracellular Contrast Media

Safety	Generally safe; low incidence of adverse event
Adverse events	Similar type to those seen after iodinated contrast media
Management	See ESUR guidelines on management
Prophylaxis	If there has been a previous hypersensitivity-like reaction to gadolinium based compounds, consider an alternative modality or premedication (see ESUR guidelines on prophylaxis)
Contrast medium-induced nephropathy	May occur – see ESUR guidelines on nephrotoxicity
Dialysis	See ESUR guidelines on dialysis
S-creatinine Hydration	No special precautions are recommended
Pregnancy and Lactation	See ESUR guidelines on pregnancy and lactation
Interaction	See ESUR guidelines on interaction
Radiography	Not approved for this use

21.3.9 Safety of Liver Specific MR Contrast Media

Types of adverse reactions	Similar to reactions observed with other types of contrast media such as nausea, vomiting, urticaria, rash, generalized anaphylactoid reactions. Back pain may also occur with superparamagnetic iron oxides. Serious life threatening reactions are rare
Patients < 18 years old	Safety has not yet been established
Contraindications	Iron oxides – Known allergy or hypersensitivity to parenteral iron or dextran Manganese based contrast media – Known allergy to the preparation – Pregnancy – Lactation – Severe liver impairment, Gadolinium based contrast media – Known allergy to the preparation
Cautions	Iron oxides – In patients with hemosiderosis or hemochromatosis: iron-overload may be aggravated Manganese based contrast media – Liver impairment and heart failure Gadolinium based contrast media • Agent with high hepatocyte uptake: liver and renal failure • Agent with low hepatocyte uptake: renal failure

21.3.10 Safety of Barium Contrast Media

	Recommended action	
Contraindications	Integrity of gut wall compromised	Use iodinated water-soluble contrast media In neonates and patients at risk of leakage into mediastinum and/or lungs use low- or isoosmolar contrast media
	Previous allergic reactions to barium products	Use iodinated water-soluble contrast media and be prepared to treat a reaction
Cautions	Bowel strictures	Use only small amounts
	Extensive colitis	Avoid barium enemas
Complications	Reduced bowel motility	Encourage fluid intake
	Venous intravasation	Early identification and careful observation Antibiotics and intravenous fluids Emergency treatment may be needed
	Aspiration	Bronchoscopic removal for large amounts Chest physiotherapy Antibiotics

ESUR Statement

21.3.11 Effects of Iodinated Contrast Media on Blood and Endothelium

The clinically important adverse effect of iodinated contrast media on blood and endothelium is thrombosis. It is recognized that:

- All contrast media have anticoagulant properties, especially ionic agents.
- High osmolar ionic contrast media may induce thrombosis due to endothelial damage, particularly in phlebographic procedures.
- Drugs and interventional devices that decrease the risk of thromboembolic complications during interventional procedures minimize the importance of the effects of contrast media.

Guidelines

- Meticulous angiographic technique is mandatory and is the most important factor in reducing thromboembolic complications.
- Low or iso-osmolar contrast media should be used for diagnostic and interventional angiographic procedures including phlebography.

21.4 Publications from the Contrast Media Safety Committee of the European Society of Urogenital Radiology

Bellin M-F, Jakobsen JÅ, Tomassin I, Thomsen HS, Morcos SK, Members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (2002) Contrast medium extravasation injury: guidelines for prevention and management. Eur Radiol 12:2807–2812

Bellin M-F, Webb JAW, Molen AJvd, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) Safety of MR liver specific contrast media. Eur Radiol 15:1607–1614

Jakobsen JÅ, Oyen R, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) Safety of ultrasound contrast agents. Eur Radiol 15:941–945

Molen AJvd, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2004) Effect of iodinated contrast media on thyroid function in adults. Eur Radiol 14:902–906

Morcos SK, Thomsen HS, Exley CM, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) Contrast media: interaction with other drugs and clinical tests. Eur Radiol 15:1463–1468)

Morcos SK, Thomsen HS, Webb JAW and members of contrast media safety committee of the European Society of Urogenital Radiology (ESUR) (1999) Contrast media induced nephrotoxicity: a consensus report. Eur Radiol 9:1602–1613

Morcos SK, Thomsen HS, Webb JAW and members of contrast media safety committee of the European Society of Urogenital Radiology (ESUR) (2001) Prevention of generalized reactions to contrast media: a consensus report and guidelines. Eur Radiol 11:1720–1728

Morcos SK, Thomsen HS, Webb JAW, Members of the Contrast Media Safety Committee of European Society of Urogenital Radiology (2002) Dialysis and contrast media. Eur Radiol 12:3026–1629

Thomsen HS, Almén T, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (2002) Gadolinium-containing contrast media for radiographic examinations: a position paper. Eur Radiol 12:2600–2605

Thomsen HS, Morcos SK and members of contrast media safety committee of the European Society of Urogenital Radiology (ESUR) (1999) Contrast media and metformin. Guidelines to diminish the risk of lactic acidosis in non-insulin dependent diabetics after administration of contrast media. Eur Radiol 9:738–740

Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2004) Management of acute adverse reactions to contrast media. Eur Radiol 14:476–481

Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) In which patients should serum-creatinine be measured before contrast medium administration? Eur Radiol 15:749–754

Webb JAW, Stacul F, Thomsen HS, Morcos SK, Members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) (2003) Late adverse reactions to intravascular iodinated contrast media. Eur Radiol 13:181–184

Webb JAW, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) (2005) The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol 15:1234–1240

Subject Index

List of Contributors

Peter Aspelin, MD
Professor, Department of Radiology
Karolinska University Hospital
14186 Stockholm
Sweden

Marie-France Bellin, MD
Professor, Department of Radiology
University Paris-Sud 11
Paul Brousse Hospital, AP-HP
12-14 avenue Paul Vaillant Couturier
94804 Villejuif Cedex
France

Remy W. F. Geenen, MD
Department of Radiology
Erasmus MC – University Medical Center Rotterdam
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands

Jarl Å. Jakobsen, MD
Professor, Department of Diagnostic Radiology
Rikshospitalet
0017 Oslo
Norway

Gabriel P. Krestin, MD
Professor, Department of Radiology
Erasmus MC – University Medical Center Rotterdam
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands

Sameh K. Morcos, FRCS, FFRRCSI, FRCR
Department of Diagnostic Imaging
Northern General Hospital
Sheffield Teaching Hospitals NHS Trust
Herries Road
Sheffield S5 7AU
UK

Raymond Oyen, MD, PhD
Professor, Adjunct Clinic Head
Department of Radiology
Catholic University of Leuven
Herestraat 49
3000 Leuven
Belgium

June M. Raine, MD
Medicines Control Agency
Market Towers
1 Nine Elms Lane
London, SW8 5NQ
UK

Fulvio Stacul, MD
Institute of Radiology
Ospedale di Cattinara
34149 Trieste
Italy

Henrik S. Thomsen, MD
Professor, Department of
Diagnostic Radiology 54E2
Copenhagen University Hospital at Herlev
Herlev Ringvej 75
2730 Herlev
Denmark

Aart J. van der Molen, MD
Department of Radiology – C2-S
Leiden University Medical Center
P.O. Box 9600
2300 RC Leiden
The Netherlands

Judith A.W. Webb, MD
Department of Diagnostic Imaging
St. Bartholomew's Hospital
West Smithfield
London EC1 A 7BE
UK

Medical Radiology Diagnostic Imaging and Radiation Oncology

Titles in the series already published

Diagnostic Imaging

Innovations in Diagnostic Imaging
Edited by J. H. Anderson

Radiology of the Upper Urinary Tract
Edited by E. K. Lang

The Thymus - Diagnostic Imaging, Functions, and Pathologic Anatomy
Edited by E. Walter, E. Willich, and W. R. Webb

Interventional Neuroradiology
Edited by A. Valavanis

Radiology of the Pancreas
Edited by A. L. Baert, co-edited by G. Delorme

Radiology of the Lower Urinary Tract
Edited by E. K. Lang

Magnetic Resonance Angiography
Edited by I. P. Arlart, G. M. Bongartz, and G. Marchal

Contrast-Enhanced MRI of the Breast
S. Heywang-Köbrunner and R. Beck

Spiral CT of the Chest
Edited by M. Rémy-Jardin and J. Rémy

Radiological Diagnosis of Breast Diseases
Edited by M. Friedrich and E.A. Sickles

Radiology of the Trauma
Edited by M. Heller and A. Fink

Biliary Tract Radiology
Edited by P. Rossi, co-edited by M. Brezi

Radiological Imaging of Sports Injuries
Edited by C. Masciocchi

Modern Imaging of the Alimentary Tube
Edited by A. R. Margulis

Diagnosis and Therapy of Spinal Tumors
Edited by P. R. Algra, J. Valk, and J. J. Heimans

Interventional Magnetic Resonance Imaging
Edited by J.F. Debatin and G. Adam

Abdominal and Pelvic MRI
Edited by A. Heuck and M. Reiser

Orthopedic Imaging
Techniques and Applications
Edited by A. M. Davies and H. Pettersson

Radiology of the Female Pelvic Organs
Edited by E. K.Lang

Magnetic Resonance of the Heart and Great Vessels
Clinical Applications
Edited by J. Bogaert, A.J. Duerinckx, and F. E. Rademakers

Modern Head and Neck Imaging
Edited by S. K. Mukherji and J. A. Castelijns

Radiological Imaging of Endocrine Diseases
Edited by J. N. Bruneton in collaboration with B. Padovani and M.-Y. Mourou

Trends in Contrast Media
Edited by H. S. Thomsen, R. N. Muller, and R. F. Mattrey

Functional MRI
Edited by C. T. W. Moonen and P. A. Bandettini

Radiology of the Pancreas
2nd Revised Edition
Edited by A. L. Baert
Co-edited by G. Delorme and L. Van Hoe

Emergency Pediatric Radiology
Edited by H. Carty

Spiral CT of the Abdomen
Edited by F. Terrier, M. Grossholz, and C. D. Becker

Liver Malignancies
Diagnostic and Interventional Radiology
Edited by C. Bartolozzi and R. Lencioni

Medical Imaging of the Spleen
Edited by A. M. De Schepper and F. Vanhoenacker

Radiology of Peripheral Vascular Diseases
Edited by E. Zeitler

Diagnostic Nuclear Medicine
Edited by C. Schiepers

Radiology of Blunt Trauma of the Chest
P. Schnyder and M. Wintermark

Portal Hypertension
Diagnostic Imaging-Guided Therapy
Edited by P. Rossi
Co-edited by P. Ricci and L. Broglia

Recent Advances in Diagnostic Neuroradiology
Edited by Ph. Demaerel

Virtual Endoscopy and Related 3D Techniques
Edited by P. Rogalla, J. Terwisscha Van Scheltinga, and B. Hamm

Multislice CT
Edited by M. F. Reiser, M. Takahashi, M. Modic, and R. Bruening

Pediatric Uroradiology
Edited by R. Fotter

Transfontanellar Doppler Imaging in Neonates
A. Couture and C. Veyrac

Radiology of AIDS
A Practical Approach
Edited by J.W.A.J. Reeders and P.C. Goodman

CT of the Peritoneum
Armando Rossi and Giorgio Rossi

Magnetic Resonance Angiography
2nd Revised Edition
Edited by I. P. Arlart, G. M. Bongratz, and G. Marchal

Pediatric Chest Imaging
Edited by Javier Lucaya and Janet L. Strife

Applications of Sonography in Head and Neck Pathology
Edited by J. N. Bruneton in collaboration with C. Raffaelli and O. Dassonville

Imaging of the Larynx
Edited by R. Hermans

3D Image Processing
Techniques and Clinical Applications
Edited by D. Caramella and C. Bartolozzi

Imaging of Orbital and Visual Pathway Pathology
Edited by W. S. Müller-Forell

Medical Radiology Diagnostic Imaging and Radiation Oncology

Titles in the series already published

Pediatric ENT Radiology
Edited by S. J. King
and A. E. Boothroyd

Radiological Imaging of the Small Intestine
Edited by N. C. Gourtsoyiannis

Imaging of the Knee
Techniques and Applications
Edited by A. M. Davies
and V. N. Cassar-Pullicino

Perinatal Imaging
From Ultrasound to MR Imaging
Edited by Fred E. Avni

Radiological Imaging of the Neonatal Chest
Edited by V. Donoghue

Diagnostic and Interventional Radiology in Liver Transplantation
Edited by E. Bücheler, V. Nicolas,
C. E. Broelsch, X. Rogiers,
and G. Krupski

Radiology of Osteoporosis
Edited by S. Grampp

Imaging Pelvic Floor Disorders
Edited by C. I. Bartram
and J. O. L. DeLancey
Associate Editors: S. Halligan,
F. M. Kelvin, and J. Stoker

Imaging of the Pancreas
Cystic and Rare Tumors
Edited by C. Procacci
and A. J. Megibow

High Resolution Sonography of the Peripheral Nervous System
Edited by S. Peer and G. Bodner

Imaging of the Foot and Ankle
Techniques and Applications
Edited by A. M. Davies,
R. W. Whitehouse,
and J. P. R. Jenkins

Radiology Imaging of the Ureter
Edited by F. Joffre, Ph. Otal,
and M. Soulie

Imaging of the Shoulder
Techniques and Applications
Edited by A. M. Davies and J. Hodler

Radiology of the Petrous Bone
Edited by M. Lemmerling
and S. S. Kollias

Interventional Radiology in Cancer
Edited by A. Adam, R. F. Dondelinger,
and P. R. Mueller

Duplex and Color Doppler Imaging of the Venous System
Edited by G. H. Mostbeck

Multidetector-Row CT of the Thorax
Edited by U. J. Schoepf

Functional Imaging of the Chest
Edited by H.-U. Kauczor

Radiology of the Pharynx and the Esophagus
Edited by O. Ekberg

Radiological Imaging in Hematological Malignancies
Edited by A. Guermazi

Imaging and Intervention in Abdominal Trauma
Edited by R. F. Dondelinger

Multislice CT
2nd Revised Edition
Edited by M. F. Reiser, M. Takahashi,
M. Modic, and C. R. Becker

Intracranial Vascular Malformations and Aneurysms
From Diagnostic Work-Up to Endovascular Therapy
Edited by M. Forsting

Radiology and Imaing of the Colon
Edited by A. H. Chapman

Coronary Radiology
Edited by M. Oudkerk

Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology
Edited by A. Jackson, D. L. Buckley,
and G. J. M. Parker

Imaging in Treatment Planning for Sinonasal Diseases
Edited by R. Maroldi and P. Nicolai

Clinical Cardiac MRI
With Interactive CD-ROM
Edited by J. Bogaert,
S. Dymarkowski, and A. M. Taylor

Focal Liver Lesions
Detection, Characterization, Ablation
Edited by R. Lencioni, D. Cioni,
and C. Bartolozzi

Multidetector-Row CT Angiography
Edited by C. Catalano
and R. Passariello

Paediatric Musculoskeletal Diseases
With an Emphasis on Ultrasound
Edited by D. Wilson

Contrast Media in Ultrasonography
Basic Principles and Clinical Applications
Edited by Emilio Quaia

MR Imaging in White Matter Diseases of the Brain and Spinal Cord
Edited by M. Filippi, N. De Stefano,
V. Dousset, and J. C. McGowan

Diagnostic Nuclear Medicine
2nd Revised Edition
Edited by C. Schiepers

Imaging of the Kidney Cancer
Edited by A. Guermazi

Magnetic Resonance Imaging in Ischemic Stroke
Edited by R. von Kummer and T. Back

Imaging of the Hip & Bony Pelvis
Techniques and Applications
Edited by A. M. Davies, K. J. Johnson,
and R. W. Whitehouse

Imaging of Occupational and Environmental Disorders of the Chest
Edited by P. A. Gevenois and
P. De Vuyst

Contrast Media
Safety Issues and ESUR Guidelines
Edited by H. S. Thomsen

Virtual Colonoscopy
A Practical Guide
Edited by P. Lefere and S. Gryspeerdt

Vascular Embolotherapy
A Comprehensive Approach
Volume 1
Edited by J. Golzarian. Co-edited by
S. Sun and M. J. Sharafuddin

Vascular Embolotherapy
A Comprehensive Approach
Volume 2
Edited by J. Golzarian. Co-edited by
S. Sun and M. J. Sharafuddin

Springer

Medical Radiology Diagnostic Imaging and Radiation Oncology

Titles in the series already published

Radiation Oncology

Lung Cancer
Edited by C.W. Scarantino

Innovations in Radiation Oncology
Edited by H. R. Withers
and L. J. Peters

Radiation Therapy
of Head and Neck Cancer
Edited by G. E. Laramore

Gastrointestinal Cancer –
Radiation Therapy
Edited by R.R. Dobelbower, Jr.

Radiation Exposure
and Occupational Risks
Edited by E. Scherer, C. Streffer,
and K.-R. Trott

Radiation Therapy of Benign Diseases
A Clinical Guide
S. E. Order and S. S. Donaldson

Interventional Radiation
Therapy Techniques – Brachytherapy
Edited by R. Sauer

Radiopathology of Organs and Tissues
Edited by E. Scherer, C. Streffer,
and K.-R. Trott

Concomitant Continuous Infusion
Chemotherapy and Radiation
Edited by M. Rotman
and C. J. Rosenthal

Intraoperative Radiotherapy –
Clinical Experiences and Results
Edited by F. A. Calvo, M. Santos,
and L.W. Brady

Radiotherapy of Intraocular
and Orbital Tumors
Edited by W. E. Alberti and
R. H. Sagerman

Interstitial and Intracavitary
Thermoradiotherapy
Edited by M. H. Seegenschmiedt
and R. Sauer

Non-Disseminated Breast Cancer
Controversial Issues in Management
Edited by G. H. Fletcher and
S.H. Levitt

Current Topics in
Clinical Radiobiology of Tumors
Edited by H.-P. Beck-Bornholdt

Practical Approaches to
Cancer Invasion and Metastases
A Compendium of Radiation
Oncologists' Responses to 40 Histories
Edited by A. R. Kagan with the
Assistance of R. J. Steckel

Radiation Therapy in Pediatric Oncology
Edited by J. R. Cassady

Radiation Therapy Physics
Edited by A. R. Smith

Late Sequelae in Oncology
Edited by J. Dunst and R. Sauer

Mediastinal Tumors. Update 1995
Edited by D. E. Wood
and C. R. Thomas, Jr.

Thermoradiotherapy
and Thermochemotherapy
Volume 1:
Biology, Physiology, and Physics
Volume 2:
Clinical Applications
Edited by M.H. Seegenschmiedt,
P. Fessenden, and C.C. Vernon

Carcinoma of the Prostate
Innovations in Management
Edited by Z. Petrovich, L. Baert,
and L.W. Brady

Radiation Oncology
of Gynecological Cancers
Edited by H.W. Vahrson

Carcinoma of the Bladder
Innovations in Management
Edited by Z. Petrovich, L. Baert,
and L.W. Brady

Blood Perfusion and
Microenvironment of Human Tumors
Implications for
Clinical Radiooncology
Edited by M. Molls and P. Vaupel

Radiation Therapy of Benign Diseases
A Clinical Guide
2nd Revised Edition
S. E. Order and S. S. Donaldson

Carcinoma of the Kidney and Testis,
and Rare Urologic Malignancies
Innovations in Management
Edited by Z. Petrovich, L. Baert,
and L.W. Brady

Progress and Perspectives in the
Treatment of Lung Cancer
Edited by P. Van Houtte,
J. Klastersky, and P. Rocmans

Combined Modality Therapy of
Central Nervous System Tumors
Edited by Z. Petrovich, L. W. Brady,
M. L. Apuzzo, and M. Bamberg

Age-Related Macular Degeneration
Current Treatment Concepts
Edited by W. A. Alberti, G. Richard,
and R. H. Sagerman

Radiotherapy of Intraocular
and Orbital Tumors
2nd Revised Edition
Edited by R. H. Sagerman,
and W. E. Alberti

Modification of Radiation Response
Cytokines, Growth Factors,
and Other Biolgical Targets
Edited by C. Nieder, L. Milas,
and K. K. Ang

Radiation Oncology for Cure and Palliation
R. G. Parker, N. A. Janjan,
and M. T. Selch

Clinical Target Volumes in Conformal and
Intensity Modulated Radiation Therapy
A Clinical Guide to Cancer Treatment
Edited by V. Grégoire, P. Scalliet,
and K. K. Ang

Advances in Radiation Oncology
in Lung Cancer
Edited by Branislav Jeremić

New Technologies in Radiation Oncology
Edited by W. Schlegel, T. Bortfeld,
and A.-L. Grosu

Springer