Syed Tabish R. Zaidi · Jason A. Roberts
*Editors*

# Drug Dosing in Obesity

## Volume I: Antimicrobials

Springer

# Drug Dosing in Obesity

Syed Tabish R. Zaidi · Jason A. Roberts
Editors

# Drug Dosing in Obesity

## Volume I: Antimicrobials

Springer

*Editors*
Syed Tabish R. Zaidi
Division of Pharmacy, School of Medicine
University of Tasmania
Hobart, TAS
Australia

Jason A. Roberts
School of Medicine and School
of Pharmacy, Burns Trauma
and Critical Care Research Centre
The University of Queensland
Brisbane, QLD
Australia

ISBN 978-3-319-44032-3 ISBN 978-3-319-44034-7 (eBook)
DOI 10.1007/978-3-319-44034-7

Library of Congress Control Number: 2016947787



Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

# Foreword

Use of antibiotics is becoming increasingly challenging as we are required to treat different types of patients, including the elderly as well as those that are profoundly immunosuppressed and/or critically ill. The presence of multi-drug resistant pathogens and the association of their emergence with suboptimal antibiotic exposures also present major challenges for clinicians. Indeed, despite all the *in vitro* and *in vivo* studies on antibiotic pharmacokinetics and pharmacodynamics over the last 30–40 years, therapeutic failures are still relatively common for some patient groups such as the critically ill.

An increasingly common question that now pervades the health system and affects our ability to give optimal antibiotic therapy is, "How do we dose antibiotics in obese patients?" While this issue is not significant for some countries, Western countries including USA, UK, and Australia all have relatively high rates of obesity in the population meaning that the rates of patients with obesity is similarly high. In this book, data is presented which highlights the worse clinical outcomes for infected obese patients relative to non-obese comparators. While some physiological rationale exists for this, including maldistribution of blood flow into peripheral tissues and altered endocrine function, a controllable factor for clinicians is the dose of antibiotic that these patients are administered. This textbook provides a very detailed summary of the literature describing the data of altered pharmacokinetics of various antibiotics in obese patients and translates these data into dosing guidance. At the same stage, where there are severe deficiencies in data, these gaps are also highlighted as areas requiring further research.

Although I am biased because I have been involved in the development of this book, I believe it to be a highly valuable resource and recommend it to pharmacists,

doctors, and other antibiotic prescribers as well as basic and translational scientists that have an interest in antibiotic pharmacokinetics and pharmacodynamics.

Brisbane, Australia

Jason A. Roberts, Ph.D.
Professor of Medicine
NHMRC Career Development Fellow

and

Professor of Pharmacy
Chair of Research Strategies Committee

# Preface

No matter how depressing it sounds, obesity is here to stay! Despite a significant increase in the awareness of causes of obesity, extensive media campaign from public health organizations and government bodies, and availability of modern medical interventions, the global incidence of obesity is rising exponentially. The official product information for medications is based on the data derived from normal weight individuals and therefore, cannot be applied to obese patients. As such, clinicians are struggling to make dosing decisions for obese patients on a daily basis. Antimicrobials are one of the most frequently used medications, and limited information is available about antimicrobials in obese patients. Like any other situation in the practice of medicine where limited information is available, clinical decisions are often guided by the best use of available data and expert advice on the matter. In a nutshell, this is all what the first clinical reference on "Drug Dosing in Obesity-Volume I: Antimicrobials" is all about.

Three years ago when I made a transition from full-time clinical pharmacist role to an academic, I contemplated the idea of having a clinical drug reference for dosing medication in obesity. Springer publishers were kind enough to accept the idea, and I started contacting doctors, pharmacists, and academics to gauge the support for this idea. The response was overwhelming, and many individuals volunteered to write chapters for the antimicrobials section of the book. The response for the non-antimicrobials chapters was less encouraging. Springer was once again kind enough to allow breaking the book into two volumes; the first one for the antimicrobials and the second one for the rest of medications.

Dosing antimicrobials in any patient population requires thoughtful considerations of patients, diseases, and drug factors; therefore, this book is not meant to replace clinical judgment. The aim of this book is to assist clinicians by providing an up-to-date summary of the literature coupled with the expert advice on dosing antimicrobials in obesity. Each chapter represents a summary of the relevant pharmacokinetic changes in obese patients followed by a discussion of the available literature on the use of a particular antimicrobial in obese patients. Dosing recommendations are provided based on the available literature and expert advice

considering important patient-related factors, where applicable. Selected cases have been presented as an appendix to the book to demonstrate clinical decision-making in the dosing of antimicrobials for obese patients. To the best of our knowledge, there is no reference book available on the dosing of antimicrobials in obesity and we believe that this book will serve as a useful reference source for clinicians, academics, and researchers.

I would like to thank all the authors for their time and efforts in making this book a reality. Special thanks to the Division of Pharmacy, School of Medicine at the University of Tasmania for allowing me to complete this important piece of scientific literature. Thanks to Sarah Germans and Thijs van Vlijmen at the Springer office. Last but not least, thanks to Prof. Jason Roberts for providing two chapters for the book and accepting my invitation to become a co-editor of this book. There is an urgent need to conduct pharmacokinetics and clinical studies on many routinely used antimicrobials in obese patients where the literature is simply nonexistent. I will encourage all clinicians involved in providing care for obese patients to collaborate with the universities in conducting the necessary research.

Best wishes,

Hobart, Australia

Syed Tabish R. Zaidi
Lecturer and Course Coordinator
Postgraduate Clinical Pharmacy Coursework

# Contents

# Abbreviations

| | |
|---|---|
| μg/ml | Microgram per milliliter |
| ABW | Adjusted body weight |
| ARC | Augmented renal clearance |
| AUC | Area under the concentration–time curve |
| $AUC_{tissue}/AUC_{plasma}$ | Tissue penetration |
| BMI | Body mass index |
| BSA | Body surface area |
| C&G | Cockcroft and Gault |
| $C_{ave}$ | The average plasma concentration |
| CBA | Colistin base activity |
| CFR | Cumulative fraction of response |
| CK | Creatinine kinase |
| Cl | Renal clearance |
| cm | Centimeter |
| $C_{max}$ | The maximum plasma concentration or the crest concentration |
| $C_{max,ss}$ | The maximum plasma concentration at steady state |
| $C_{min}$ | The minimum plasma concentration or the trough concentration |
| CMS | Colistimethate sodium |
| CNS | Central nervous system |
| CPK | Creatine phosphokinase |
| CPM | Clinical pharmacokinetic monitoring |
| Crcl | Creatinine clearance |
| CSF | Cerebrospinal fluid |
| CVVH | Continuous venovenous hemofiltration |
| CVVHDF | Continuous venovenous hemodiafiltration |
| CYP | Cytochrome P450 enzymes |
| DILI | Drug-induced liver injury |
| ECMO | Extracorporeal membrane oxygenation |

| | |
|---|---|
| ECW | Extracellular water |
| EGFR | Estimated glomerular filtration rate |
| ESBLs | Extended-spectrum β-lactamases |
| f | The free fraction of drug |
| FFW | Fat-free weight |
| *ft* > MIC | Free concentration above the minimum inhibitory concentration |
| GFR | Glomerular filtration rate |
| GVHD | Graft versus host disease |
| HLA | Human leukocyte antigen |
| HSCT | Hematopoietic stem cell transplant |
| IBW | Ideal body weight |
| IFS | Interstitial fluid space |
| IV | Intravenous |
| Kg | Kilogram |
| $Kg/m^2$ | Kilogram per square meter |
| L | Liter |
| L/h | Liters per hour |
| L/hr/kg | Liters per hour per kilogram |
| L/kg | Liters per kilogram |
| L-AMB | Liposomal amphotericin B |
| LBM | Lean body mass |
| LBW | Lean body weight |
| m | Meter |
| MDRD | Modified Diet in Renal Diseases |
| MEC | Minimum effective concentration |
| mg | Milligram |
| mg.h/L | Milligram and hour per liter |
| mg/kg | Milligram per kilogram |
| mg/kg/day | Milligram per kilogram per day |
| mg/L | Milligram per liter |
| MIC | Minimum inhibitory concentration |
| ml/min | Milliliters per minute |
| MRSA | Methicillin-resistant *S. Aureus* |
| MSSA | Methicillin sensitive *Staphylococcus aureus* |
| NFLD | Nonalcoholic fatty liver disease |
| OPTIMO trial | Oseltamivir PK in morbid obesity trial |
| PAFE | Post-antifungal effect |
| PBP | Penicillin binding protein |
| PD | Pharmacodynamic |
| Penicillin G | Benzylpenicillin |
| Penicillin V | Phenoxymethylpenicillin |
| PK | Pharmacokinetic |
| Polymyxin E | Colistin |
| PTA | Probability of target attainment |

| | |
|---|---|
| Q/D | Quinupristin/Dalfopristin |
| RRT | Renal replacement therapy |
| SSI | Surgical site infection |
| T > MIC | The time the antibiotic concentration is maintained above the MIC |
| $t_{½}$ | Half-life |
| TBW | Total body weight |
| TDM | Therapeutic drug monitoring |
| $t_{max}$ | Time to peak plasma concentration |
| TZP | Piperacillin–tazobactam |
| V | Volume of distribution |
| VRE | Vancomycin-resistant enterococci |

# Chapter 1
# Introduction

**Syed Tabish R. Zaidi**

**Abstract** Significant physiological changes in obese patients limit the generalisability of dosing information of antimicrobials to this increasingly prevalent group of patients. Individualised approaches to drug dosing in obese patients are warranted to address the significant changes in the pharmacokinetics of antimicrobials in this patient group. Nevertheless, differences in the chemical, physiological and clinical characteristics of antimicrobials limit the application of established pharmacokinetics in obese patients. Important considerations when designing an antimicrobial regimen include an understanding of the focus of infection, relative susceptibilities of the micro-organism involved, the best match of the body size descriptor for the antimicrobial in question and the renal function of the patients under treatment.

**Keywords** Obesity · Physiological changes · Body-size descriptors · Dosing · Antimicrobials · Pharmacokinetics · Pharmacodynamics

Obesity is a medical condition of excessive accumulation of body fat, which can be identified by a simple index of weight-for-height, i.e. the body mass index (BMI) [1, 2]. BMI is defined as body weight (in kg) divided by the height squared (in m; $kg/m^2$), with obesity defined as having a BMI $\geq 30$ $kg/m^2$ [2]. Further classification divides obesity into three distinct classes: type I refers to a BMI of $\geq 30$ $kg/m^2$ and $<35$ $kg/m^2$, type II refers to a BMI of $\geq 35$ and $\leq 40$ $kg/m^2$ and type III or morbid obesity is defined as having a BMI of $>40$ $kg/m^2$ [3]. Despite an ongoing debate in the medical literature regarding the validity of BMI as a measure of obesity, BMI remains the universal standard for measuring obesity and has been used by the World Health Organization (WHO) for studies of obesity internationally [4].

S.T.R. Zaidi (✉)
Pharmacy, School of Medicine, University of Tasmania, Private Bag 26, Hobart, TAS 7001, Australia
e-mail: Tabish.razizaidi@utas.edu.au



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_1

Obesity is a growing concern for healthcare authorities worldwide. According to recent statistics (2014) by the WHO, approximately 13 % of the world's population are obese [4], which represents more than 600 million individuals. The United States has the highest prevalence of obesity among western nations, with one-third (33.7 %) of the total adult population classified as being obese [4]. An increasing trend in the prevalence of obesity is observed in other western countries where obesity occurrence is, at least, greater than 20 % of the total population, e.g. Australia, Canada, France, Germany, Ireland and the United Kingdom [4]. Middle Eastern countries are increasingly recording a high prevalence of obesity, with close to one-third of the populations in Bahrain, Qatar, Saudi Arabia and the United Arab Emirates being obese [4].

Posology information for many antimicrobials lacks specific recommendations of how to dose these agents in obese patients [5]. Given the significant physiological changes that occur in obesity and the absence of an appropriate size descriptor to base antimicrobial dosing decisions on [6], antimicrobial dosing in obese patients is a challenging task. The following sections of this introductory chapter will briefly discuss the rationale for individualising antimicrobial dosing in obese patients, examine the physiological changes responsible for pharmacological variability in obesity and determine the various factors that should be considered before making dosing decisions for antimicrobials in obese patients.

## Rationale for Individualised Dosing of Antimicrobials

Obese patients have a higher risk of infection-related mortality than normal weight patients do [7]. Moreover, obese patients may have impaired tissue penetration of antimicrobials and often receive sub-optimal doses of antimicrobials during clinical practice [7]. Delayed administration of appropriate antimicrobials has been shown to be an independent predictor of patient mortality [8]. Given the significant variation in the pharmacokinetics of antimicrobials in obese patients [6, 9], administration of standardised doses can result in a sub-therapeutic concentration of antimicrobials and subsequent treatment failure in this group of patients [10–12].

Indiscriminate use of official antimicrobial dosing recommendations to treat obese patients has been associated with a higher than expected incidence of adverse drug reactions in these patients [13, 14]. Antimicrobials with a narrow therapeutic index, such as colistin and aminoglycosides, are often used as the last resort in treating life-threatening infections. Using a common mg/kg dose of colistin recommended for non-obese patients in obese individuals results in a higher incidence of nephrotoxicity. The same is true for other narrow therapeutic index antimicrobials such as aminoglycosides and vancomycin [13, 15].

Another important reason to individualise dosing in obese patients is the relative variability of body composition within identical BMI values [5]. BMI is based on

an individual's body weight and height, and a taller person may have an entirely different body composition, and subsequent antimicrobial disposition, than a fatter, shorter person. Such variations, together with gender and ethnic differences in body composition, warrants thoughtful consideration of multiple factors before making dosing decisions in obese patients [6].

Lastly, antimicrobials agents have a significantly different pharmacokinetic response to similar obesity-related physiological changes due to their physiochemical characteristics [5]. Therefore, careful consideration of body composition of individual patients, the relative toxicity of the antimicrobial under consideration and available pharmacokinetic data is required to calculate doses to ensure the safe and effective use of antimicrobials in obese patients.

## Physiological Changes in Obesity and Antimicrobial Dosing

A number of physiological changes occur in obese individuals compared to normal weight individuals, such as an increase in body volume; relative increase in adipose tissues; a significant increase in inflammation secondary to increased adiposity, endocrine changes and associated metabolic syndrome; a comparative decrease in lung volume and reduced tissue perfusion due to limited cardiac output [16]. Therefore, obese patients are at a higher risk of developing various medical conditions including hypertension, coronary artery diseases, diabetes mellitus, obstructive sleep apnoea, gastroesophageal reflux disease and venous-thromboembolic disorders [16]. Our understanding of the implications of antibiotic dosing due to the physiological changes related to obesity is limited, with the following section briefly outlining some of the important physiological changes that have an established relationship concerning antibiotic dosing.

## Increase in Extracellular Water

Obese individuals have lower total body water per unit of weight but higher extracellular water than normal weight individuals do [17]. Apart from contributing to cardiovascular and renal complications, this increase in extracellular water in obese patients is directly related to an increase in the volume of distribution (V) of the majority of antimicrobials independent of their hydrophilic or lipophilic nature. Blood flow to adipose tissue is significantly lower than to muscle and other vital organs in the body. It is estimated that around 5 % of cardiac output reaches adipose tissue; therefore, it is assumed that the V of hydrophilic antimicrobials (such as penicillins, carbapenems and aminoglycosides) should not be increased owing to this limited blood flow [9]. Nevertheless, pharmacokinetic studies of

penicillins, carbapenems and aminoglycosides in obese patients have shown a considerable increase in the V of these antimicrobials [18–21], with studies also revealing similar results for lipophilic quinolone antimicrobials with an increase in the V of ciprofloxacin and levofloxacin in obese patients [10, 22].

## Poor Tissue Perfusion

Poor tissue perfusion and reduced peripheral perfusion is a common problem in obesity [23]. Additionally, obese patients may have poor lymphatic drainage that contributes towards tissue inflammation and leads to further limitation of tissue perfusion [24]. This limited blood flow in obese patients has been linked to an independent increase in the incidence of hypertension compared to non-obese populations [23].

Tissue penetration is an important determining factor in the effectiveness of any antibiotic. Given the poor tissue perfusion in obese patients, a lower tissue to serum ratio of ciprofloxacin is expected in obese patients than what appears in normal weight individuals [10, 25]. Limited tissue perfusion of antimicrobials in obese patients becomes more important in skin and soft-tissue infections, deep-seated infections such as necrotising pancreatitis and localised abscesses, pneumonia and surgical prophylaxis [26].

## Impaired Liver Function

Non-alcoholic fatty liver disease (NFLD) is a common complication of obesity. Obese patients are three times more likely to develop NFLD than non-obese patients [27]. Apart from metabolic complications associated with NFLD, studies have shown that NFLD can significantly affect the metabolism of various medications [28, 29]. The extent of the variability in drug metabolism in NFLD is dependent on the type of drug metabolising enzyme involved [28, 29].

Drugs that are metabolised via the CYP3A4 pathway are likely to have lower metabolic clearance in obese patients than in normal weight subjects [28]. On the contrary, drugs that are the substrate of CYP2E1 and undergo xanthine oxidase or N-acetyltransferase reactions have higher metabolic clearance in obese patients than in non-obese patients [28]. Limited information is available on the effects of obesity-related NFLD on the metabolism of antimicrobials. The majority of the information is available for drugs acting on the central nervous system, cardiovascular system and anti-cancer drugs [28, 29]. Voriconazole, a commonly used anti-fungal agent in clinical practice that is predominantly metabolised by the liver, has significantly lower clearance in obese patients than in normal weight individuals [30]. Macrolides and some triazole anti-fungals are metabolised by CYP3A4, with metabolism of these compounds likely to be reduced in obese patients also.

## Abnormal Renal Function

The kidney uses three individual yet interdependent processes to eliminate waste and excrete drugs from the body, namely glomerular filtration, tubular secretion and tubular re-absorption [31]. Although limited information is available regarding the effect of obesity on the tubular secretion and re-absorption, obesity has shown to increase the estimated glomerular filtration rate (eGFR) up to 62 % [32]. Given the relatively higher incidence of proteinuria and chronic kidney disease in obese patients than in normal weight individuals [33, 34], the possibility of reduced tubular functions cannot be ruled out in obese patients.

The significant changes in renal function observed in obese patients may lead to high renal clearance of antimicrobials that are predominantly cleared by the kidneys, such as vancomycin, aminoglycosides and daptomycin [11, 35, 36]. The mean vancomycin clearance rate in obese patients was found to be 2.5 times greater than in non-obese patients [11]. Similarly, a higher daptomycin renal clearance rate was observed in obese patients than in non-obese patients (1.01 vs. 0.70 L/h, respectively) [35]. Tubular secretion and subsequent renal clearance of ciprofloxacin were also higher in obese patients than in normal weight individuals (60 vs. 53.3 L/h, respectively) [10].

## Selection of an Antimicrobial Dosing Regimen in Obese Patients

The following section will outline various factors that should be considered when selecting an antibiotic regimen for obese patients, with several of these factors being equally important in the selection of antimicrobial regimen for non-obese patients. A summary of these factors is included in Table 1.1 for quick review and subsequent reference.

1. **Focus of infection and tissue penetration**

One of the important factors that determine the therapeutic effectiveness of antimicrobials is the ability of an agent to penetrate at the site of infection. This means that the focus of infection is an important consideration for dose estimation, and in some cases, the choice of an antimicrobial agent. For example, the concentration of vancomycin in various bodily fluids and tissues varies significantly, and such variation should be taken into consideration when selecting a particular dosing strategy [37]. Comparative studies of intermittent and continuous infusion have demonstrated that the trough concentration of vancomycin in cerebrospinal fluid was significantly higher (more than three times) in the continuous infusion group than in the intermittent group [37]. Similar limitations have been observed with other antimicrobials in the treatment of nosocomial pneumonia and intra-abdominal infections [9, 12, 38].

**Table 1.1** Summary of important factors in determining dose for antimicrobials in obese patients

| Factor | Impact on dosing decision | Examples of antimicrobials affected |
|---|---|---|
| Focus of infection and tissue penetration | Deep-seated infections such as meningitis and pneumonia are difficult to treat owing to poor antibiotic penetration. Antimicrobials with limited tissue penetration should be avoided | Gentamicin in the treatment of pneumonia and vancomycin in meningitis |
| Minimum inhibitory concentration (MIC) | Antimicrobials with higher MIC values within the sensitive range often require high doses. For some antimicrobials, this is not practical owing to their pharmacokinetics limitations. These antimicrobials will never attain a desirable serum concentration to MIC ratio; therefore, they should be avoided in obese patients | Ciprofloxacin in the treatment of infections caused by Enterobacteriaceae<br>MRSA infections where MIC of vancomycin is >1 μg/mL |
| Body size descriptor | A number of body size descriptors have been proposed for dosing antimicrobials in obese patients such as TBW, IBW, ABW, LBW, FFW and BSA. The limitations of these body size descriptors should be noted and their indiscriminate use may lead to inappropriate dosing decisions | TBW is routinely used for vancomycin although the majority of doses are capped at 2 g/dose. ABW was derived for aminoglycosides although it has been used for quinolones for no scientific reason |
| Renal function | Estimation of renal function is confusing owing to a number of equations being available that quantifies GFR and CrCl. All available equations either over- or under-estimate renal function in obese patients. Renal dose adjustment should be based on measured 24 h CrCl. Limited data supports the use of the C&G equation with $LBW_{2005}$ instead of with TBW or IBW. Importantly, the widely accepted Salazar-Corcoran equation significantly overestimates CrCl and may lead to substantially high incorrect doses in obese patients | A 200 kg 50 year old male who is 180 cm tall with a serum creatinine of 250 μmol/L will have a CrCl of >50 mL/min as per the Salazar-Corcoran equation and will receive no dose adjustment for the majority of antimicrobials. Applying the C&G equation using $LBW_{2005}$ will administer 25 mL/min and is more accurate to a serum creatinine of 250 μmol/L |

*MIC* Minimum inhibitory concentration; *MRSA* Methicillin-resistant *Staphylococcus aureus*; *TBW* Total body weight; *IBW* Ideal body weight; *ABW* Adjusted body weight; *LBW* Lean body weight; *FFW* Fat-free body weight; *BSA* Body surface area; *GFR* Glomerular filtration rate; *CrCl* Creatinine clearance; $LBW_{2005}$ LBW based on 2005 equation and C&G Cockcroft and Gault

Obesity is also an independent risk factor for infection, with obese individuals having a comparatively poorer clinical outcome in infections than their non-obese counterparts [26]. Additionally, obesity may limit the penetration of antimicrobials

in tissues [25], which means that the focus of infection becomes more important when choosing the antimicrobial regimen for obese patients. Therefore, antimicrobials with limited tissue penetration for particular clinical indications, such as aminoglycosides in pneumonia and vancomycin in meningitis, should be avoided in obese patients. However, if the use of a particular antibiotic is unavoidable, such as in the case of methicillin-resistant *Staphylococcus aureus* infection and vancomycin, alternative modes of dose administration (for example continuous infusion) should be employed to achieve better tissue penetration [37].

2. **Minimum Inhibitory Concentration**

Frequently a neglected parameter in antimicrobial dosing consideration is the minimum inhibitory concentration (MIC) of an antibiotic against the targeted pathogen. MIC values are often used to simplify the categorisation of antimicrobials as either susceptible or resistant. Nevertheless, clinical studies have shown differences in clinical outcomes within the susceptible range of different MIC values for vancomycin and colistin [39, 40].

A number of preferred pharmacodynamic indices have been proposed to maximise the effectiveness of antimicrobials such as the fraction of the time (*fT*) above the MIC ($fT > \text{MIC}$); the maximum plasma concentration (Cmax) and MIC ratio (Cmax/MIC); and the area under the curve (AUC) and MIC ratio (AUC/MIC) [41]. Given the significant physiological changes in obese patients mentioned earlier, attaining these pharmacodynamic indices is nearly impossible for pathogens in the higher range of MIC values. Where available, the specific MIC of a pathogen or the usual range of MIC values for the pathogen in a given institute needs to be considered when selecting an antimicrobial as well as determining its dose. For example, treatment failure rates for blood stream infections caused by Enterobacteriaceae were significantly higher in patients receiving ciprofloxacin and had higher MIC values within the sensitive range [42]. Therefore, choosing ciprofloxacin in obese patients for the treatment of similar infections would be inappropriate and more potent agent should be considered in such cases.

3. **Body size descriptors and weight based dosing**

BMI is the most commonly used body size descriptor to define obesity. However, a number of various body size descriptors have been proposed to guide dosing of antimicrobials including body surface area (BSA); ideal body weight (IBW); adjusted body weight (ABW); fat-free weight (FFW); lean body weight (LBW) and total body weight (TBW) [6]. BSA is primarily used to estimate dosing of chemotherapeutic agents and has a limited role in antimicrobial dosing [43].

IBW is based on the height of an individual and a direct correlation between individual height and weight is assumed. As noted by Pai [6], there are several limitations in using IBW as a dosing weight, and it should be avoided in calculating drug doses. In a previous study, the use of IBW was shown to produce inaccurate dosing estimates in an obese patient that led to the development of the ABW equation for dosing gentamicin [20]. Nevertheless, IBW is often used to calculate doses for acyclovir and colistin, often to limit the toxicity potential of these narrow

therapeutic index antimicrobials [44]. Given the lack of physiological underpinning for IBW, it is uncertain if IBW-based dosing may affect clinical outcomes with these drugs in obese patients.

ABW is a derivative of IBW that adds the difference between the IBW and TBW after multiplying it by a numerical factor for weight-based dosing of antimicrobials [6]. The numerical factor depends on the particular antimicrobial; for example, the most common factor for aminoglycosides is 0.4 whereas 0.45 is used for ciprofloxacin [43]. Conflicting evidence exists regarding the weight-based dosing of other antimicrobials using ABW; therefore, this body weight descriptor should not be uniformly applied to other antimicrobials [43].

LBW and FFW aim to quantify the weight of the muscles and bone while eliminating the weight contributed by the fat component. Technically speaking, FFW and LBW are computed differently, although they are closely related to each other and have similar values in most cases [6]. Some experts have argued for the routine use of LBW in estimating antimicrobial dosing for obese patients while others disagree with this approach [5, 9]. LBW has traditionally been calculated using an equation derived from a study that comprised a maximum body weight of 125 kg; therefore, estimating LBW in obese patients using this equation results in erroneous results when a patient weighs greater than 125 kg [45]. The more recent equation of LBW ($LBW_{2005}$) addresses this limitation [45]. LBW has been advocated for the estimation of anaesthetics and is seldom used for the calculation of the initial dose of antimicrobials [16].

TBW has been utilised for the estimation of vancomycin dose in obese patients, although the majority of studies have capped the dose to a particular maximum dose (frequently 2 g) [46, 47]; therefore, technically speaking, the approach applied by these studies contradicts the TBW approach. Given the widespread routine use of vancomycin serum drug concentration monitoring in clinical practice, subsequent adjustment of vancomycin doses is based on the observed levels in a given patient. There is some data to support the use of TBW in estimating doses for antifungal agents (fluconazole and amphotericin B) [43, 48], as well as daptomycin [35].

## 4. **Estimating renal function in obese patients**

A significant proportion of antimicrobials are cleared from kidneys; therefore, estimating renal functions to estimate drug clearance is a routine practice in clinical settings. The Modified Diet in Renal Diseases (MDRD) equation is the most commonly used method for estimating renal function in clinical settings [49]. The majority of pathology departments globally automatically report eGFR using the MDRD equation. While the MDRD method has been routinely accepted to quantify eGFR, little information is available about the relative drug dosing adjustment (including antimicrobials) based on the MDRD equation [50]. This is because the Cockcroft and Gault (C&G) equation has been traditionally used to estimate creatinine clearance (CrCl) and subsequent dose adjustment of antimicrobials based on a particular range of CrCl values [50].

The development of the C&G equation was based on healthy individuals with normal body weight and, as such, using either IBW or TBW can significantly

under- or over-estimate CrCl values in obese patients [50]. A number of alternatives to the C&G equation are available to estimate CrCl in obese patients, with the most commonly used being the Salazar-Corcoran equation that is based on the obese rat model being extrapolated to humans [51]. The majority of available equations provide an estimate of CrCl; therefore, the best method to estimate CrCl in clinical practice is to measure the 24 h urine creatinine value and calculate the real-time CrCl in a given patient. Nevertheless, it is often difficult and time consuming in most obese patients and clinicians often have to rely on estimates using the available equations instead.

Demirovic et al. [50] reported one of the most comprehensive analysis of several available equations used to estimate CrCl in morbidly obese patients. The authors measured 24 h urinary CrCl in 54 obese patients (BMI of 50.5 ± 12.6 kg/m$^2$) and compared the results with the estimated CrCl from the MDRD, Salazar-Corcoran and C&G equations. Weight descriptors included in the C&G equation were TBW, IBW, ABW (using a correctional factor of 0.4), FFW and $LBW_{2005}$ [50]. The authors discovered that using the MDRD equation and CrCl with IBW underestimated the CrCl, whereas the Salazar-Corcoran equation and TBW or ABW in the C&G equation overestimated the CrCl in obese patients. FFW or LBW substituted in the C&G equation provided the least unbiased assessment of CrCl [50]. Given the complexity of measuring FFW in clinical practice and the availability of a simple equation to measure $LBW_{2005}$, the use of the C&G equation using $LBW_{2005}$ is the most reliable and practical method to measure CrCl in obese patients.

## Conclusion

In conclusion, this chapter has introduced several important factors that should be considered when dosing decisions of antimicrobials in obese patients are made. Some of these factors are more relevant to the initial dose selection, whereas others are more relevant to the ongoing maintenance dose. For example, the initial dose (or loading dose for some antimicrobials) is highly dependent on V, which is often increased in obese patients. However, a maintenance dose is highly dependent on the drug clearance rate. It is extremely likely that clinicians will use the higher end of the licensed doses of antimicrobials or at times, higher than the maximum recommended dose when treating obese patients. Therefore, close observation of dose-related adverse effects is crucial for the monitoring and subsequent adjustment of antimicrobials in these scenarios. Given the direct relationship between the MIC and clinical effectiveness of antimicrobials, it is important that antimicrobials that are at the higher end of the susceptibility MIC range be avoided in obese patients. This is because high doses of antimicrobials will often fail to achieve the required bactericidal tissue concentration in these patients with an unjustified risk of adverse effects. Where uncertainty exists, and reliable assays are available, therapeutic drug monitoring should be utilised to enable optimised dosing.

## References


1. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–63.
2. World Health Organisation. Obesity and overweight. Fact sheet no. 311 (updated January 2015, 30 January 2015). Available from: http://www.who.int/.
3. Vogtle LK. Measuring body composition: the limitations of body mass index. Dev Med Child Neurol. 2015;57(11):991–2.
4. Organisation WH. Prevelance world map and statistics of Obesity, age 18+ 2014 data 2015 (cited 2015 27/10/2015). Available from: http://gamapserver.who.int/gho/interactive_charts/ncd/risk_factors/obesity/atlas.html.
5. Falagas ME, Karageorgopoulos DE. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet. 2010;375(9710):248–51.
6. Pai MP. Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. Pharmacotherapy. 2012;32(9):856–68.
7. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes. 2013;37(3):333–40.
8. Muscedere JG, Shorr AF, Jiang X, Day A, Heyland DK, Canadian Critical Care Trials G. The adequacy of timely empiric antibiotic therapy for ventilator-associated pneumonia: an important determinant of outcome. J Crit Care. 2012;27(3):322 e7–14.
9. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy. 2007;27(8):1081–91.
10. Allard S, Kinzig M, Boivin G, Sorgel F, LeBel M. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Ther. 1993;54(4):368–73.
11. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol. 1998;54(8):621–5.
12. Muzevich KM, Lee KB. Subtherapeutic linezolid concentrations in a patient with morbid obesity and methicillin-resistant Staphylococcus aureus pneumonia: case report and review of the literature. Ann Pharmacother. 2013;47(6):e25.
13. Corcoran GB, Salazar DE, Schentag JJ. Excessive aminoglycoside nephrotoxicity in obese patients. Am J Med. 1988;85(2):279.
14. Gauthier TP, Wolowich WR, Reddy A, Cano E, Abbo L, Smith LB. Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. Antimicrob Agents Chemother. 2012;56(5):2392–6.
15. Davies SW, Efird JT, Guidry CA, Dietch ZC, Willis RN, Shah PM, et al. Vancomycin-Associated Nephrotoxicity: The Obesity Factor. Surg Infect (Larchmt). 2015.
16. Ortiz VE, Kwo J. Obesity: physiologic changes and implications for preoperative management. BMC Anesthesiol. 2015;15:97.
17. Waki M, Kral JG, Mazariegos M, Wang J, Pierson RN, Jr., Heymsfield SB. Relative expansion of extracellular fluid in obese vs. nonobese women. Am J Physiol. 1991;261(2 Pt 1):E199–203.
18. Chung EK, Cheatham SC, Fleming MR, Healy DP, Shea KM, Kays MB. Population pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese and nonobese patients. J Clin Pharmacol. 2015;55(8):899–908.
19. Pai MP, Cojutti P, Pea F. Pharmacokinetics and pharmacodynamics of continuous infusion meropenem in overweight, obese, and morbidly obese patients with stable and unstable kidney function: a step toward dose optimization for the treatment of severe gram-negative bacterial infections. Clin Pharmacokinet. 2015;54(9):933–41.
20. Sketris I, Lesar T, Zaske DE, Cipolle RJ. Effect of obesity on gentamicin pharmacokinetics. J Clin Pharmacol. 1981;21(7):288–93.
21. Sturm AW, Allen N, Rafferty KD, Fish DN, Toschlog E, Newell M, et al. Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. Pharmacotherapy. 2014;34(1):28–35.

22. Pai MP, Cojutti P, Pea F. Levofloxacin dosing regimen in severely morbidly obese patients (BMI >/= 40 kg/m(2)) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. Clin Pharmacokinet. 2014;53 (8):753–62.
23. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, et al. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. Circulation. 2008;118(9):968–76.
24. Brook RD, Bard RL, Bodary PF, Eitzman DT, Rajagopalan S, Sun Y, et al. Blood pressure and vascular effects of leptin in humans. Metab Syndr Relat Disord. 2007;5(3):270–4.
25. Hollenstein UM, Brunner M, Schmid R, Muller M. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. Int J Obes Relat Metab Disord. 2001;25(3):354–8.
26. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes (Lond). 2013;37(3):333–40.
27. Wei JL, Leung JC, Loong TC, Wong GL, Yeung DK, Chan RS, et al. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy. Am J Gastroenterol. 2015;110(9):1306–14.
28. Brill MJ, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN, Knibbe CA. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet. 2012;51(5):277–304.
29. Merrell MD, Cherrington NJ. Drug metabolism alterations in nonalcoholic fatty liver disease. Drug Metab Rev. 2011;43(3):317–34.
30. Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother. 2011;55(6):2601–5.
31. Hall JE, Guyton AC. Guyton and Hall textbook of medical physiology. 2011.
32. Pai MP. Estimating the glomerular filtration rate in obese adult patients for drug dosing. Adv Chronic Kidney Dis. 2010;17(5):e53–62.
33. Alicic RZ, Patakoti R, Tuttle KR. Direct and indirect effects of obesity on the kidney. Adv Chronic Kidney Dis. 2013;20(2):121–7.
34. Amann K, Benz K. Structural renal changes in obesity and diabetes. Semin Nephrol. 2013;33 (1):23–33.
35. Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. J Clin Pharmacol. 2005;45(1):48–56.
36. Velissaris D, Karamouzos V, Marangos M, Pierrakos C, Karanikolas M. Pharmacokinetic changes and dosing modification of aminoglycosides in critically ill obese patients: a literature review. J Clin Med Res. 2014;6(4):227–33.
37. Giuliano C, Haase KK, Hall R. Use of vancomycin pharmacokinetic–pharmacodynamic properties in the treatment of MRSA infections. Expert Rev Anti-infective Ther. 2010;8 (1):95–106.
38. Panidis D, Markantonis SL, Boutzouka E, Karatzas S, Baltopoulos G. Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia. Chest. 2005;128(2):545–52.
39. Chen SY, Liao CH, Wang JL, Chiang WC, Lai MS, Chie WC, et al. Method-specific performance of vancomycin MIC susceptibility tests in predicting mortality of patients with methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2014;69 (1):211–8.
40. Zaidi STR, Al Omram S, Al Aithan ASM, Al Sultan M. Efficacy and safety of low-dose colistin in the treatment for infections caused by multidrug-resistant gram-negative bacteria. J Clin Pharm Ther. 2014;39(3):272–6.
41. Gillespie EL, Kuti JL, Nicolau DP. Pharmacodynamics of antimicrobials: treatment optimisation. Expert Opin Drug Metab Toxicol. 2005;1(3):351–61.
42. Zelenitsky SA, Ariano RE. Support for higher ciprofloxacin AUC 24/MIC targets in treating Enterobacteriaceae bloodstream infection. J Antimicrob Chemother. 2010;65(8):1725–32.

43. Wurtz R, Itokazu G, Rodvold K. Antimicrobial dosing in obese patients. Clin Infect Dis. 1997;25(1):112–8.
44. Payne KD, Hall RG 2nd. Dosing of antibacterial agents in obese adults: does one size fit all? Expert Rev Anti Infect Ther. 2014;12(7):829–54.
45. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051–65.
46. Denetclaw TH, Yu MK, Moua M, Dowling TC, Steinke D. Performance of a divided-load intravenous vancomycin dosing strategy for obese patients. Ann Pharmacother. 2015;49 (8):861–8.
47. Reynolds DC, Waite LH, Alexander DP, DeRyke CA. Performance of a vancomycin dosage regimen developed for obese patients. Am J Health Syst Pharm. 2012;69(11):944–50.
48. Cohen LG, DiBiasio A, Lisco SJ, Hurford WE. Fluconazole serum concentrations and pharmacokinetics in an obese patient. Pharmacotherapy. 1997;17(5):1023–6.
49. Levey AS, Greene T, Schluchter MD, Cleary PA, Teschan PE, Lorenz RA, et al. Glomerular filtration rate measurements in clinical trials. Modification of Diet in Renal Disease Study Group and the Diabetes Control and Complications Trial Research Group. J Am Soc Nephrol. 1993;4(5):1159–71.
50. Demirovic JA, Pai AB, Pai MP. Estimation of creatinine clearance in morbidly obese patients. Am J Health Syst Pharm. 2009;66(7):642–8.
51. Salazar DE, Corcoran GB. Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med. 1988;84(6):1053–60.

# Chapter 2
# Penicillins

**Iain J. Abbott and Kelly A. Cairns**

**Abstract** Penicillins are among the most widely used class of antibiotics, utilised for a wide variety of clinical indications, including critical illnesses and sepsis. Clinical efficacy and the prevention of the emergence of resistance are critically dependent upon the correct dosing strategy in order to meet the required time-dependent pharmacodynamic target. Penicillins mainly experience increases in volume of distribution and renal clearance in obese patients, such that standard doses may not be sufficient to achieve target attainment. The dosing recommendation for penicillin antibiotics in obesity is, however, complex and lacking clinical evidence. This chapter will review the current literature and make suggestions for altered dosing for commonly prescribed penicillin antibiotics. Fortunately, given the relative safety profile of the penicillin antibiotics, greater flexibility at upper range of the dosing schedule, or frequency of administration, is available. Strategies such as extended and continuous infusions are explored, together with reference to front-loading dosing, therapeutic drug monitoring and Bayesian estimation techniques and software to promote individualised drug dosing. Critical illness in obese patients warrants careful consideration of penicillin dosing and must take into consideration the pharmacokinetic and pharmacodynamic changes and altered targets.

**Keywords** Penicillin · Obesity · Extended infusion · Continuous infusion · Pharmacokinetics · Pharmacodynamics

I.J. Abbott (✉)
Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia
e-mail: iainabbott@gmail.com

K.A. Cairns
Department of Pharmacy, Alfred Hospital, Melbourne, Australia



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_2

## Introduction

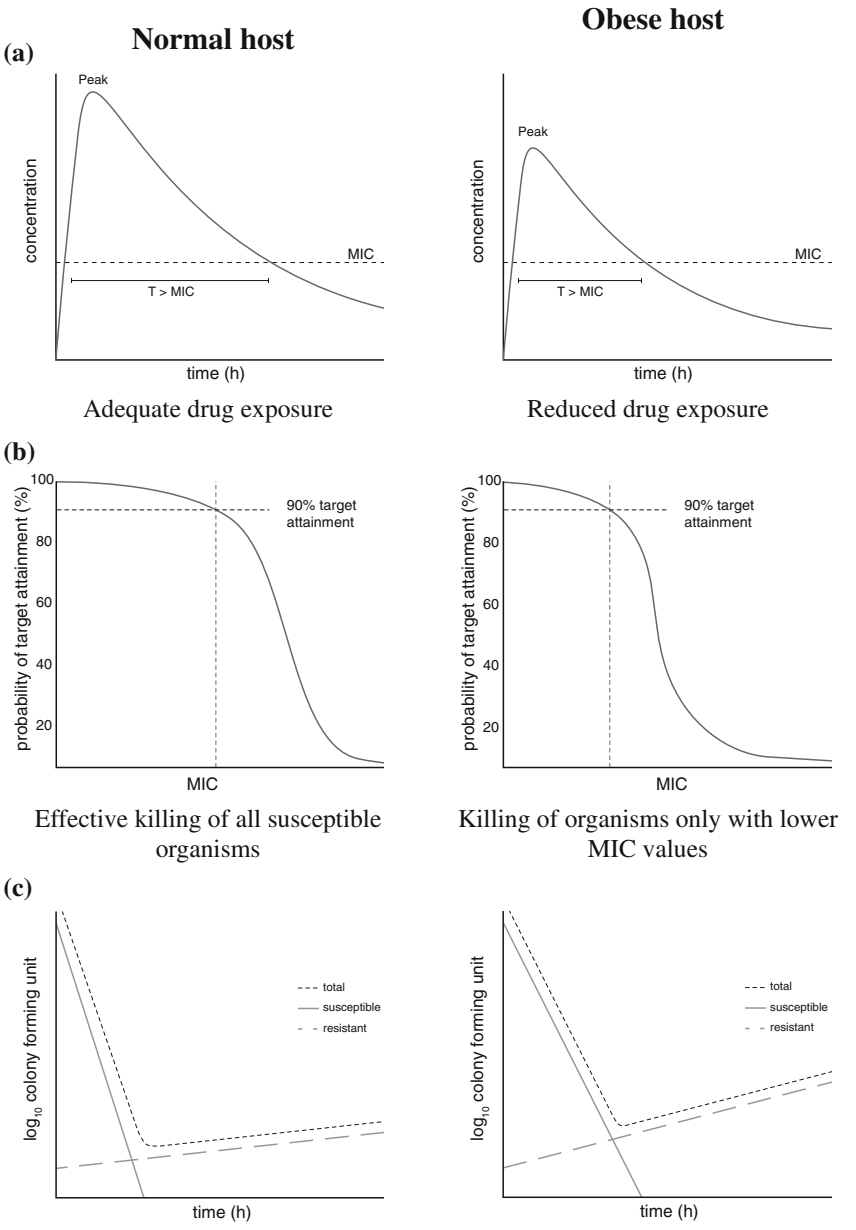
Penicillins represent the oldest class of antibiotics, since their discovery in 1928, and have been in clinical use since the 1940s. Over the years, this class of beta-lactams has expanded from the narrow spectrum penicillins, to combinations with beta-lactamase inhibitors, providing a broad spectrum of activity [1]. Narrow spectrum penicillins, such as intraveneous benzylpenicillin (penicillin G), intramuscular procaine penicillin and benzathine penicillin, and oral phenoxymethylpenicillin (penicillin V), are mainly active against Gram-positive organisms, but are inactivated by beta-lactamase enzymes. Despite their narrow spectrum, these penicillins remain the treatment of choice for many infections, including *Streptococcus pyogenes*, pneumococcal pneumonia, and syphilis. Antistaphylococcal pencillins, dicloxacillin and flucloxacillin, are stable to beta-lactamases, and are the standard of care for infections caused by methicillin-susceptible *Staphylococcus aureus*. The aminopenicillins, amoxycillin and ampicillin, have a relatively narrow spectrum of activity against susceptible Gram-negative pathogens, such as *Escherichia coli*, which is the most common urinary tract pathogen, but are again inactivated by strains that produce beta-lactamase enzymes. Broad-spectrum penicillins, piperacillin and ticarcillin, have an expanded spectrum that includes *Pseudomonas aeruginosa* species. The combination of a penicillin antibiotic and a beta-lactamase inhibitor, such as clavulanate and tazobactam, which in themselves have little inherent antibacterial activity, inhibit the enzymes produced by a variety of Gram-positive, Gram-negative and anaerobic bacteria. In combination, amoxycillin and ticarcillin with clavulanate, and piperacillin with tazobactam, the spectrum of activity is significantly expanded. Piperacillin-tazobactam (TZP) is currently a standard of care as empiric therapy for a number of critical infections, such as febrile neutropenia [2, 3], ventilator associated pneumonia [4], and severe diabetic foot infections [5]. All currently available penicillin antibiotics are vulnerable to expanded resistance mechanisms, either newly acquired or intrinsic in some organisms. Extended-spectrum beta-lactamases (e.g. $bla_{\text{CTX-M}}$), cephalosporinases (e.g. AmpC-type $bla_{\text{CMY}}$) and carbapenamases (e.g. metallo beta-lactamases, $bla_{\text{KPC}}$, and $bla_{\text{OXA}}$) all potentially inactivate antibiotics in the penicillin class. Despite their longstanding and widespread use, very little information is available about dosing in patients with an increased body-mass-index (BMI) for the class as a whole. Given that the penicillin class of antibiotics are frequently used in critical illness, where time to adequate antibiotic exposure is critical for survival, more studies are required to further understand the true impact of obesity on the pharmacokinetic/pharmacodynamic (PK/PD) targets, together with clinical outcomes.

## Pharmacodynamic Target

Penicillins, like other beta-lactam antibiotics, display time-dependent pharmacodynamics (PD) (see Fig. 2.1, panel a). The antibiotic activity is due to inhibition of bacterial cell wall synthesis, which occurs over time to result in a relatively slow bactericidal action [6]. Bacterial kill and efficacy correlates best with the length of time ($fT$) that free (unbound) serum concentrations of the drug exceeds the organism's minimum inhibitory concentration (MIC) (i.e. $fT_{>MIC}$) [7]. Maximal organism kill occurs when drug concentrations are maintained at four-times the MIC [8]. The target for penicillin antibiotics is $fT_{>MIC}$ of roughly 50 % of the dosing schedule [9]. A post antibiotic effect is seen against Gram-positive organisms, but is minimal against Gram-negatives [10], thereby suggesting Gram-negative infections would benefit from a higher percentage $fT_{>MIC}$. Penicillins are also affected by an inoculum effect, such that infections with a high bacterial density require higher antibiotic concentrations, for longer durations, to inhibit growth [10]. In the setting of concurrent immunosuppression or critical illness a $fT_{>MIC}$ target approaching 100 % has been suggested [11]. In clinical practice, the MIC of the infecting organism is often not known at the time antibiotics are started, such that empiric dosing is required to cover organisms with a range of MICs, including those at the higher end of the susceptible range. Adequate drug exposure is also critical to prevent the emergence of resistance within an organism population [12], factoring in also the impact of the inoculum size, the duration of therapy and the presence of immune dysfunction [13].

## Pharmacokinetic Changes in Obesity

Penicillins are hydrophilic antibiotics that are essentially eliminated by renal clearance, have a low volume of distribution (V) and a lower intracellular and tissue penetration [14]. The summary of expected changes in the PK of penicillins to be seen in obesity is presented in Table 2.1. Penicillins mainly experience increases in V and renal/creatinine clearance (CrCl) in obese patients, suggesting that standard doses may not be sufficient to achieve target attainment (50 % $fT_{>MIC}$), especially for bacteria with higher MICs (see Fig. 2.1, panel b). Despite applying adjusted body weight (ABW) and/or lean body weight (LBW) as size descriptors for dose adjustment for hydrophilic medications, an assessment of individual's calculated BMI and how that relates to the changes in the PK of the penicillins is more complex. Individuals with a raised BMI will not only have an increase in adipose tissue but also variable amounts of concurrent increases in lean muscle weight and blood volume. An elite athlete with a BMI $\geq$ 30 kg/m$^2$, for example, who has a large proportional increase in lean muscle mass, will have vastly different penicillin antibiotic PK changes compared with an individual with the same BMI but whose excess weight is predominantly made up of an increase in adipose tissue. This




Adequate drug exposure

Reduced drug exposure

Effective killing of all susceptible organisms

Killing of organisms only with lower MIC values

Effective suppression of resistant subpopulation by rapid kill and normal functioning immune system

Potential for re-growth of resistant sub-population by slower kill and obesity-related impaired immune system

◀ **Fig. 2.1** Schematic representation of the potential changes in PK/PD seen in obesity. Figure adapted from [9, 11]. *Panel a* Time-concentration curves. In the obese host there can be a reduced peak concentration due to the increased V, although obesity-related reduction in protein binding may counteract this for heavily protein-bound drugs such as di/flucloxacillin. Augmented renal/creatinine clearance accounts for a steeper clearance curve. Both factors impact on the $fT_{>MIC}$. *Panel b* MIC-target attainment curves. There is a quicker drop off in the percentage target attainment in the obese host as the organism becomes more resistant (i.e. increasing MIC). *Panel c* Time-organism re-growth curves. A theoretical risk of the emergence of a resistant sub-population during antibiotic treatment course. This is not only impacted upon by the reduction in $fT_{>MIC}$ but also the impact of immune dysregulation seen in obesity that would normally assist the antibiotic in organism kill

**Table 2.1** Overview of penicillins ppharmacokinetic (PK) changes in obesityObesity

| PK parameter | Effect of obesity |
|---|---|
| *Absorption* | |
| Oral<br>Intramuscular<br>Intravenous | Minimal change<br>Avoid<br>No change |
| *Distribution* | |
| Protein binding<br>Volume of distribution | Reduced[a]<br>Increased |
| Metabolism | No change |
| Excretion | Increased[b] (augmented renal/creatinine clearance) |

[a]Results in an increase in the unbound penicillin concentrations, contributing to increased clearance

[b]Occurs in the absence of co-morbidities impacting on renal function

differentiation is important when dosing penicillins given the potential that the degree of increase in V may be unrecognized, which in turn has the potential to result in decreased plasma drug concentrations.

## Review of Existing Literature

There is a dearth of clinical PK/PD studies examining dosing of penicillin antibiotics in obesity, and much of the more recent literature deals only with TZP (see Table 2.2). When compared to parameters in reference populations [1, 15, 16], there are consistent reports of increases in V and CrCl in obese subjects who have been administered TZP. In the critically ill cohort, however, it seems that severe sepsis alters the PK/PD more than obesity alone [17]. Similarly, renal function and the use of continuous renal replacement therapy have a large impact on PK/PD targets. In general, the doses of TZP studied were either at the upper end of the recommended dosing schedule (e.g. 4.5 g 6-hourly, 30 min infusion), or utilised extended infusions over 4 h.

**Table 2.2** Piperacillin-tazobactam (TZP) pharmacokinetic/pharmacodynamic (PK/PD) changes in obesity: review of the literature

| Study | No. | BMI (mean) | V | CrCl | t½ | Dose (infusion time) | Comments |
|---|---|---|---|---|---|---|---|
| *Reference population* [15, 16, 56–58] | | | 8.2–15.8 L | 8.0–14.5 L/h | 0.6–1.1 h | 4.5 g (30 min) | |
| Sturm et al. (2014) [59] | 9 | 57 kg/m$^2$ | 31.0 L | 6.0 L/h | 3.7 h | 4.5 g Q6H (30 min) | Surgical ICU patients. Despite altered PK, use of high-dose TZP was appropriate (%$T_{>MIC}$ 100 % for all patients, MIC = 16 mg/L) |
| Hites et al. (2014) [58] | 31 | 36 kg/m$^{2a}$ | 31.4 L | 8.9 L/h | 2.2 h | 4.5 g Q8H (30 min) | Non-critically ill patients. Augmented renal/creatinine clearance (CrCl > 80 ml/min) responsible for low serum concentrations (V 26.9 L, CrCl 13.1 L/h, t½ 1.5 h). Standard dose was inadequate to treat less susceptible bacteria |
| Hites et al. (2013) [17] | 49 | 40 kg/m$^2$ | 29.6 L | 5.4 L/h | 3.2 h | Daily dose 16 g (na) | Critically ill patients; obese vs. non-obese. No differences in PK. Only 47 % TZP drug levels were adequate. CRRT a risk factor for overdosage. CrCl: CRRT 4.5 L/h; without CRRT 10 L/h |
| Cheatham et al. (2013) [60] | 14 | 52.3 kg/m$^2$ | 33.4 L | 13.7 L/h | 1.9 h | 4.5 g/6.75 g Q8 H (4 h) | Hospitalized patients. Extend infusions provide target attainment of >90 % for pathogens with MICs $\leq$ 16 ug/mL |
| Zakrison et al. (2012) [49] | 23 | 37 kg/m$^{2b}$ | na | na | na | 3.375 g Q6 H (na) | Complicated intra-abdominal infections. Post hoc analysis. Trend towards a lower cure rate in the high BMI group receiving TZP |
| Demam et al. (2012) [61] | 1 | 55 kg/m$^2$ | 33 L | 21 L/h | 1.1 h | 4.5 g Q6H (30 min) | Case report. Surgical site infection. PK/PD targets for a MIC 8 mg/L: %$T_{>MIC}$ 60 % and %$T_{>4xMIC}$ 25 % |
| Newman et al. (2007) [56] | 1 | 50 kg/m$^2$ | 54.3 L | 26.6 L/h | 1.4 h | 3.375 g Q4H (30 min) | Case report. Cellulitis. Achieved piperacillin %$T_{>MIC}$ 90.9 % for the cultured *P. aeruginosa* with MIC 8.0 mg/L |

*V* volume of distribution; *CrCl* clearance; t½ half-life; *MIC* Minimum inhibitory concentration; *BMI* Body mass index

[a]Includes 14 patient who received meropenem and 11 patients who received cefepime

[b]Includes 32-patients who were randomised to receive ertapenem

For penicillin antibiotics that have been administered via the intravenous route, the impact of obesity on absorption should be minimal. The impact of obesity on oral penicillin absorption is also largely unaffected by obesity [18, 19]. Miskowiak et al. determined that in a small cohort of eight female patients, the absorption of phenoxymethypenicillin was no different before and three months after gastroplasty [20]. The absorption of phenoxymethylpenicillin and flucloxacillin is impaired by the presence of food in the stomach, and patients should be appropriately counseled by their pharmacist on the correct administration. For the remaining oral penicillin antibiotics, the increased splanchnic blood flow and delayed gastric emptying should also have minimal effects on absorption [21, 22]. Intramuscular administration represents a small proportion of penicillin administration. Where possible, the intramuscular administration of penicillins, such as benzathine penicillin and procaine penicillin, should be avoided in obese patients. Inadvertent administration of penicillin antibiotics into subcutaneous tissue, also known as 'intralipomatous' injections [23], may cause pain, altered absorption kinetics and potential tissue necrosis. General recommendations for tissue damage associated with the extravasation of injectable medications include those with a pH below 5.5 or greater than 8.5. The pH of both benzathine pencillin and procaine penicillin is reported to be between 5 and 7.5 [24].

The impact of obesity on the distribution of penicillin antibiotics represents a complex dilemma and is dependent on a number of variables. Penicillin antibiotics are generally hydrophilic [19, 25] and their V is generally low [26]. As such, they have poor distribution into adipose tissue [19]. Excess weight associated with obesity also includes increased lean mass to carry the adipose tissue thereby, providing an increased V for penicillin drugs [18, 19]. Kampmann et al. [27] reported a higher V for ampicillin in a small cohort of patients prior to gastric bypass surgery (0.60 L/kg, in patients with an average weight of 131 kg) compared to the same patients one year later when they were on average 44 kg lighter (V of 0.41 L/kg). Yuk et al. [28] measured nafcillin serum levels in a single morbidly obese (162 kg) endocarditis patient, and also identified an increased volume of distribution. Based on this, the authors were able to provide nafcillin dosing recommendations in obese patients. The predicted proportion of plasma protein binding of the penicillin antibiotics in the standard population varies markedly from 20 % for ampicillin to up to 93 % for flucloxacillin, although there are significant differences between measured and predicted unbound drug concentrations for the highly protein-bound beta-lactams [29]. The increased levels of lipoproteins, cholesterol and free fatty acids observed in obese patients has the potential to bind to serum proteins, such as albumin [19]. Suh et al. demonstrated that high levels of free fatty acids significantly reduced the protein binding of dicloxacillin, but increased the protein binding of benzylpenicillin [30]. As the free concentration of drug is responsible for therapeutic effects, a reduction in the availability of albumin increases the free concentration of the penicillin. In this previous work by Suh et al. there was a fivefold increase in the free dicloxacillin fraction and a 50 % reduction in the free fraction of benzylpenicillin observed [30]. The increase in free fraction of a protein-bound antibiotic will increase the peak penicillin concentration, but more

importantly, will increase the amount of drug available for renal clearance. Given the time-dependent efficacy of penicillins, decreased protein binding has the potential to reduce target attainment of adequate $\%fT_{>MIC}$.

It is recognized that obese patients have a higher hepatic clearance of drugs due to increased glucuronidation and the activity of specific cytochrome P450 enzymes [31]. In particular, an increase in CYP2E1, CYP2C9, CYP2D6 and CYP2C19 enzyme activity and a reduction in CYP3A4 has been reported [18, 31]. The involvement of the cytochrome P450 enzyme system is thought to be minimal for penicillin antibiotics. Most penicillins are excreted by the kidneys as intact molecules, with only a minor degree of metabolism [26, 32]. Van Seane et al. [31] also report the potential of impairment of hepatic antimicrobial clearance due to hepatic steatosis in late obesity, which is of minimal impact in the metabolism of penicillins. Hepatic steatosis and diabetes does, however, contribute to the risks of drug induced liver injury (DILI) [33, 34]. Within the penicillin class, flucloxacillin and amoxicillin-clavulanate are the agents most commonly associated with DILI, where there are additional risks reported, including being female, being over 55 years of age and having a human leukocyte antigen (HLA)-B*5701 genotype for flucloxacillin, and HLA-A*3002 and B*1801 for amoxicillin-clavulanate [33–36].

Penicillins are primarily excreted through the kidney and are revolved largely unchanged [26]. Beta-lactamase inhibitors (clavulanate and tazobactam) are also excreted by the kidneys, but to a lesser extent, especially that of clavulanate [1]. Renal clearance is directly influenced by V, renal blood flow and glomerular filtration rate (GFR). Renal clearance can be increased because of greater kidney mass and global filtration, as demonstrated in obese kidney donors who have been shown to have significantly higher glomerular planar surface area compared to that of non-obese donors [37, 38]. Conversely, renal clearance can be decreased because of chronic kidney insufficiency due to concurrent hypertension or diabetic nephrophathy [39, 40]. In the absence of comorbid conditions, GFR can be increased by approximately 62 % in obesity [18]. Accurate measurements, however, with existing equations to estimate GFR, especially in the setting of augmented renal clearance (ARC), are limited [41–44].

Obesity increases morbidity and mortality through multiple effects, including a reduction in immune responses, leading to an increased risk of a wide range of infections, including postoperative and other nosocomial infections, as well as the development of serious complications from common infections [45]. The specific impact of obesity on clinical antibiotic treatment failure is less well established. In a historical cohort study, where 16.0 % received amoxicillin and 8.8 % received phenoxymethylpenicillin, obesity was a significant risk factor for antibiotic treatment failure, after accounting for other potential confounding variables [46]. The role of penicillin antibiotics in surgical prophylaxis, where adequate tissue concentrations of drug are critical, is also limited and the poor penetration of penicillins into adipose tissue could be of concern [47]. Gulluoglu et al. [48] demonstrated the successful administration of 1 g of intravenous ampicillin-sulbactam as a pre-operative prophylaxis for breast cancer surgery in patients with a BMI $\geq$ 25 kg/m$^2$, and showed a significant decreased in the rate of surgical site

infection compared to placebo (65 % reduction). In regard to the studies examining TZP administration in obesity, few studies also collected clinical outcome data. Zakrison et al. [49] reported, in a post hoc analysis, a reduced response rate in complicated intra-abdominal infections in patients with a BMI $\geq$ 30 kg/m$^2$ who received TZP (response rate 65 % compared with 86 % for patients with a BMI < 30 kg/m$^2$). More clinical outcome studies with PK/PD data are warranted.

Increasing antimicrobial resistance is a significant challenge to treating clinicians and represents a global problem. What is not known, however, is whether the obese cohort also have a greater tendency for the emergence of resistance while on therapy due to their altered PK/PD and relative immune dysfunction related to obesity (see Fig. 2.1, panel c) [9, 12, 13, 45]. One study, which examined the risk factors for postoperative mediastinitis due to methicillin-resistant *S. aureus* (MRSA), found that obesity was an independent predictor for infection with methicillin-sensitive *S. aureus*, only diabetes, female gender and age >70 years were found to be independent predictors for MRSA [50]. Despite this, adequate penicillin drug exposure, for the shortest effective duration, is paramount for suppressing the emergence of the resistant sub-population [12].

## Recommendations

The dosing recommendation for penicillin antibiotics in obesity is complex and lacking clinical evidence. The PK changes of antibiotics in obesity have been likened to those seen in septic patients [31]. In the absence of controlled trials to provide clear dosing recommendations for penicillin antibiotics in obese patients, extrapolation of dosing evidence in sepsis is generally required. Fortunately, given the relative safety profile of the penicillin antibiotics, greater flexibility at upper range of the dosing schedule, or in the frequency of administration, is available.

An accurate assessment of renal function is paramount, given that there may be normal renal function, ARC, or renal insufficiency. When classified as obese, the proportion of the increased BMI that represents increased lean muscle mass, as well as adipose tissue, is important when predicting the impact on V. In the obese patient in ICU, the concurrent use of organ support, such as continuous renal replacement therapy, will further impact upon the dose required [51, 52]. Although additional supports, such as extracorporeal membrane oxygenation (ECMO), does not seem to significantly impact specifically on TZP levels [53], they could impact on more highly protein bound penicillin drugs, such as flucloxacillin, which are prone to sequestration in ECMO circuits [54]. Underlying co-morbid conditions, such as surgery, trauma, burns, and immune dysfunction for example, will further alter the PK via changes in cardiac output and fluid balance, development of ARC, and immune response to infection. Finally, the specific infecting pathogen(s), the MIC and the site of infection will impact upon the required dosing schedule.

Despite the limitations in published data and clinical evidence, the following recommendations can be made in regard to dosing penicillin antibiotics in patients with a BMI in the obese range ($\geq$30 kg/m$^2$).

- Dosing should be at the upper end of recommended doses, or increased frequency of dosing, such that the highest effective dose that can be safely administered with minimal side effects, especially in those obese patients with normal renal function or ARC.
- Consider using a front-loading strategy, where antibiotics are given at higher doses initially and then reduced to standard dosing, depending on culture results, organ function and response to therapy.
- Extended or continuous infusions, after an initial bolus dose, will best ensure that $fT_{>MIC}$ is maintained at greater than the minimum target of 40–60 % of the dosing interval, and can provide a means to achieve a $fT_{>MIC}$ closer to 100 % when faced with critical illness or immune system compromise.

There is insufficient evidence to provide specific weight-based dosing schedules for each penicillin antibiotic. Table 2.3 outlines general recommendations for specific common penicillin antibiotics. Future aims should be to utilize therapeutic drug monitoring of penicillin antibiotics in order to provide individualised drug dosing, using Bayesian estimation techniques and dosing software, in patients with increased BMIs with altered and difficult to predict PK/PD changes. This will facilitate adequate drug exposure and promote optimal clinical outcomes, similar to what has been proposed for dosing in critically ill patients [52, 55].

**Table 2.3** Recommended dosing of common penicillin antibiotics in obesity

| Antibiotic | Usual adult dose | Dosing in obesity | Comments |
|---|---|---|---|
| *Narrow spectrum penicillins* | | | |
| Benzylpenicillin, iv | 1.2 Q6H—2.4 g Q4H | 1.2–2.4 g Q4H | Consider extended infusion (12 h stability at room temperature) |
| Procaine penicillin, im | 1.5 g | *Avoid if possible* | Risk of intra-lipomatous infection |
| Benzathine penicillin, im | 900 mg–1.8 g[a] | | |
| Phenoxymethylpenicillin, oral | 500 mg Q12H | 500 mg Q6H | Risk of poor adherence with more frequent dosing |
| *Antistaphylococcal penicillins* | | | |
| Dicloxacillin, oral | 500 mg Q6H | 1 g Q6H | Dicloxacillin preferred to flucloxacillin to limit the risk of drug induced liver injury |

(continued)

**Table 2.3** (continued)

| Antibiotic | Usual adult dose | Dosing in obesity | Comments |
|---|---|---|---|
| Flucloxacillin, iv | 1–2 g Q6H-Q4H | 2 g Q6H-Q4H | High dose and frequent administration via a small peripheral cannula may be limited by thrombophlebitis. Consider also extended infusions (24 h stability at room temperature) |
| *Aminopenicillins* | | | |
| Amoxycillin, oral | 500 mg–1 g Q12H-Q8H | 1 g Q8H | Amoxycillin concentrates in the urine such that increased doses may not be necessary for urinary tract infections |
| Amoxycillin-clavulanate, oral | 500/125 mg Q12H-Q8H; 875/125 mg Q12H | 875/125 mg Q12H-Q8H; 1000/62.5 mg ER (2 tabs Q12H[b]) | Less clavulanate and less diarrhoea with Q12H regimen. Amoxycillin-clavulanate (875/125 mg) can be combined with an additional amoxycillin dose |
| Ampicillin, iv Amoxycillin, iv | 2 g Q6H-Q4H | 2 g Q4H | Extended infusions limited by lack of stability at room temperature (stable only for 3 h at 30 mg/ml, stable 8 h at 10–20 mg/ml) |
| *Antipseudomonal penicillins* | | | |
| Ticarcillin-calvulanate, iv | 3.1 g Q6H | 3.1 g Q6H-Q4H | Consider administration by extended or continuous infusion, after an initial bolus dose (TIC stable for 48 h at room temperature; TZP stable for 24 h at room temperature and 12 h in an ambulatory pump) |
| Piperacillin-tazobactam, iv | 3.375 g[b] Q6H; 4.5 g Q8H | 3.375 g[b] q4 h; 6.75 g[b] Q8H (over 4 h); 4.5 g Q6H; 13.5–18 g (over 24 h) | |

[a]Equivalent to 1.2–2.4 million units

[b]Dose/formulation not available in Australia. ER, extended release

The doses listed below are general recommendations only, based upon the maximum dosing recommendations and assume good renal function. This table serves as a guide only and the choice of agent and dose is dependent upon on the infection treated, the susceptibility of the organism and host factors. The use of prolonged infusion of beta-lactam antibiotics, either as extended infusion, defined as a discontinuous infusion of $\geq$2 h, or as continuous infusion, will maximize $fT_{>MIC}$, but should only be used following an initial loading dose, when intravenous access and drug stability is ensured [62, 63]

## References


1. Penicillins and Related Drugs. Kucers' The Use of Antibiotics. 6th ed. CRC Press; 2010. p. 3.
2. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2011;52(4):e56–93.
3. Tam CS, O'Reilly M, Andresen D, Lingaratnam S, Kelly A, Burbury K, et al. Use of empiric antimicrobial therapy in neutropenic fever. Australian Consensus Guidelines 2011 Steering Committee. Intern Med J. 2011;41(1b):90–101.
4. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388–416.
5. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2012;54(12):e132–73.
6. Lodise TP, Drusano GL. Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the intensive care unit. Crit Care Clin. 2011;27(1):1–18.
7. Crandon JL, Nicolau DP. Pharmacodynamic approaches to optimizing beta-lactam therapy. Crit Care Clin. 2011;27(1):77–93.
8. Mouton JW, Vinks AA. Is continuous infusion of beta-lactam antibiotics worthwhile? Efficacy and pharmacokinetic considerations. J Antimicrob Chemother. 1996;38(1):5–15.
9. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004;2(4):289–300.
10. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am. 2009;23(4):791–815, vii.
11. Abbott IJ, Roberts JA. Infusional beta-lactam antibiotics in febrile neutropenia: has the time come? Curr Opin Infect Dis. 2012;25(6):619–25.
12. Mouton JW, Ambrose PG, Canton R, Drusano GL, Harbarth S, MacGowan A, et al. Conserving antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. Drug Resist Updates: Rev Commentaries Antimicrob Anticancer Chemother. 2011;14(2):107–17.
13. Drusano GL, Fregeau C, Liu W, Brown DL, Louie A. Impact of burden on granulocyte clearance of bacteria in a mouse thigh infection model. Antimicrob Agents Chemother. 2010;54(10):4368–72.
14. Al-Dorzi HM, Al Harbi SA, Arabi YM. Antibiotic therapy of pneumonia in the obese patient: dosing and delivery. Curr Opin Infect Dis. 2014;27(2):165–73.
15. Hayashi Y, Roberts JA, Paterson DL, Lipman J. Pharmacokinetic evaluation of piperacillin-tazobactam. Expert Opin Drug Metab Toxicol. 2010;6(8):1017–31.
16. Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. J Antimicrob Chemother. 1993;31 Suppl A:39–60.
17. Hites M, Taccone FS, Wolff F, Cotton F, Beumier M, De Backer D, et al. Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother. 2013;57(2):708–15.
18. Tucker C, Lockwood A, Nguyen N. Antibiotic dosing in obesity: the search for optimum dosing strategies. Clin Obes. 2014;4(6):287–95.
19. Wurtz R, Itokazu G, Rodvold K. Antimicrobial dosing in obese patients. Clin Infect Dis: Off Publ Infect Dis Soc Am. 1997;25(1):112–8.
20. Miskowiak J, Andersen B, Nielsen VG. Absorption of oral penicillin before and after gastroplasty for morbid obesity. Pharmacology. 1985;31(2):115–20.
21. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39(6):584–608.

22. Alexander JK, Dennis EW, Smith WG, Amad KH, Duncan WC, Austin RC. Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. Cardiovasc Res Cent Bull. 1962;1:39–44.
23. Cockshott WP, Thompson GT, Howlett LJ, Seeley ET. Intramuscular or intralipomatous injections? N Engl J Med. 1982;307(6):356–8.
24. Australian Injectable Drugs Handbook. 6th ed. Collingwood, Victoria, Australia: The Society of Hospital Pharmacists of Australia; 2014.
25. Janson B, Thursky K. Dosing of antibiotics in obesity. Curr Opin Infect Dis. 2012;25(6):634–49.
26. McKenzie C. Antibiotic dosing in critical illness. J Antimicrob Chemother. 2011;66 Suppl 2: ii25–31.
27. Kampmann JP, Klein H, Lumholtz B. Molholm Hansen JE. Ampicillin and propylthiouracil pharmacokinetics in intestinal bypass patients followed up to a year after operation. Clin Pharmacokinet. 1984;9(2):168–76.
28. Yuk J, Nightingale CH, Sweeney K, Levitz RE, Quintiliani R. Pharmacokinetics of nafcillin in obesity. J Infect Dis. 1988;157(5):1088–9.
29. Wong G, Briscoe S, Adnan S, McWhinney B, Ungerer J, Lipman J, et al. Protein binding of beta-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? Antimicrob Agents Chemother. 2013;57(12):6165–70.
30. Suh B, Craig WA, England AC, Elliott RL. Effect of free fatty acids on protein binding of antimicrobial agents. J Infect Dis. 1981;143(4):609–16.
31. Van Saene HK, Silvestri L. Obesity and antibiotic dosing. Minerva Anestesiol. 2014;80 (9):980–2.
32. Cole M, Kenig MD, Hewitt VA. Metabolism of penicillins to penicilloic acids and 6-aminopenicillanic acid in man and its significance in assessing penicillin absorption. Antimicrob Agents Chemother. 1973;3(4):463–8.
33. Ghabril M, Chalasani N, Bjornsson E. Drug-induced liver injury: a clinical update. Curr Opin Gastroenterol. 2010;26(3):222–6.
34. Chalhoub WM, Sliman KD, Arumuganathan M, Lewis JH. Drug-induced liver injury: what was new in 2013? Expert Opin Drug Metab Toxicol. 2014;10(7):959–80.
35. Russmann S, Kaye JA, Jick SS, Jick H. Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: cohort study using data from the UK General Practice Research Database. Br J Clin Pharmacol. 2005;60(1):76–82.
36. Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet. 2009;41(7):816–9.
37. Rea DJ, Heimbach JK, Grande JP, Textor SC, Taler SJ, Prieto M, et al. Glomerular volume and renal histology in obese and non-obese living kidney donors. Kidney Int. 2006;70 (9):1636–41.
38. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy. 2007;27(8):1081–91.
39. Decleves AE, Sharma K. Obesity and kidney disease: differential effects of obesity on adipose tissue and kidney inflammation and fibrosis. Curr Opin Nephrol Hypertens. 2015;24(1):28–36.
40. Snyder S, Turner GA, Turner A. Obesity-related kidney disease. Prim Care. 2014;41(4):875–93.
41. Pai MP. Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. Pharmacotherapy. 2012;32(9):856–68.
42. Aggarwal N, Porter AC, Tang IY, Becker BN, Akkina SK. Creatinine-based estimations of kidney function are unreliable in obese kidney donors. J Transplant. 2012;2012:872894.
43. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
44. Bosma RJ, Krikken JA, Homan van der Heide JJ, de Jong PE, Navis GJ. Obesity and renal hemodynamics. Contributions to nephrology. 2006;151:184-202.
45. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis. 2006;6(7):438–46.

46. Longo C, Bartlett G, Macgibbon B, Mayo N, Rosenberg E, Nadeau L, et al. The effect of obesity on antibiotic treatment failure: a historical cohort study. Pharmacoepidemiol Drug Saf. 2013;22(9):970–6.
47. Antibiotic Expert Groups. Therapeutic guidelines: antibiotic. Version 15. Melbourne: Therapeutic Guidelines Limited; 2014.
48. Gulluoglu BM, Guler SA, Ugurlu MU, Culha G. Efficacy of prophylactic antibiotic administration for breast cancer surgery in overweight or obese patients: a randomized controlled trial. Ann Surg. 2013;257(1):37–43.
49. Zakrison TL, Hille DA, Namias N. Effect of body mass index on treatment of complicated intra-abdominal infections in hospitalized adults: comparison of ertapenem with piperacillin-tazobactam. Surg Infect. 2012;13(1):38–42.
50. Dodds Ashley ES, Carroll DN, Engemann JJ, Harris AD, Fowler VG Jr, Sexton DJ, et al. Risk factors for postoperative mediastinitis due to methicillin-resistant Staphylococcus aureus. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2004;38(11):1555–60.
51. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis: Off Publ Infect Dis Soc Am. 2014;58 (8):1072–83.
52. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498–509.
53. Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, et al. beta-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case-control study. Int J Antimicrob Agents. 2014.
54. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care. 2012;27(6):741 e9–18.
55. Felton TW, Roberts JA, Lodise TP, Van Guilder M, Boselli E, Neely MN, et al. Individualization of piperacillin dosing for critically ill patients: dosing software to optimize antimicrobial therapy. Antimicrob Agents Chemother. 2014;58(7):4094–102.
56. Newman D, Scheetz MH, Adeyemi OA, Montevecchi M, Nicolau DP, Noskin GA, et al. Serum piperacillin/tazobactam pharmacokinetics in a morbidly obese individual. Ann Pharmacother. 2007;41(10):1734–9.
57. Bulitta JB, Duffull SB, Kinzig-Schippers M, Holzgrabe U, Stephan U, Drusano GL, et al. Systematic comparison of the population pharmacokinetics and pharmacodynamics of piperacillin in cystic fibrosis patients and healthy volunteers. Antimicrob Agents Chemother. 2007;51(7):2497–507.
58. Hites M, Taccone FS, Wolff F, Maillart E, Beumier M, Surin R, et al. Broad-spectrum beta-lactams in obese non-critically ill patients. Nutr Diab. 2014;4:e119.
59. Sturm AW, Allen N, Rafferty KD, Fish DN, Toschlog E, Newell M, et al. Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. Pharmacotherapy. 2014;34(1):28–35.
60. Cheatham SC, Fleming MR, Healy DP, Chung CE, Shea KM, Humphrey ML, et al. Steady-state pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese patients. Int J Antimicrob Agents. 2013;41 (1):52–6.
61. Deman H, Verhaegen J, Willems L, Spriet I. Dosing of piperacillin/tazobactam in a morbidly obese patient. J Antimicrob Chemother. 2012;67(3):782–3.
62. De Waele JJ, Lipman J, Carlier M, Roberts JA. Subtleties in practical application of prolonged infusion of beta-lactam antibiotics. Int J Antimicrob Agents. 2015. http://dx.doi.org/10.1016/j.ijantimicag.2015.01.007 (in press).
63. Mouton JW, Vinks AA. Continuous infusion of beta-lactams. Curr Opin Crit Care. 2007;13 (5):598–606.

# Chapter 3
# Cephalosporins

**Carmela Corallo and Syed Tabish R. Zaidi**

**Abstract** Dose adjustment in obesity is particularly important for cephalosporins since these agents are widely used for surgical prophylaxis and treatment of infections. Compared with other antibiotics such as vancomycin and aminoglycosides, there is a paucity of data on the pharmacokinetics of cephalosporins in obesity and dosing recommendations are scarce. The purpose of this chapter is to review and summarise the published data to assist in developing dosing recommendations for the use of cephalosporins in obesity.

**Keywords** Cephalosporins · Obesity · Surgical prophylaxis · Dosing

## Introduction

Cephalosporins are widely used from surgical prophylaxis to treatment in critically ill patients. Moderate-spectrum cephalosporins include cephalexin, cephalothin, cephazolin, cefuroxime, cefaclor and cefoxitin. Cephalexin, cephalothin and cephazolin have a similar range of antimicrobial activity and are active against streptococci and staphylococci, including β-lactamase–producing staphylococci, but inactive against enterococci or *Listeria monocytogenes*. Their Gram-negative spectrum includes *Escherichia coli* and most *Klebsiella* species, but they are inactive against many Gram-negative aerobes (e.g. *Serratia*, *Enterobacter* or *Pseudomonas* species). None of these cephalosporins have useful activity against the Gram-negative anaerobe *Bacteroides fragilis* and related species. Cephalothin has been largely replaced by cephazolin, as the short half-life of cephalothin makes it inadequate for the treatment of Gram-negative infections [1, 2]. Cephalothin is considered to have a superior anti-staphylococcal activity to cephazolin and hence

C. Corallo (✉)
Pharmacy Services, Alfred Health, 55 Commercial Road, Melbourne, VIC 3004, Australia
e-mail: C.corallo@alfred.org.au

S.T.R. Zaidi
Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_3

may be used for the treatment of severe staphylococcal infections such as septicaemia and endocarditis [1]. By contrast, cephazolin is somewhat less stable than cephalothin and is therefore, not a good drug for the treatment of these types of infections. However, comparative animal data is conflicting and clinically, cephazolin has been used to treat endocarditis. These differing results may be explicable by the fact that different strains of *Staphylococcus aureus* produce different β-lactamases, where some easily hydrolyse cephazolin and some do not [1].

Cefuroxime and cefaclor are more stable than standard moderate-spectrum cephalosporins to some Gram-negative β-lactamases and more active against *Haemophilus influenzae*. For respiratory tract infections, cefuroxime is preferred to cephalexin or cefaclor because of superior pneumococcal activity [1, 2].

Cefoxitin has significant anaerobic activity, with 60–70 % of *Bacteroides fragilis* being susceptible. It has a limited role for prophylaxis in the bowel and gynaecological surgery and for the treatment of severe pelvic inflammatory disease. However, metronidazole provides superior cover against most anaerobes [1, 2]. Cefoxitin is also used in the treatment of non-tuberculous *Mycobacteria* [3, 4].

Broad-spectrum cephalosporins include cefotaxime, ceftriaxone, cefepime, ceftazidime and ceftaroline. Cefotaxime and ceftriaxone have a wide spectrum of activity covering the majority of community-associated enteric Gram-negative rods. The activity of these drugs against *B. fragilis* varies, but neither is as active as cefoxitin. These drugs are less active against staphylococci than earlier cephalosporins and are inactive against methicillin-resistant *Staphylococcus aureus* (MRSA). They do not have clinically useful activity against enterococci. However, unlike earlier cephalosporins, they are effective in meningitis, because of better penetration and a higher intrinsic activity in the cerebrospinal fluid. Some organisms (e.g. *Serratia*, *Citrobacter* and *Enterobacter* species) have chromosomal cephalosporinases and resistance may develop during treatment. Plasmid-mediated extended-spectrum β-lactamases (ESBLs) (e.g. in *E. coli*, *Klebsiella pneumoniae*, *Enterobacter* species) also inactivate both of these drugs, so alternative therapy is indicated. Cefotaxime has better activity against staphylococci than ceftriaxone, and does not require co-administration with flucloxacillin for empirical therapy of staphylococcal infections. Ceftriaxone has a longer half-life than cefotaxime and is usually given once daily except in ICU where twice daily dosing is often used [2].

Ceftazidime and cefepime have an extended spectrum of activity covering the majority of the enteric Gram-negative rods, including *Pseudomonas aeruginosa*. Both drugs are inactivated by the ESBL enzymes, and ceftazidime may be inactivated by the chromosomal cephalosporinases. Cefepime is more active than ceftazidime against Gram-positive organisms [1, 2].

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a new cephalosporin with in vitro bactericidal activity against a broad range of pathogens commonly implicated in complicated skin and soft tissue infections and community-acquired pneumonia [2]. Due to its high affinity for penicillin binding protein (PBP)-2a, ceftaroline is active against MRSA. Compared with alternative β-lactam antibiotics within the penicillin and cephalosporin classes, ceftaroline also has relatively high binding affinities to PBP-AA, -2B and -2X proteins, conferring

its activity toward penicillin resistant *Streptococcus pneumoniae*. Currently, based on in vitro susceptibility testing, ceftaroline is active against various Gram-positive bacteria, including vancomycin and lincomycin resistant *Staphylococcus aureus* and *Streptococcus pyogenes*. It is also active against *Enterococcus faecalis*, including vancomycin resistant strains. With respect to Gram-negative bacteria, ceftaroline is active against *Klebsiella pneumoniae* and *Haemophilus influenza*, including β-lactamase positive strains [5].

## Pharmacodynamic Target

Cephalosporins are hydrophilic drugs with limited solubility in adipose tissue and are dosed based on the duration of the drug's free concentration above the minimum inhibitory concentration (MIC) i.e. $fT_{>MIC}$. Cephalosporins are deemed efficacious when the $fT_{>MIC}$ exceeds 60–70 % of the dosing interval [6]. In other words, the efficacy of cephalosporins is time dependent or proportional to the time that the target concentration is kept above the MIC. In surgical prophylaxis, effective treatment requires effective tissue concentrations at incision and closure [7]. The optimal concentration is mostly two to four times the MIC of the pathogen, but this will be higher for some organisms.

The MIC for 90 % ($MIC_{90}$) of methicillin sensitive *Staphylococcus aureus* (MSSA) isolates may differ between countries and hospitals, but it is usually around 1 mg/L in Europe [8]. For Gram-negative organisms and/or in the treatment of critically ill patients, in general, β-lactam therapy is considered adequate when serum concentrations remain above 4 mg/L and less than 8 mg/L during an optimal period of time i.e. 70 % for cephalosporins [9].

For organisms for which the $fT_{>MIC}$ is important, it follows that increasing doses or frequency or even using continuous infusions will improve the pharmacodynamics of the antibiotic [10, 11].

## Pharmacokinetic Changes in Obesity

Hydrophilic medications such as cephalosporins have relatively low volume of distribution (V), which usually require ideal or adjusted (0.4 (total body weight-ideal body weight) body weight dosing, however this has not been shown with all drugs [10].

V and clearance of cephalosporins are both increased in obese subjects compared with non-obese subjects; however the change in clearance is less well defined [12].

The increase in V can be explained by the partial distribution into adipose tissue, with concentrations ranging from 12 to 21 % of plasma concentrations [13].

The relationship between clearance and body size is not clear, with conflicting results being reported from different studies. In one study, in which obese patients were treated with ceftazidime or cefepime, an augmented renal clearance, i.e. creatinine clearance >150 mL/min, was associated with a failure to attain therapeutic concentrations for *Pseudomonas aeruginosa* with the potential for worse clinical outcome. There was no association between clinical outcome and body size descriptors [9].

On pharmacokinetic grounds, it is hypothesized that adequate free-antibiotic tissue concentrations are more important than plasma concentrations in determining prophylactic antibiotic efficacy. Multiple factors influence the distribution of antibiotic molecules from the plasma into the tissues. Such factors include simple diffusion rates, plasma protein binding, active transport, and tissue-site metabolism [14].

Tissue distribution is particularly important in surgical prophylaxis, where high tissue concentrations for the duration of surgery are required. Under normal conditions and weight, blood flow in fat is poor and accounts for approximately 5 % of cardiac output, whereas in the lean tissues this is 22 %. In morbid obesity, the percentage of fat per kilogram of total body weight is increased relative to lean tissue mass. Therefore, blood flow per gram of fat is greatly reduced in the morbidly obese patient compared with moderately overweight or lean individuals [15].

Tissue levels of prophylactic antibiotics in obese patients have been found to be inadequate and sub therapeutic concentrations have been associated with an increase in wound infections [16]. However, whilst an increase in the dose of cephalosporins will result in an increase in blood concentrations, this does not correlate with increased tissue concentrations and/or efficacy [14].

It is generally accepted that only the free unbound drug concentration in tissue target site mediates antibacterial effects [7]. Any changes in plasma proteins could be expected to affect free concentrations of drugs. For cephalosporins, the extent of distribution into interstitial fluid space (IFS) appears to depend on the degree of protein binding [11], which has been shown to be important in critically ill patients where standard doses may result in inadequate drug exposure. However, the effect of obesity on plasma protein binding of drugs is largely unknown. Based on available data, protein binding of cephalosporins does not seem to alter in obesity [8].

Changes in hepatic metabolism associated with obesity are also largely unknown [10]. This pharmacokinetic parameter is not generally discussed in studies on cephalosporins and obesity. Little data exists on changes in absorption of cephalosporins in obesity. Intramuscular injections may inadvertently be administered deep subcutaneously but it is unknown if this will have an impact on absorption or efficacy [10].

## Review of Existing Literature

A summary of relevant studies is shown in Table 3.1. Most of the data concerning dose optimization of cephalosporins comes from their use in surgical prophylaxis to prevent surgical site infection. Obesity remains an independent risk factor for development of surgical site infections, despite use of antimicrobial prophylaxis. While other factors are responsible for the additional risk of surgical site infection, dose optimization has decreased surgical site infection rates [17].

A number of studies on surgical prophylaxis have been conducted for cephazolin. The pivotal 1989 study by Forse et al. showed that a 2 g dose in obese patients produced similar plasma and tissue levels as a 1 g dose in normal patients [16]. On this basis a 2 g dose was adopted for obese patients and the surgical site infection (SSI) rate reduced from 16.5 to 5.6 %. Another study in 38 morbidly obese patients who were given 2 g of cephazolin at incision and another 2 g at 3 h during operation, showed that even a 2 g dose did not reach therapeutic tissue concentrations, defined as less than 8 μg/g. Tissue concentrations were sub-inhibitory for 80 % of *Staphylococcal* and 39 % of Gram-negative pathogens recovered from the institution's surgical site infections [15]. A third study, involving patients with a body-mass-index (BMI) from 38 to 79 kg/m$^2$ showed that 2 g of cephazolin was sufficient for MSSA with a breakpoint of 1 mg/L. But the authors note that higher doses or more frequent dosing is required for intermediate resistance [8].

A study by Ho et al. did not show any advantage in increasing the dose of cephazolin from 2 to 3 g in morbidly obese patients [18]. They found that a 2 g dose was adequate for surgical prophylaxis, irrespective of the BMI for most common general surgical procedures lasting less than 5 h.

A more recent study by Pevzner et al. showed that a 2-g dose of cephazolin administered 30–60 min prior to a Caesarean delivery in obese patients (BMI 30–39.9 kg/m$^2$) or extremely obese (BMI $\geq$ 40 kg/m$^2$) patients failed to achieve a targeted MIC of 4 μg/g in 20 and 33 %, respectively, of patients at the time of skin incision and in 20 and 40 % of patients at the time of incision closure [19]. The main objective of this study was to assess if the antibiotic tissue concentrations of prophylactic cephazolin administered as a 2 g dose prior to a Caesarean delivery in patients with a first-trimester BMI $\geq$ 35 kg/m$^2$ were above the MIC breakpoint for organisms common in these SSIs, i.e. Gram-negative rods. A targeted cephazolin concentration threshold of 4 μg/mL for plasma and 4 μg/g for tissue samples was used as a surrogate measure of adequate treatment. All specimens demonstrated therapeutic cephazolin levels for Gram-positive cocci (>1 μg/g).

When cefoxitin was administered as a 2 g dose to 14 obese patients, tissue penetration was markedly reduced compared with normal weight patients who had received a 1 g dose [7]. Sub cutaneous and adipose tissue concentrations of cefoxitin were about 22 % that of non-obese patients, despite 2-fold higher plasma levels being achieved [7]. The authors concluded that a 2 g dose of cefoxitin did not provide a therapeutic antimicrobial concentration in tissue. Higher doses may be required in morbidly obese patients.

**Table 3.1** Summary of published data on cephalosporins and obesity

| Drug [Reference] and Study Dose | | Patients numbers and procedures | BMI | Outcome and recommendations |
|---|---|---|---|---|
| Cephazolin [16] | 1 g<br>2 g | N = 30<br>N = 10<br>Gastric bypass | 46–47 kg/m$^2$ | Plasma and tissue concentrations in obese patients after 2 g similar to those in normal after 1 g. Surgical site infection rate reduced from 16.5 to 5.6 % for obese patients in 4 months |
| | 1 g | N = 8 normal control | 22 kg/m$^2$ | Use 2 g for surgical prophylaxis in morbidly obese patients |
| Cephazolin [15] | 2 g before incision and 2 g at 3 h during operation | N = 38<br>Gastric bypass | 40 to $\geq$60 kg/m$^2$ | Tissue concentrations were sub therapeutic for 80 % of *Staph* pathogens recovered from institution's surgical site infections<br>A 2 g dose did not result in therapeutic tissue concentrations. Target was MIC $\geq$ 8 mcg/g |
| Cephazolin [8] | 2 g before incision | N = 20<br>Gastric banding or bypass | 38–79 kg/m$^2$ | Overall protein binding was 79 % which is similar to non-obese patients. Saturable protein binding<br>A 2 g dose was sufficient for MSSA breakpoint of 1 mg/L. Higher or more frequent doses may be required to cover intermediate resistance |
| Cephazolin [14] | 2 g | N = 11<br>Caesarean surgery | 35–60 kg/m$^2$ | Aim was to achieve concentrations > 4mcg/mL or 4mcg/g at incision. The 4 g dose produced significantly higher levels in blood and tissues, however, both the 2 g and 4 g doses produced levels well above the target<br>A 2 g dose is adequate for surgical prophylaxis in obese patients undergoing Caesarean section.<br>BMI and weight did not correlate with levels |
| | 4 g | N = 9 | | |
| Cephazolin [18] | 2 g bolus<br>2 g over 30 min<br>3 g bolus<br>3 g over 30 min | N = 10<br>N = 5<br>N = 5<br>N = 5 | 40–50 kg/m$^2$<br>40–50 kg/m$^2$<br>>50 kg/m$^2$<br>>50 kg/m$^2$ | Aim was *f*T > MIC for 70 % of dosing interval using a breakpoint of 8 mg/L<br>2 g provided antibiotic exposure sufficient for most common general surgical procedures of < 5 h, regardless of BMI |

(continued)

**Table 3.1** (continued)

| Drug [Reference] and Study Dose | | Patients numbers and procedures | BMI | Outcome and recommendations |
|---|---|---|---|---|
| Cefuroxime [20] | 1.5 g 30–60 min before surgery | N = 6<br>Abdominal surgery-gastric bypass, colectomy or banding | 44–53 kg/m$^2$ | All levels (adipose tissue, plasma, skeletal muscle) remained above 2 mg/L during 6 h period and were adequate to eradicate MSSA. Insufficient tissue concentrations for eradication of enteric organisms with an MIC breakpoint of >8 mg/L |
| Cefoxitin [7] | 2 g | N = 14<br>Elective abdominal or pelvic surgery | 43 ± 10 kg/m$^2$ | Tissue concentrations in obese patients were significantly lower than in non-obese patients and were inversely related to BMI<br>In obese patients tissue concentrations at incision and closure were 7.8 and 2.7 mcg/g, respectively, below the MIC of 8 and mcg/mL, respectively for aerobic and anaerobic micro-organisms<br>Administer a second dose of cefoxitin 2–3 h after the initial dose to obese patients undergoing prolonged surgeries |
| | 1 g | N = 2 non obese<br>N = 11 healthy non-obese | 20 ± 2 kg/m$^2$ | |
| Cefotaxime [20] | 1 g | N = 11 obese | 190–210 % of IBW | Plasma concentration profiles were similar in both groups |
| | 1 g | N = 12 normal | 10 % IBW | Use standard dosing of 1–2 g 6–12 hourly |
| Ceftaroline [22] | Standard dose and duration<br>6.1 (±5.5 days) overall<br>5.8 ± 5.5 days in obese | N = 134<br>N = 335<br>Acute bacterial skin and skin structure infections | Overweight 25 to less than 30 kg/m$^2$<br>Obese ≥30 kg/m$^2$ | The Vd was increased by 50 % in obese patients and drug clearance was slightly increased. Overall clinical success rate was 85 %. In overweight and obese patients similar results were obtained i.e. 83 % and 88 %, respectively<br>Use standard doses in obesity |

(continued)

**Table 3.1** (continued)

| Drug [Reference] and Study Dose | | Patients numbers and procedures | BMI | Outcome and recommendations |
|---|---|---|---|---|
| Cefepime [6] | 2 g | N = 10<br>Weight loss surgery | 40 kg/m$^2$ | Results indicate that to maintain tissue concentrations $\geq$fT > MIC the mean dosing interval was 10.2 h<br>Authors recommend 8-hourly dosing for post-operative infections |
| Cefepime [26] | 1 g every 12, 8 and 6 h | N = 30 | <40 (20) kg/m$^2$ and $\geq$40 (10) kg/m$^2$ | Cefepime pharmacokinetics were altered in morbid obesity i.e. Vd was significantly related to total body weight |
| Cefepime, ceftazidime [9, 23] | 2 g tds initially | N = 11—non ICU and non-septic patients | $\geq$30 kg/m$^2$ | *Treatment was considered adequate when f*T > MIC for 70 % of dosing interval and T > 4MIC, the clinical breakpoint for Pseudomonas<br>These targets were achieved in 73 and 18 % patients, respectively. For Pseudomonas and less susceptible organisms the T > 4MIC needs to be achieved. Only small number of patients achieved this. Adequate for Enterobacteriaceae but not Pseudomonas. Augmented renal clearance (>150 mL/min) was the only risk factor for not achieving levels |

Cefuroxime, when administered as a single 1.5 g dose for surgical prophylaxis, resulted in an adequate tissue concentration to eradicate MSSA for up to 6 h. However, tissue levels were not adequate for eradication of enteric organisms with an MIC breakpoint >8 mg/L. No data on oral cefuroxime [20].

In a study involving 11 obese patients and 12 normal weight patients, a 1 g dose of cefotaxime resulted in similar plasma concentration profiles [21]. The Vd was increased in the obese group by 50 % and there was a slight increase in clearance. The authors concluded that standard doses of cefotaxime (i.e. 1–2 g every 12–6 h) can be used in obese patients. However, based on available data, plasma concentrations are not indicative of tissue levels.

For ceftaroline there are no specific studies on dosing in obesity, however, there is one publication on the clinical outcome of ceftaroline therapy in a large cohort, including obese patients [22]. The data was also analysed for a subset of people considered to be at special risk i.e. obesity defined as a BMI $\geq$ 30 kg/m$^2$, overweight BMI > 25 and <30 kg/m$^2$ with diabetes. Standard doses were used in all patients and clinical success rates (>80 %) were similar in all groups.

For cefepime and ceftazidime there is one study which examined the pharmacokinetics of a single 2 g dose of cefepime in 10 morbidly obese patients [6]. The dosing interval calculated to maintain $fT_{>MIC}$ for 60 % of the interval was determined to be 10.2 h including time for infusion. Based on this analysis, an increase dose of 2 g every eight hours would be necessary in morbidly obese patients with post-operative infections.

Hites et al. conducted a case control study comparing the pharmacokinetics of β-lactams, including ceftazidime and cefepime, in obese and non-obese critically ill patients [9]. No differences were found but there was large variability in plasma levels and the only recommendation that can be made is to routinely perform clinical pharmacokinetic monitoring (CPM) this group of patients.

The same authors conducted a study in obese, non-critically ill patients who received standard doses of cefepime or ceftazidime initially, with adjustments according to renal function. For *Pseudomonas* and less susceptible organisms, a pharmacodynamic target of T > 4MIC needs to be achieved. Only a small number of patients received this target. In this study, augmented creatinine clearance (>150 mL/min) was identified as a significant risk factor in failing to achieve target levels. There are no significant studies for ceftriaxone on its use for treatment of infections in obese patients [24, 25, 27].

## Recommendations

When using cephalosporins for surgical prophylaxis in obese patients a number of strategies have been described, keeping in mind that most of the data relates to cephazolin. Doubling the usual dose (1 g) for surgical prophylaxis in patients >80 kg has now been widely implemented. This was based on the usual dose of cephazolin being 1 g [7]. Higher doses and/or more frequent dosing of cephazolin

**Table 3.2** Recommended doses of selected cephalosporins in obesity

| Drug | Dose in Obesity | Comment |
|---|---|---|
| Cephazolin | Prophylaxis 2 g | Give a 2nd dose if anticipated surgery is >3 h or if cover of organisms with intermediate sensitivities is required |
| | Treatment:<br>2 g every 6 h | For the treatment of serious infections doses up to 12 g/day have been used i.e. 2 g every 4 h |
| Cefoxitin | Prophylaxis: 2 g | Administer a second dose of cefoxitin 2–3 h after the initial dose to obese patients undergoing prolonged surgeries |
| | Treatment:<br>2 g every 4 h | Consider continuous infusion if high concentrations are required |
| Cefotaxime | Use standard doses up to a maximum of 12 g a day | |
| Ceftaroline | 600 mg every 12 h | No data |
| Cefepime | 2 g every 8–12 h, initially | For Pseudomonas and less susceptible organisms consider continuous infusions and therapeutic drug monitoring |
| Ceftazidime | 2 g every 8 h, initially | For Pseudomonas and less susceptible organisms consider continuous infusions and therapeutic drug monitoring |
| Ceftriaxone | Use standard doses up to a maximum of 4 g a day in two divided doses | |

may be required in patients with BMIs $\geq 60$ kg/m$^2$, when aiming to cover organisms with intermediate resistance [17]. However, there is no data on increased efficacy associated with doses of cephazolin >2 g for surgical prophylaxis. Repeat doses, e.g. a second dose after the initial prophylactic dose, have been recommended for obese patients undergoing prolonged surgery (see Table 3.2).

For treatment, use the maximum recommended doses. A shorter dosing interval may be used for some cephalosporins (cephazolin, cefepime and ceftazidime). In critically ill patients who are being treated with anti-Pseudomonal cephalosporins, CPM has been recommended in combination with a consideration for continuous infusions. This strategy could also be applied when anti-Pseudomonal cover is required in non-critically ill obese patients, especially in patients with augmented clearance, i.e. creatinine clearance > 150 mL/min. A summary of these recommendations is shown as Box 1 below.

- For surgical prophylaxis, doubling the "usual" dose is recommended when referring to 1 g doses.
- For surgical prophylaxis—in general—give a second dose in obesity when prolonged surgery is anticipated and/or when covering organisms with intermediate resistance.

- For treatment, use standard doses more frequently, up to the maximum daily dose.
- When treating Pseudomonas, consider continuous infusions and clinical pharmacokinetic monitoring where applicable.

## References


1. Lindsay Grayson, editor. Kucers' the use of antibiotics. 6th ed. London: Hodder Arnold; 2010.
2. Antibiotic Therapeutic Guidelines version 15, 2014. Melbourne, Therapeutic Guidelines (Accessed 09/10/2015). Available from: https://www.tg.org.au.
3. Lavollay M, Dubee V, Heym B, et al. In vitro activity of cefoxitin and imipenem against Mycobacterium abscessus complex. Clin Microbiol Infect. 2014;20(5):297–300.
4. Czaja CA, Levin A, Moridani M, et al. Cefoxitin continuous infusion for lung infection caused by the mycobacterium abscessus group. Antimicrob Agents Chemo. 2014;58(6):3570–1.
5. Kiang TKL, Wilby KJ, Ensom MHH. A critical review on the clinical pharmacokinetics, pharmacodynamics, and clinical trials of ceftarline. Clin Pharmacokinet. 2015;54:915–31.
6. Rich BS, Keel R, Ho VP, Turbendian H, Afaneh CI, et al. Cefepime dosing in the morbidly patient population. Obes Surg. 2012;22(3):465–71.
7. Toma O, Suntrup P, Stefanescu A, et al. Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical site infection. Anesth Analg. 2011;113(4):730–7.
8. Van Kralingen S, Taks M, Diepstraten J, et al. Pharmacokinetics and protein binding of cephazolin in morbidly obese patients. Eur J Clin Pharmacol. 2011;67(10):985–92.
9. Hites M, Taccone FS, Wolff F, et al. Case-control study of drug monitoring of β-lactams in obese critically ill patients. Antimicrob Agents Chemother. 2013;57(2):708–15.
10. Janson B, Thursky K. Dsoing of antibiotics in obesity. Curr Opin Infect Dis. 2012;25:634–49.
11. Kiang TKL, Hafeli UP, Ensom MHH. A comprehensive review of the pharmacokinetics of antibiotics in interstitial fluid space in humans; implications on dosing and clinical pharmacokinetic monitoring. Clin Pharmacokinet. 2014;33:695–730.
12. Roe JL, Fuentes JM, Mullins ME. Underdosing of common antibiotics for obese patients in the ED. Am J Emerg Med. 2012;30:1212–4.
13. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adults. Pharmacotherapy. 2007;27(8):1081–91.
14. Stitely M, Sweet M, Slain D, et al. Plasma and tissue cefazolin concentrations in obese patients undergoing Cesarean delivery and receiving differing pre-operative doses of drug. Surg Infect. 2013;14(5):455–9.
15. Edmiston CE, Krepel C, Kelly H, et al. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery. 2004;136(4):738–47.
16. Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. Surgery. 1989;106(4):750–6.
17. Payne KD, Hall RG II. Dosing of antibacterial agents in obese adults: does one size fit all? Expert Rev Infect Ther. 2014;12(1):829–54.
18. Ho VP, Nicolau DP, Dakin GF, et al. Cefazolin dosing for surgical prophylaxis in morbidly obese patients. Surg Infect. 2012;13(1):33–7.
19. Pevzner L, Swank M, Krepel C, et al. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during Caesarian delivery. Obstet Gynecol. 2011;117(4):877–82.

20. Barbour A, Schmidt S, Rout WR, et al. Soft tissue penetration of cefuroxime determined by clinical microdialysis in morbidly obese patients undergoing abdominal surgery. Int J Antimicrob Agents. 2009;34(3):231–5.
21. Yost RI, Derendorf H. Disposition of cefotaxime and its desacetyl metabolite in morbidly obese male and female subjects. Ther Drug Monit. 1986;8(2):189–94.
22. Santos PD, David A, Jandourek A, et al. Ceftaroline fosamil and treatment of acute bacterial skin and skin structure infections: CAPTURE study experience. J Chemotherapy. 2013; 25(6):341–6.
23. Hites M, Taccone FS, Maillart E, Beurmier M, Surin R, Cotton F, Jacobs F. Broad-spectrum β-lactams in obese non-critically ill patients. Nutr Diab. 2014;4:e119.
24. Lovering AM, Walsh TR, Bannister GC, MacGowan AP. The penetration of ceftriaxone and cefamandole into bone, fat and haematoma and relevance of serum protein binding to their penetration into bone. J Antimicrob Chemother. 2001;47:483–6.
25. Satofumi I, Kinoshita H, Kawanishi T, Hayashi M. The pharmacokinetics of ceftriaxone based on population pharmacokinetics and the prediction of efficacy in Japanese adults. Eur J Drug Metab Pharmacokinet. 2009;34(2):107–15.
26. Georges B, Conil J, Seguin T, et al. Cefepime in intensive care unit patients: validation of a population pharmacokinetic approach and influence of covariables. Int J Clin Pharmacol Ther. 2008;46(4):157–64.
27. Jiang L, Shi YK, Gao W, et al. Studies of prophylactic ceftriaxone plasma concentrations in pulmonary and esophageal surgery. Chin J Antibiot. 2003;28(5):286–8.

# Chapter 4
# Aminoglycoside Dosing in Obesity

**Janattul-Ain Jamal and Jason A. Roberts**

**Abstract** Achieving a high $C_{max}$/MIC ratio is necessary for maximal killing efficacy of aminoglycosides. Although the effect of obesity on aminoglycoside pharmacokinetics can be variable, a higher initial aminoglycoside dose is generally required to rapidly achieve the desired therapeutic target concentration. Accurate initial dosing regimens can be achieved by using a correction factor for obesity when estimating a volume of distribution (V). While for subsequent doses, therapeutic drug monitoring (TDM) remains an essential tool to guide dosing and to prevent unwanted adverse events such as nephrotoxicity.

**Keywords** Aminoglycoside · Dosing · Obesity

## Introduction

Aminoglycoside antibiotics are obtained from microorganisms of the genus Streptomyces (e.g. streptomycin, neomycin, kanamycin, tobramycin and amikacin) or the genus Micromonospora (e.g. gentamicin, sisomicin and netilmicin), which structurally contain either two or three amino sugars that are linked with

J.-A. Jamal · J.A. Roberts (✉)
Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia
e-mail: j.roberts2@uq.edu.au

J.A. Roberts
Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia

J.A. Roberts
Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, Australia

J.A. Roberts
School of Pharmacy, The University of Queensland, Brisbane, Australia

J.A. Roberts
Royal Brisbane and Women's Hospital, Butterfield St, Herston, QLD 4006, Australia



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_4

2-deoxystreptamine [1]. Generally, the aminoglycosides are strongly polar cations, stable in the pH range of 6–8, with basic characteristics. They are water soluble and distribute widely throughout the extracellular space in humans (e.g. 25 % of the lean body mass). They are primarily (~95 %) excreted via the kidneys. Aminoglycosides have poor absorption from the intestinal tract and poor penetration into the cerebrospinal fluid and the intracellular space.

Aminoglycosides have a very broad spectrum of microbiological activity, which includes organisms from Gram-positive cocci to Gram-negative bacilli [2, 3]. However, aminoglycosides are not clinically effective against any anaerobic organisms. The mechanism of action of aminoglycosides involves binding to the surface of bacteria, transportation through the cell wall, and binding to the 30s ribosomal subunit. This action interferes with protein synthesis which will eventually lead to bacterial death [1].

## Pharmacodynamic Targets

Aminoglycosides predominantly display concentration-dependent bactericidal activity against most aerobic Gram-negative bacilli and select Gram-positive, such as methicillin-resistant staphylococci (in combination with other agents) [2–4]. Generally, many studies have identified that achieving a high ratio of maximum concentration and minimum inhibitory concentration ($C_{max}$/MIC), is likely to result in maximal killing efficacy by aminoglycosides (see Fig. 4.1) [5–7]. A high peak concentration, relative to the MIC of the infecting pathogen ($C_{max}$/MIC), has been a strong predictor of clinical response for aminoglycoside therapy in a retrospective analysis of patients with Gram-negative bacterial infection [5]. Additionally, other studies have quantified an optimal $C_{max}$/MIC ratio of 8–10 to be associated with a high level of therapeutic response to aminoglycoside therapy [6, 7].

The area under the concentration-time curve (AUC) has also been identified as a significant parameter related to efficacy of aminoglycosides, in animal infection models (see Fig. 4.1) [8]. In addition, data also supports the use of the $AUC_{0–24}$/MIC ratio as a predictor to guide dosing that can maximise aminoglycoside efficacy [9, 10]. In this context, achieving the $AUC_{0–24}$/MIC ratio between 80 and 160 has been advocated as an aminoglycoside exposure associated with maximal bacterial killing effects [9, 11].

## Pharmacokinetic Changes in Obesity

The pathophysiological changes related to obesity could alter the main pharmacokinetic parameters related to dosing, the volume of distribution (V) and clearance of many drugs, including aminoglycosides. Generally, obesity may not have a significant impact on drug absorption [12]. However, varied changes are expected

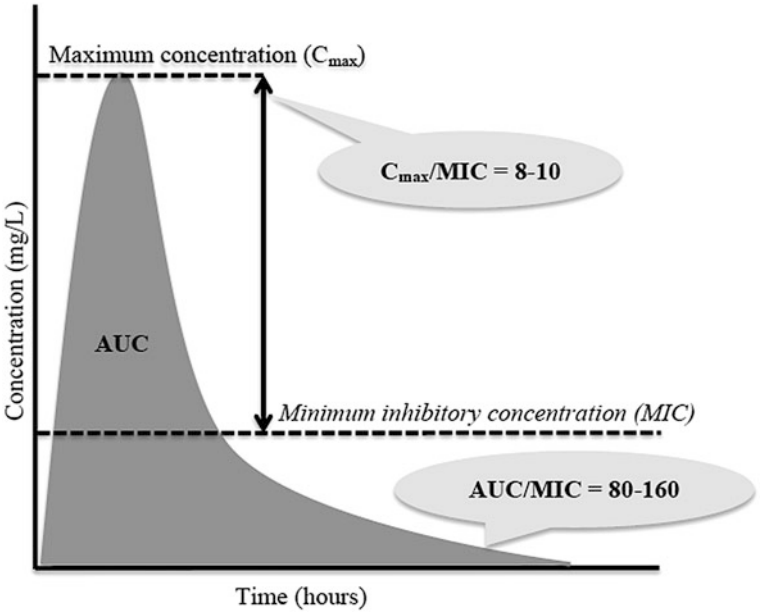



**Fig. 4.1** The pharmacokinetics/pharmacodynamics indices of aminoglycoside. *Abbreviations* AUC = area under the concentration-time curve; $C_{max}$ = maximum concentration and MIC = minimum inhibitory concentration

on drug V, which depends on body composition, regional blood flow, drug lipophilicity and plasma protein binding. Significant changes in drug clearance can be expected, particularly for those drugs that are primarily renally eliminated, due to influence of increasingly body weight on increasing glomerular filtration [13].

The effect of obesity on aminoglycoside V is variable. A lower relative aminoglycoside V has been observed in pharmacokinetic studies of tobramycin and gentamicin in obese patients when compared to normal subjects [14, 15]. Conversely, other studies have shown that the aminoglycoside V is significantly larger in morbidly obese patients [14–18]. Overall, most studies are in agreement that a correction factor, between 0.3 and 0.5 should be added to a calculation using total body weight (TBW) and ideal body weight (IBW), to normalize the V to that observed in non-obese patients (non-obese patient V $\sim$ 0.26 L/kg) [14–18]. Accurately predicting aminoglycoside V using a correction factor (e.g. 0.4) (see Eq. 4.1), will lead to a better estimation of the initial dose of aminoglycosides that is required to rapidly achieve the desired aminoglycoside therapeutic targets, particularly when treating less susceptible pathogens.

$$\mathrm{V(L)} = 0.26 \times [\mathrm{IBW} + \text{correction factor}\,(\mathrm{TBW} - \mathrm{IBW})] \tag{4.1}$$

The clearance of different aminoglycosides (e.g. gentamicin, tobramycin and amikacin) was found to significantly increase in morbidly obese patients as

compared to normal weight patients. Overall, no significant difference was observed in the elimination half-life between the morbidly obese and normal weight patients [19], because the relative changes to clearance and V cancel each other out, leaving the elimination half-life unchanged. Although calculating the creatinine clearance (CrCL) using the Cockcroft-Gault equation has led to a better prediction of the gentamicin elimination rate constant, clearance and elimination half-life [20], it is recommended that, when based on TBW, the Salazar-Corcoran calculation [21] (see Eq. 4.2) is overall more accurate in estimating the CrCL of the obese patients [22, 23]. Therefore, this calculation should be considered when adjusting drug dosing in obesity.

$$\begin{aligned}
&1.\ \text{Creatinine clearance (male) (mL/min)} \\
&= \frac{[137 - \text{Age}] \times [(0.285 \times \text{Weight (kg)}) + (12.1 \times \text{Height (m}^2))]}{51 \times \text{Serum creatinine (mg/dL)}} \\
&2.\ \text{Creatinine clearance (women) (mL/min)} \\
&= \frac{[146 - \text{Age}] \times [(0.287 \times \text{Weight (kg)}) + (9.74 \times \text{Height (m}^2))]}{60 \times \text{Serum creatinine (mg/dL)}}
\end{aligned} \tag{4.2}$$

## Review of Existing Literature

Gentamicin and tobramycin pharmacokinetics were evaluated in 26 obese and non-obese subjects who received a low dose of 1 mg/kg [14]. The observed serum concentrations were significantly higher in obese patients, while the observed V was relatively lower in these patients. However, based on lean body mass, the observed V was greater in obese subjects, which has highlighted that gentamicin and tobramycin do not penetrate significantly into adipose tissue. Normalization of V using a value corresponding to 40 % of likely adipose mass in obese subjects resulted in a V value that closely resembled that of the non-obese subjects (note that this 40 % value is more likely to reflect extra lean muscle rather than adipose tissue) [14]. Similarly, another study has showed that the normalization of the observed tobramycin V values using 58 % of adipose weight has resulted in values close to that observed in non-obese patients [18]. This finding was also observed in other studies, in which a correction factor between 30 and 45 % was required to normalize the V of aminoglycoside in obese patients [15, 17].

Higher drug clearance has commonly been observed in obese patients as compared to the normal-weight patients [19, 24]. In one study, gentamicin pharmacokinetics were evaluated in 60 patients that were grouped into obese and non-obese [24]. Overall, the observed gentamicin clearance was 25 % higher in the obese group. Similarly, in another pharmacokinetic study evaluating different aminoglycosides (gentamicin, tobramycin and amikacin), all drug clearances were approximately 90 % higher in the morbidly obese group when compared to the normal-weight group [19]. Although the observed aminoglycoside clearance was

higher in the obese group, the increment is usually proportional to the increased in V in these patients, thus a similar elimination rate constant and elimination half-life is observed between obese and non-obese patients [14, 18–20, 24]. Therefore, this might indicate that adjustment of the dosing interval may not be necessary when dosing in obese patients, but the magnitude of the dose should be tailored to the patients adjusted body weight.

## Recommendations

Aminoglycoside dosing in obesity is challenging, because of the interrelationship between physiological changes related to obesity and the physicochemical characteristics of this class of drugs. Concentration-dependency is the predominant killing effect for aminoglycosides. Therefore, administration of a higher initial dose is required to rapidly achieve the desired peak concentration that can exceed the target MIC by a ratio of 8–10. Appropriate V estimation using a correction factor (see Eq. 4.1) is useful in determining the correct initial dose, based on the desired peak concentration that can achieve the targeted PK/PD target.

For subsequent doses, the usual standard dosing regimens can be used as a guide, such as 5–8 mg/kg for gentamicin, tobramycin and netilmicin, and 15–30 mg/kg for amikacin. Dosing weight correction factors should be considered for accurate aminoglycoside dosing [16] (see Eq. 4.3). Extended interval dosing (>24 hourly) should be considered in patients with renal dysfunction, which can occur in obese patients with nephropathy secondary to diabetes mellitus. TDM remains essential to guide time to next dose, particularly due to its narrow therapeutic index. While the timing of re-dosing based on TDM data (or accurate GFR determination) is beneficial to describe the clearance of a particular drug in an individual patient.

$$\text{Dosing weight} = 0.4 \times (\text{TBW} - \text{IBW}) + \text{IBW} \tag{4.3}$$

Equation 4.3 defines the recommended equations that should be used for obese patients.

## References

1. Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM. Aminoglycosides: activity and resistance. Antimicrob Agents Chemother. 1999;43:727–37.
2. Kumana CR, Yuen KY. Parenteral aminoglycoside therapy. Selection, administration and monitoring. Drugs. 1994;47:902–13.
3. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the committee on rheumatic fever, endocarditis, and Kawasaki disease, council on cardiovascular disease in the young, and the councils on clinical

cardiology, stroke, and cardiovascular surgery and anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. 2005;111:e394–434.
4. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26:1–10.
5. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987;155:93–9.
6. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother. 1999;43:623–9.
7. Zelenitsky SA, Harding GK, Sun S, Ubhi K, Ariano RE. Treatment and outcome of Pseudomonas aeruginosa bacteraemia: an antibiotic pharmacodynamic analysis. J Antimicrob Chemother. 2003;52:668–74.
8. Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis. 1988;158:831–47.
9. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis. 2007;45:753–60.
10. Mouton JW, Vinks AA. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics: the minimum inhibitory concentration versus stationary concentration. Clin Pharmacokinet. 2005;44:201–10.
11. Smith PF, Ballow CH, Booker BM, Forrest A, Schentag JJ. Pharmacokinetics and pharmacodynamics of aztreonam and tobramycin in hospitalized patients. Clin Ther. 2001;23:1231–44.
12. Abernethy DR, Greenblatt DJ. Drug disposition in obese humans. An update. Clin Pharmacokinet. 1986;11:199–213.
13. Bosma RJ, Krikken JA, Homan van der Heide JJ, de Jong PE, Navis GJ. Obesity and renal hemodynamics. Contrib Nephrol. 2006;151:184–202.
14. Schwartz SN, Pazin GJ, Lyon JA, Ho M, Pasculle AW. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. J Infect Dis. 1978;138:499–505.
15. Korsager S. Administration o gentamicin to obese patients. Int J Clin Pharmacol Ther Toxicol. 1980;18:549–53.
16. Traynor AM, Nafziger AN, Bertino JS Jr. Aminoglycoside dosing weight correction factors for patients of various body sizes. Antimicrob Agents Chemother. 1995;39:545–8.
17. Bauer LA, Blouin RA, Griffen WO Jr, Record KE, Bell RM. Amikacin pharmacokinetics in morbidly obese patients. Am J Hosp Pharm. 1980;37:519–22.
18. Blouin RA, Mann HJ, Griffen WO Jr, Bauer LA, Record KE. Tobramycin pharmacokinetics in morbidly obese patients. Clin Pharmacol Ther. 1979;26:508–12.
19. Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol. 1983;24:643–7.
20. Leader WG, Tsubaki T, Chandler MH. Creatinine-clearance estimates for predicting gentamicin pharmacokinetic values in obese patients. Am J Hosp Pharm. 1994;51:2125–30.
21. Salazar DE, Corcoran GB. Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med. 1988;84:1053–60.
22. Vincent F, El-Khoury N, Rondeau E. Renal function in critically ill, morbidly obese patients. Am J Respir Crit Care Med. 2004; 169:1332; author reply 1333.
23. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy. 2007;27:1081–91.
24. Sketris I, Lesar T, Zaske DE, Cipolle RJ. Effect of obesity on gentamicin pharmacokinetics. J Clin Pharmacol. 1981;21:288–93.

# Chapter 5
# Fluoroquinolones

**Renee Dimond, Rahul P. Patel and Syed Tabish R. Zaidi**

**Abstract** Fluoroquinolone antibiotics are frequently used in a variety of indications in hospital and outpatient settings due to the availability of an oral dosage form. The pharmacokinetics of this particular class of antibiotics varies significantly among individual agents, thus preventing a uniform approach to dose adjustment. Relatively more data is available for ciprofloxacin and levofloxacin compared to other agents in this class. This chapter outlines the available literature of pharmacokinetic changes in obese patients and the recommend dosing for specific agents. Flouroquinolone antibiotics have significant dose related adverse effects and therefore, the clinical need of a flouroquinolone should be carefully considered before using them in obese patients, who are likely to receive higher than the usually recommended doses.

**Keywords** Ciprofloxacin · Moxifloxacin · Levofloxacin · Dosing · Adverse effects · Obese

## Introduction

The fluoroquinolones are an important class of broad-spectrum antimicrobials, which are effective against a variety of bacterial agents that cause community and nosocomial infections [1]. Notable members of this class are ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin. They are bactericidal and work by blocking the enzymes DNA gyrase and topoisomerase IV to inhibit bacterial DNA synthesis [1]. The development of increasing bacterial resistance to these enzymes has limited the use of fluoroquinolones to infections where other agents are considered ineffective or contraindicated [1].

R. Dimond
Department of Pharmacy, Ballarat Health Service, Ballarat, VIC, Australia

R.P. Patel · S.T.R. Zaidi (✉)
Pharmacy, School of Medicine, University of Tasmania, Private Bag 26, Hobart, TAS 7001, Australia
e-mail: Tabish.razizaidi@utas.edu.au



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_5

## Pharmacodynamics Target

Fluoroquinolone antibiotics are generally considered broad-spectrum agents. Significant differences exist within their spectrum; for example, moxifloxacin has an extended spectrum of activity against Gram-positive and anaerobic organisms, whereas it has less activity against Gram-negative organisms. On the other hand, ciprofloxacin is comparatively more active against resistant Gram-negative organisms such as *Pseudomonas, Shigella, Salmonella and Neisseria spp* when compared to moxifloxacin [1]. Notably, levofloxacin is effective against *S. pneumonia* while retaining its anti-pseudomonal activity [1].

Two pharmacodynamics indices have been reported that correlate with the anti-infective efficacy of the fluoroquinolones:

- The area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio (i.e. AUC/MIC)
- The maximum plasma concentration at steady state ($C_{max,\ ss}$) and MIC ratio (i.e. $C_{max,\ ss}$/MIC) [2–4].

As such, larger doses given less frequently can maximize the bacterial cell killing when fluoroquinolones are used for clinical infections.

## Pharmacokinetics Changes in Obesity

The pharmacokinetics (PK) of this particular class of antibiotics varies significantly among individual agents, thus preventing a uniform approach to dose adjustment. Alterations in pharmacokinetic parameters in obese patients have been noted in several studies [3, 5–8]. The following section will summarize the available pharmacokinetic data for each agent.

The clearance (CL) of ciprofloxacin has been shown to increase in obese individuals [5]. The increase in clearance is likely to be due to an increase in volume of distribution (V), suggesting that ciprofloxacin distributes less into adipose tissue than other body tissues [2]. Peak plasma concentration has been shown to reduce in obesity as well as AUC, likely due to the increased V displayed in obese patients [5, 6]. Oral bioavailability of ciprofloxacin has been shown to be impaired in obese patients in the early post-operative period. Given the possible confounding of post-surgical changes in V of medications, the observed reduction in oral bioavailability cannot be attributed solely to obesity [6].

Levofloxacin displays high inter-individual variability with regards to its PK in obesity [3, 8]. In a single case report of levofloxacin, using double the recommended dose in treating a morbidly obese patient for pneumonia, the authors found CL and $C_{max}$ to be similar to non-obese patients [8]. The AUC was twice the normally reported value and V was substantially increased as well [8]. Pai et al.

studied the effects of various size descriptors on the CL and AUC of levofloxacin in 68 patients ranging in weight from 98 to 250 kg [3]. Levofloxacin doses of 250 to 1500 mg per day were used and the AUC values only exceeded 250 mg.h/L in patients receiving >1000 mg (higher than the recommended doses) who also have mild to moderate renal impairment (Creatinine clearance [Cr CL] <50 ml/min) [3]. The total body weight of patients has no effects on the CL. Patient height was the only parameter that correlated well with the CL of Levofloxcain [3].

The only study reporting the PK of moxifloxacin in obese patients (Body Mass Index [BMI] 43–58 kg/m$^2$) is by Kees et al. [7]. The authors studied the disposition of moxifloxacin in 17 obese males undergoing gastric bypass surgery. All patients received a daily oral dose of moxifloxacin (400 mg) for three consecutive days prior to surgery, followed by an intravenous (IV) dose of 400 mg on the day of surgery [7]. Adequate blood samples were taken at regular intervals following each oral dose and after the IV dose to calculate various PK parameters. Additionally, tissue samples of small intestine, greater momentum and subcutaneous tissues were collected to examine the tissue distribution of moxifloxacin. There were no significant differences observed in V, CL, AUC or $C_{max}$ of moxifloxacin in the study when compared to the reported values of these parameters from normal weight subjects [7]. Tissue concentrations in the small intestine were greater, whereas the concentrations in adipose tissues were lower in obese patients when compared to the published values of normal subjects [7]. Ideal body weight (IBW) and lean body mass have a higher correlation with CL when compared to total body weight (TBW) in this study [7].

The authors of this chapter were unable to locate any study of other flouroquinolones (ofloxacin, gatifloxacin etc.) in obesity.

## Review of Existing Literature

### *Ciprofloxacin*

Significant changes in the pharmacokinetics of ciprofloxacin in obese patients were noted in a single dose by Allard et al. [5]. A single intravenous dose of ciprofloxacin 400 mg was given to 17 obese male adults (BMI of 36.4 ± 3.9 kg/m$^2$) with 11 matched normal weight controls. Total body and renal clearance was significantly increased in obese subjects compared to controls. The increase in total body clearance was attributed to a 23 % increase in V at steady state observed in the obese group [5]. Significant decreases in $C_{max}$ and AUC were also noted in the obese group compared to the normal weight controls with no changes in the time to peak plasma concentration ($t_{max}$) or elimination half-life. Based on their results, the authors recommend adding 45 % of the difference between TBW and IBW [0.45 × (TBW − IBW)] without a clear justification for such a recommendation [5].

Hackam et al. investigated the effect of the early post-operative period on the oral bioavailability of a single 750 mg dose of ciprofloxacin in 31 adults; 9 healthy

controls (group 1), 15 patients within 24 h of elective laparotomy for abdominal surgery (group 2) and 7 patients within 24 h of laparotomy for peritonitis (group 3) [6]. Statistically significant reductions in mean AUC and $C_{max}$ were found for groups 2 and 3 along with a non-significant increase in $t_{max}$, suggesting reduced oral bioavailability in these groups. No absorption occurred in 27 % (4/15) of the elective surgery group and 14 % (1/7) of the peritonitis group [6]. Non-absorbers were noted to be significantly heavier than absorbers (29 % ± 6 % over IBW compared to 15 % ± 3 % over IBW, $p < 0.05$) [6]. The authors conclude that the inhibitory effect of increased body weight on AUC and $C_{max}$ most likely results from an increase in V, although concomitant effects on absorption or metabolism could not be excluded [6].

The authors noted the probability of eradicating infections was dependent on the type of bacteria involved. This predictability was based on the differences in the AUC/MIC ratios [6]. All patients achieved a sufficient AUC/MIC ratio to effectively eradicate *E. coli* infections; however, only the non-obese control group and 'absorbers' obese in the elective surgery group achieved a sufficient AUC/MIC ratio to eradicate infections due to *P. mirabilis* [6]. Whereas participants from all three study groups manifested insufficient levels of ciprofloxacin to successfully eradicate an infection with *S. aureus* [6].

Hollenstein et al. [9] compared interstitial space fluid levels of ciprofloxacin in 12 obese adults (BMI 41 ± 7.8) and 12 age- and sex-matched lean controls (BMI 19.8 ± 1.4). Interstitial space fluid was chosen because most infections take place in the interstitial space fluid of tissue rather than within cells. Each participant was given a weight-adjusted intravenous bolus dose of ciprofloxacin (2.85 mg/kg). No significant difference was found in peak ciprofloxacin concentration or interstitial space fluid AUC between study groups. Tissue penetration ($AUC_{tissue}/AUC_{plasma}$) was significantly lower in the obese group suggesting that penetration into the interstitial space fluid is impaired in obesity. The authors concluded that ciprofloxacin dose should be based on actual body weight to achieve the same tissue concentration as those found in lean subjects [9].

A 57 year old, 250 kg man was treated with intravenous ciprofloxacin (800 mg 12 hourly) to manage complicated cellulitis [10]. The ciprofloxacin dose was based on the work of Allard et al. [5]. Treatment continued for 19 days, the peak ciprofloxacin levels were estimated on day four and were found to be within the therapeutic range. No apparent adverse reactions were reported and clinical cure was achieved [10]. Another case report involving a 45 year old critically ill male with a BMI 53.7 $kg/m^2$ and receiving continuous venovenous hemodiafiltration, was administered an intravenous dose of 800 mg every 12 h to treat presumed lumbar osteomyelitis. Microbiological cure was achieved though the patient died from a non-infectious aetiology. The authors based their dose on the findings of Hollenstein et al. [9], which was equivalent to a weight-adjusted dose based on actual body weight of 4.3 mg/kg [11]. This equates to the recommended dose of 400 mg (4–5 mg/kg) for non-obese patients.

## *Levofloxacin*

Luque et al. [8] reported a pharmacokinetic study of a single adult patient with severe morbid obesity (BMI 56.2 kg/m$^2$), receiving levofloxacin for a lower respiratory tract infection. The dose was based on an actual body weight adjusted calculation of 4 mg/kg 12 hourly (750 mg per dose IV), which the authors note is based on the ciprofloxacin dosing recommendation from the study by Holleinstein et al. [9]. The half-life and steady state V were increased in the obese patient as compared to values reported in the non-obese. The authors attributed this finding to the significant distribution of levofloxacin into excess weight [8]. The AUC was doubled, which most likely reflects the twice daily dosing regimen and the $C_{max}$ and CL were similar to that reported with standard daily dosing. No adverse reactions related to levofloxacin occurred. IV levofloxacin continued for 6 days followed by a switch to oral levofloxacin (500 mg 12 hourly for 4 days) which resulted in clinical cure [8].

Sanchez-Navarro et al. [4] investigated the pharmacokinetics of levofloxacin in 9 Caucasian, critically ill adults, requiring artificial respiratory support for deterioration of chronic respiratory impairment [4]. Seven of the nine enrolled participants had a TBW greater than 30 % above their IBW. All received standard dosing with 500 mg intravenous levofloxacin per day administered over 60 min. High inter-individual variability was shown for the plasma concentration profiles achieved, as well as steady state $C_{max}$, CL, V and AUC [4]. In terms of bacteriological response, the probability of not obtaining the recommended AUC/MIC and steady state $C_{max}$/MIC ratios, as estimated by Monte Carlo simulation, was approximately 30 % and 60 %, respectively, in the patients studied [4].

Pai et al. [3] retrospectively reviewed 68 morbidly obese (BMI $\geq$ 40 kg/m$^2$) Caucasian adults receiving intravenous and oral levofloxacin, to assess body size and renal function as predictors of levofloxacin clearance and AUC. The findings showed that levofloxacin clearance was significantly related to height but not TBW ($p < 0.05$) [3]. The authors noted that renal function may be augmented in obesity due to glomerular hyper-filtration, which may impact the efficacy of levofloxacin, as it is primarily eliminated unchanged via the kidneys [3]. In patients with augmented renal function (CrCl > 110 mL/min) a fixed levofloxacin dose (750 mg) was unlikely to achieve the AUC target required for antimicrobial efficacy [3]. As a result, the authors concluded that an empiric four-category daily-dose regimen (500, 750, 1000, 1250 mg) of levofloxacin, stratified by creatinine clearance (using the Cockcroft-Gault equation and based on ideal body weight) is expected to have greater than 90 % probability of achieving effective therapeutic exposure (AUC) in morbidly obese patients [3].

Cook et al. [12] described the levofloxacin pharmacokinetics following a single dose (750 mg IV) in 12 hospitalised and 3 ambulatory obese adults (mean BMI 50 kg/m$^2$). The authors found no difference in $C_{max}$ and V of levofloxacin between ambulatory and hospitalised obese patients when compared to normally reported published values [12]. Variable AUC and clearance were noted and ambulatory

obese patients were found to have increased levofloxacin clearance and a subsequently lower AUC when compared with the acutely ill hospitalised patients [12]. Additionally, the mean AUC of both obese groups was slightly higher when compared with the AUC of non-obese individuals [12].

### *Moxifloxacin*

Kees et al. [7] investigated the pharmacokinetics of moxifloxacin in 12 morbidly obese adults (BMI > 40 kg/m$^2$) scheduled for gastric bypass surgery. Plasma pharmacokinetics from the study patients were reported as comparable to that of historic data in normal weight subjects [7]. Mean tissue concentrations in the small intestine were found to be double the plasma moxifloxacin concentration. Comparatively, adipose tissue concentrations were significantly lower in obese patients when compared to normal weight individuals. No serious or clinically relevant adverse events, drug related adverse reactions or changes in laboratory or electrocardiographic parameters occurred during the study. The authors conclude that the pharmacokinetics of moxifloxacin is not significantly affected by morbid obesity and no dose adjustment seems to be necessary in this particular population [7].

Colin et al. [13] undertook a population pharmacokinetics analysis in combination with pharmacokinetic-pharmacodynamic simulations to determine if adequate moxifloxacin concentrations are achieved in obese patients. The twelve enrolled participants had previously undergone bariatric surgery at least 6 months prior to inclusion. Moxifloxacin was administered as 2 doses of 400 mg, separated by a one-week washout period [13]. The first dose was administered as a tablet and the second as an intravenous infusion. The authors found that lean body mass (LBM), rather than total body mass should be used in the prediction of moxifloxacin pharmacokinetics [13]. The probability of attaining the recommended AUC/MIC target for a hypothetical *S. pneumoniae* infection approaches zero using the standard 400 mg moxifloxacin dose in patients with a LBM of $\geq$78 kg [13]. The authors conclude that the standard moxifloxacin dose of 400 mg is not sufficient for obese individuals where LBM exceeded 78 kg [13].

## Recommendations

The available evidence supports the use of higher than usually recommended dosing for ciprofloxacin and levofloxacin in obese patients. Given the limited data on the clinical effectiveness and safety of higher than usually recommended doses of these agents, a number of factors beyond the PK variations warrant close considerations. Fluoroquinolones are associated with significant adverse effects, such as QTc interval prolongation, especially when used concomitantly with interacting

medications known to increase QTc interval, hepatotoxicity, seizures, myalgia and fungal super-infections. Additionally, relevant microbiological data such as MIC of the bacteria being treated should also be considered prior to the use of fluoroquinolones in obese patients, as higher MICs are often associated with a failure to attain recommended AUC/MIC ratio.

Ciprofloxacin should be dosed as 4 mg/kg/dose using actual body weight up to a maximum of 800 mg/dose twice daily. Frequent dosing (every 8 h) may be considered in critically ill patients due to significant variability in the PK of ciprofloxacin in this patient group [14]. Given the variability in the dosing of levofloxacin among obese patients, we recommend an initial starting dose of 500–750 mg, 12 hourly, followed by a renal adjusted dose, based on the Pai et al. study, in the range of 500–1250 mg per day. This is because some increase in V has been noted for levofloxacin and an initial high dose will be able to achieve the recommended AUC/MIC ratio. Given the limited information on moxifloxacin dosing, we recommend the use of either ciprofloxacin or levofloxacin in obese patients to treat non-tuberculosis regimen. It is extremely important that obese patients receiving high dose fluoroquinolones are closely monitored for cardiovascular, neurological and metabolic adverse effects.

## References

1. Oliphant CM, Green GM. Quinolones: a comprehensive review. Am Fam Physician. 2002;65 (3):455–64.
2. Bhavnani SM, Forrest A, Hammel JP, Drusano GL, Rubino CM, Ambrose PG. Pharmacokinetics-pharmacodynamics of quinolones against Streptococcus pneumoniae in patients with community-acquired pneumonia. Diagn Microbiol Infect Dis. 2008;62(1):99–101.
3. Pai MP, Cojutti P, Pea F. Levofloxacin dosing regimen in severely morbidly obese patients (BMI $\geq$ 40 kg/m(2)) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. Clin Pharmacokinet. 2014;53(8):753–62.
4. Sanchez Navarro A, Colino Gandarillas CI, Alvarez Lerma F, Menacho YA, Dominguez-Gil A. Pharmacokinetics and pharmacodynamics of levofloxacin in intensive care patients. Clin Pharmacokinet. 2005;44(6):627–35.
5. Allard S, Kinzig M, Boivin G, Sorgel F, LeBel M. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Ther. 1993;54(4):368–73.
6. Hackam DJ, Christou N, Khaliq Y, Duffy DR, Vaughan D, Marshall JC, et al. Bioavailability of oral ciprofloxacin in early postsurgical patients. Arch Surg. 1998;133(11):1221–5.
7. Kees MG, Weber S, Kees F, Horbach T. Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients. J Antimicrob Chemother. 2011;66(10):2330–5.
8. Luque S, Grau S, Valle M, Colino CI, Ferrer A. Levofloxacin weight-adjusted dosing and pharmacokinetic disposition in a morbidly obese patient. J Antimicrob Chemother. 2011;66 (7):1653–4.
9. Hollenstein UM, Brunner M, Schmid R, Muller M. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. Int J Obes Relat Metab Disord. 2001;25(3):354–8.

10. Caldwell JB, Nilsen AK. Intravenous ciprofloxacin dosing in a morbidly obese patient. Ann Pharmacother. 1994;28(6):806.
11. Utrup TR, Mueller EW, Healy DP, Callcut RA, Peterson JD, Hurford WE. High-dose ciprofloxacin for serious gram-negative infection in an obese, critically ill patient receiving continuous venovenous hemodiafiltration. Ann Pharmacother. 2010;44(10):1660–4.
12. Cook AM, Martin C, Adams VR, Morehead RS. Pharmacokinetics of intravenous levofloxacin administered at 750 milligrams in obese adults. Antimicrob Agents Chemother. 2011;55 (7):3240–3.
13. Colin P, Eleveld DJ, Struys MM, T'Jollyn H, Bortel LM, Ruige J, et al. Moxifloxacin dosing in post-bariatric surgery patients. Br J Clin Pharmacol. 2014;78(1):84–93.
14. Lipman J, Scribante J, Gous AG, Hon H, Tshukutsoane S. Pharmacokinetic profiles of high-dose intravenous ciprofloxacin in severe sepsis. The Baragwanath Ciprofloxacin Study Group. Antimicrob Agents Chemother. 1998;42(9):2235–9.

# Chapter 6
# Carbapenems

**Tara Anderson**

**Abstract** Carbapenems are broad spectrum beta-lactam antibiotics and are important therapeutic agents for the treatment of infections caused by resistant Gram-negative bacteria. There are five agents commercially available for clinical use; imipenem, meropenem, doripenem, ertapenem and faropenem. The spectrum of activity against Gram-positive bacteria, anaerobic organisms and Gram-negative bacteria varies according to the agent. The objective of this chapter is to summarise the existing literature in relation to the pharmacodynamic targets and pharmacokinetic parameters, particularly as they relate to dosing in the obese patient. There is limited literature available related to the optimisation of a dosing strategy in this patient group but the pharmacokinetic data suggests that obesity predominantly influences both the distribution and clearance of carbapenem antibiotics. Depending on the individual circumstances (the presence of any of the following conditions: critical illness, augmented renal clearance, renal replacement therapy, less susceptible organism, *Acinetobacter* spp. or poor initial clinical response) consideration may need to be given to increasing the dose from standard dosing recommendations and/or administering the antibiotic as an extended infusion, complemented by the use of therapeutic drug monitoring.

**Keywords** Carbapenem · Imipenem · Meropenem · Doripenem · Ertapenem · Faropenem

## Introduction

The carbapenems are broad-spectrum beta-lactam antibiotics. They are important therapeutic agents for the treatment of infections caused by resistant Gram-negative bacteria. Widespread use of carbapenems, however, has been associated with

T. Anderson (✉)
Department of Infectious Diseases and Microbiology, Royal Hobart Hospital, Hobart, TAS, Australia
e-mail: tara.anderson@dhhs.tas.gov.au



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_6

increasing prevalence of multi-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* and multi-resistant Gram-negative bacteria, as well as *Clostridium difficile* infection and hence, the use of carbapenems should be reserved [1].

Imipenem, meropenem and doripenem have broad spectrum in vitro activity against Gram-positive bacteria, anaerobic organisms and Gram-negative bacteria, including *Pseudomonas* spp. and extended spectrum beta-lactamase (ESBL) and AmpC-producing *Enterobacteriaceae*. These agents do not have activity against *Stenotrophomonas maltophilia* or methicillin-resistant *S. aureus* (MRSA). Meropenem and doripenem do not provide useful activity against *Enterococcus faecalis* either, but imipenem does [2].

Ertapenem provides a similar spectrum of activity as the aforementioned carbapenems, but has poor activity against *Pseudomonas* spp., *Acinetobacter* spp. and *Enterococcus* spp. [2].

Faropenem is an orally administered carbapenem antibiotic. It provides broad spectrum in vitro activity against Gram-positive bacteria, anaerobic organisms and Gram-negative bacteria, including ESBL and AmpC-producing *Enterobacteriaceae.* It does not have activity against MRSA, vancomycin-resistant *Enterococcus faecium, Pseudomonas aeruginosa* or *S. maltophilia* [3].

## Pharmacodynamics Target

The carbapenems all have similar pharmacokinetic properties. As with other beta-lactam agents, they exhibit time-dependent bactericidal activity and the most important pharmacokinetic/pharmocodynamic (PK/PD) parameter predicting bacteriological and clinical efficacy is the time (*f*T) in which the free drug concentration remains above the minimum inhibitory concentration (MIC) ($fT_{>MIC}$). For carbapenems, a $fT_{>MIC} \geq 20$ % of the dosing interval is required for bacteriostatic effects, while a $fT_{>MIC}$ of $\geq 40$ % achieves bactericidal effects, but these data were primarily derived from in vitro and animal studies [4]. The target $fT_{>MIC}$ however may differ based on the clinical scenario, such as the site and severity of infection, causative organism and specific patient factors.

A commonly used pharmacodynamic target for carbapenems is:

> 40 % free drug concentrations (*f*T) above the minimum inhibitory concentration (MIC) (i.e. 40 % $fT_{>MIC}$).

On the basis of in vitro and in vivo experiments, a maximum killing effect is reached at a concentration of 4 × MIC, which may therefore represent the target

concentration for the pathogen strains. In critically ill patients, dosing of carbapenem therapy is often modified to maximize the carbapenem PK/PD target attainment by either increasing the drug dose, the infusion time, or both, often accompanied by therapeutic drug monitoring [2].

## Pharmacokinetic Changes in Obesity

Obesity may be associated with changes in absorption, distribution, metabolism and clearance of antimicrobials [5]. Carbapenem PKs have been found to be altered in obese patients when compared with healthy volunteers and non-obese patients [6, 7]. The changes of most significance to the carbapenem antibiotics appear to be those affecting both their distribution and clearance.

Carbapenem antibiotics are hydrophilic, preferentially distributing into lean tissues and they do not distribute well into adipose tissues. Obesity is associated with changes in both the amount and the ratio of lean and adipose tissue. The volume of distribution of these drugs may be increased in obesity, due to both the increase in lean tissue as well as an increase in total body water, as approximately 30 % of adipose tissue is water. Likewise, plasma volume is correlated with body weight [8, 9].

Clearance of carbapenem antibiotic in obesity varies and may either be increased, due to an increase in kidney mass and global filtration, or decreased, due to comorbid kidney disease, such as chronic hypertensive or diabetic nephropathy.

In non-critically ill patients, the meropenem pharmacokinetics have been found to be similar in obese and non-obese patients [6]. In critically ill patients receiving meropenem, however, the volume of distribution has been found to be larger and the clearance higher in obese patients when compared with non-obese patients, but the difference was not found to be statistically significant. The median body mass index (BMI) in this study population was 40 $kg/m^2$. The pharmacokinetics of meropenem are unknown in patients with larger BMIs [10].

The change in the volume of distribution of the central compartment has been found to be significantly larger and the area under the serum concentration-time curve (AUC) significantly smaller in morbidly obese volunteers who received a single 1 g dose of ertapenem compared with normal weight volunteers [7].

## Review of Existing Literature

The appropriate carbapenem dosage regimen in obese adults is unclear, due to the limited data available and careful consideration of the appropriate dosage regimen for each individual circumstance is critical. There is limited information in relation

to carbapenem dosing in obese children. It is recommended that extrapolation from available adult data be undertaken and that carbapenems should be dosed according to total body weight (TBW) [11].

The available literature in non-critically ill and critically ill patients is summarized below.

## *Non-critically Ill Patients*

Carbapenem pharmacokinetics and pharmacodynamics have not been well studied in obese patients outside the intensive care setting. Few studies have investigated the effects of obesity on the PK/PD of carbapenems, the studies that are available have been summarized below:

1. **Meropenem**

In a PK/PD study by Kays et al. the steady state pharmacokinetics and pharmacodynamics of meropenem were evaluated in obese patients hospitalized on a general ward. With the use of a standard dosage regimen (i.e. 1 g meropenem (30 min infusion) every 8 h), the probability of PD target (40 % $fT_{>MIC)}$ attainment was >90 % at MIC $\leq$ 4 mg/L. When the cumulative fraction of response (CFR) at 40 % $fT_{>MIC}$ was evaluated against 8 g-negative organisms, the standard dosage regimen (outlined above) achieved a CFR >98 % for the *Enterobacteriaceae*, but it only achieved a CFR of 94.3 % for *P. aeruginosa* and 70.6 % for *Acinetobacter* spp. Extending the infusion from 30 min to 3 h improved the CFR to 95.8 and 72.7 %, respectively [6].

In a recent study by Hites et al. in which obese, non-critically ill patients received a standard dosage of 1 g meropenem every 8 h, 93 % reached T > MIC for *Enterobacteriaceae* and *P. aeruginosa* but only 21 % reached T > 4 × MIC. The only risk factor detected for failure to reach the PD target was high $CrCL_{24h}$ and it was demonstrated that as the creatinine clearance ($CrCL_{24h}$) increased, the percentage of patients with adequate serum concentrations decreased. Only patients with a CrCL of less than 80 ml/min had a high probability (>90 %) of attaining therapeutic serum concentrations when treating infections due to *P. aeruginosa* [12]. Augmented renal clearance is not well recognized in obese patients outside the critically ill setting.

The evidence would suggest that the standard dosage regimen of 1 g meropenem (30 min infusion) every 8 h provides adequate exposure for *Enterobacteriaceae* and *P. aeruginosa* in the setting of a high $CrCL_{24}$, however, there is a risk that the PD target will not be obtained, particularly for *P. aeruginosa* [12]. Alternative dosage regimen or drug therapy, however, may need to be considered for *Acinetobacter* spp. [6].

2. **Doripenem**

In the recent PK/PD study by Kays et al. the steady state pharmacokinetics and pharmacodynamics of doripenem in obese patients hospitalized on a general ward was evaluated. With the use of the standard dosage regimen (i.e. 500 mg doripenem (1 h infusion) every 8 h), the probability of PD target (40 % $fT_{>MIC}$) attainment was >90 % at MIC $\leq$ 2 mg/L [6]. When the CFR at 40 % $fT_{>MIC}$ was evaluated against 8 g-negative organisms, the standard dosage regimen (outlined above) achieved a CFR >98 % for the *Enterobacteriaceae* but only achieved a CFR of 88.8 % for *P. aeruginosa* and 64.6 % for *Acinetobacter* spp. Increasing the dose to 1 g 8-hourly and extending the infusion from 1 to 4 h, improved the CFR to 96.9 % for *P. aeruginosa* and 71.1 % for *Acinetobacter* spp. [6].

The standard dosage regimen of 500 mg doripenem (1 h infusion) every 8 h, provided adequate exposure for *Enterobacteriaceae*. For *P. aeruginosa,* prolonging the infusion of 500 mg every 8–4 h and/or increasing the dose to 1 g every 8 h, will be needed to provide optimal coverage but alternative dosage regimen or drug therapy may need to be considered for *Acinetobacter* spp. as none of the dosage regimens provided optimal coverage [6].

3. **Ertapenem**

Standard dosing of ertapenem (i.e. 1 g daily), has been demonstrated to be insufficient to achieve a 90 % probability of target attainment (PTA) for maximum bactericidal activity (i.e. 40 % $fT_{>MIC}$) for organisms at any MIC (i.e. 0.25 μg/mL and above) in normal weight, obese and extremely obese adults. Obese adults were unable to achieve 90 % PTA for bacteriostatic activity (i.e. 20 % $fT_{>MIC}$) for organisms with a MIC > 0.25 mg/L [7].

A recently published study investigating the PK/PD characteristics of ertapenem, when administered to obese Caucasian female patients (BMI ranging between 42.5 and 58.5 kg/m$^2$) for surgical prophylaxis, determined that the optimal PK/PD target could not be obtained with the currently proposed dose of 1 g for organisms with a MIC within the current susceptibility breakpoints (i.e. MIC 0.25–0.5 mg/L) [13].

Optimal dosing regimens for ertapenem are unclear in the setting of obesity and should be carefully considered, particularly for treating infections due to organisms with a MIC > 0.25 mg/L.

4. **Other**

There is no published literature on the other carbapenems in obese patients in the non-critically ill setting.

## *Critically Ill Patients*

Carbapenems may be influenced by a number of pharmacokinetic changes in the intensive care setting, such as an increased volume of distribution, modified

antibiotic clearance, modified protein binding and/or modified tissue penetration. A recently published editorial summarizes the challenges of the altered pharmacokinetics and augmented renal clearance on antibiotic dosing in this patient population [14]. In addition, large carbapenem PK heterogeneity has been noted in the literature between critically ill patients, further complicating the situation [15, 16].

The use of renal replacement therapy (RRT) in the intensive care setting may also influence drug clearance in the critically ill patient and makes individual antibiotic dosing challenging. Recent publications have examined the impact of RRT on carbapenem dosing requirements in the critically ill:

- A recent paper by Jamal et al. reviewed the evidence for the impact of variation in RRT settings and meropenem clearance in the intensive care. The RRT intensity (as determined by the effluent flow rate) has been demonstrated to influence the extracorporeal elimination of meropenem. Although different dosing strategies were used, meropenem dosing achieved the desired PK/PD target in 89 % of cases for MIC $\leq$ 2 mg/L, but for pathogens with MIC > 2 mg/L, alternate dosing strategies were recommended to improve PK/PD target attainment, such as extended or continuous infusion [17].
- A recent paper by Roberts et al. described the doripenem population PK and dosing requirements for critically ill patients receiving continuous venovenous haemodiafiltration and standard dosage regimen of doripenem (500 mg infusion (60 min) 8-hourly). All patients achieved favourable PK/PD for up to a MIC of 4 mg/L [18].
- The PK of ertapenem was recently studied in 8 critically ill patients (mean weight 78.9 kg) receiving continuous venovenous haemodialysis or haemodiafiltration. Monte Carlo simulations were performed to evaluate the ability of several ertapenem dosing regimens to obtain effective unbound serum concentrations. All of the regimens used, including the standard regimen of 1 g ertapenem daily, produced unbound ertapenem concentrations above 2 mg/L for 40 % of the dosing interval for at least 96 % of the simulated patients and for a mean of 90 % of the dosing interval. The authors concluded that in patients receiving CRRT, where there is a substantial degree of ertapenem clearance, particularly in those infected with organisms with high MICs, a higher dose of ertapenem than routinely recommended, may be required [19].

Carbapenem therapy is often preserved for indications where antimicrobial resistance is suspected or confirmed, making the optimization of the dosage regimen for carbapenem therapy critical in this context. This relates to optimizing the clinical outcomes as well as minimizing the selection of drug-resistant strains. Optimizing dosage regimens in the critical care setting is highlighted by the following publications:

- Roberts et al. compared the plasma and subcutaneous tissue concentration-time profiles of meropenem, administered by intermittent bolus dosing or continuous infusion, to critically ill patients with sepsis and without renal dysfuntion in

assessing the CFR against Gram-negative pathogens, including less susceptible *P. aeruginosa* and *Acinetobacter* spp. Administration of intermittent bolus dosing (500 mg–1 g 8-hourly) was sufficient for *Enterobacteriaceae* but did not achieve 40 % $fT_{>MIC}$ against *P. aeruginosa* and *Acinetobacter* spp. High doses of meropenem by extended or continuous infusion was required to achieve 40 % $fT_{>MIC}$ against *P. aeruginosa* and *Acinetobacter* spp. [20].

- Langan et al. tested whether an extended 3-h infusion of meropenem (500 mg) achieved an equivalent proportion of time above the MIC ($\%T_{MIC}$) to that of meropenem (1 g) given over 30 min in 10 heterogeneous critically ill patients. It was identified that the 2 regimens achieved a similar PK/PD profile and for low MIC ($\leq$2 mg/L), both regimens attained a $\%T_{MIC} > 40$ % in all patients. For an MIC of 4 mg/L, this target was attained in 9 out of 10 patients but with an MIC of 8 mg/L, 3 of the patients had a $\%T_{MIC} < 40$ %. Patients who had a CrCL > 100 ml/min had significantly greater meropenem clearance than the other patients, regardless of which regimen was used, and would be at risk of poor target attainment [21].
- Jaruratanasirikul et al. have described the administration of a 4-h 2 g meropenem infusion every 8 h as having the highest PTA and CFR when treating critically ill patients with ventilator-associated pneumonia and causative organisms with an MIC of 4 mg/L, when compared with other dosage regimens [22]. Similar findings have also been demonstrated for doripenem, particularly in critically ill patients with neutropenia [23].

There is limited literature in relation to carbapenem pharmacokinetics and pharmacodynamics in the *obese, critically ill patient*. The available literature is summarized below:

1. **Meropenem**

Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese critically ill patients was studied in a recent paper by Cheatham et al. and with a dosage regimens of meropenem of 500 mg, 6 hourly or 1 g, 8 hourly, infused over 30 min, the probability of PD target ($fT_{>MIC}$ of 40 %) attainment was $\geq$90 % at a MIC of $\leq$2 mg/L. At a MIC of 4 mg/L, only 2 g every 8 h and 1 g every 6 h achieved a PTA >90 %, none of the 30-min infusions studied achieved >90 % PTA for MIC $\geq$ 8 mg/L. Prolonging the infusion time to 3 h enhanced the dosage regimen. For pathogens with an MIC of 8 mg/L, 2 g every 8 h and 1 g every 6 h, infused over 3 h achieved a PTA > 90 %. Based on this study, routine dose escalation of meropenem may not be required in morbid obesity as standard dosing regimens achieve adequate PD exposures for susceptible pathogens. However, larger doses administered by prolonged infusion will be necessary for pathogens with MIC $\geq$ 4 mg/L [24].

An example of this is demonstrated in a published case report by Taccone et al. which described a 70 year old obese man (120 kg weight and BMI 35 kg/m$^2$) who was treated with meropenem for a multi-resistant *P. aeruginosa* (MIC 8 mg/L) ventilator-associated pneumonia complicated by bacteraemia. He clinically

improved when the meropenem regimen was optimized to obtain at least 40 % of 4 × MIC by changing his regimen to 3 g, 3 h extended infusion, 6-hourly [25].

A case control study published by Hites et al. highlighted the potential role of therapeutic drug monitoring in obese critically ill patients, as the obese critically ill patients, not receiving CRRT in this study, had lower antibiotic serum concentrations of meropenem than the non-obese group, with a trend to higher clearance and total volume of distribution in the obese patients, making appropriate dosage predictions difficult [10].

### 2. **Doripenem**

Optimal doripenem dosing was simulated in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance and decreased bacterial susceptibility in a recent paper by Roberts et al. [26]. Patients were administered either 250 or 500 mg doses of doripenem as 30-min, 1 or 4-h infusions. The simulations for the 1-h infusion demonstrated that all patients achieved high PTAs against a MIC of 2 mg/L or less, but for a MIC of 4 mg/L, the 100 and 135 kg patients had a lower likelihood of achieving the PD target of 40 % $fT_{>MIC}$. Administration of 500 mg doripenem via a 4-h infusion led to higher PTAs for the heavier patients, supporting the use of extended infusions in obese patients, particularly for organisms with a MIC 4 mg/L. None of the 500 mg IV 8-hourly regimens maintained sufficient drug exposures at an MIC 8 mg/L. It was the recommendation of the authors that an extended infusion of doripenem may be considered in patients with an increased total body weight and/or elevated creatinine clearance.

**Table 6.1** Standard carbapenem dosage recommendations for adult patients

| Carbapenem | Standard dosage regimen for initial carbapenem therapy in adult patients with normal renal function | |
|---|---|---|
| | Susceptible *Enterobacteriaceae* | Susceptible *P. aeruginosa* or *Acinetobacter* spp. |
| Meropenem | Meropenem<br>MIC $\leq$ 2 mg/L<br>[a]1 g IV 8-hourly (30 min infusion) | Meropenem MIC $\leq$ 2 mg/L<br>[a]1 g IV 8-hourly (30 min infusion) |
| Doripenem | Doripenem<br>MIC $\leq$ 1 mg/L<br>[b]500 mg IV 8 hourly (1-h infusion) | Doripenem MIC $\leq$ 1 mg/L 1 g IV 8-hourly (4-h infusion) |
| Ertapenem | Ertapenem<br>MIC $\leq$ 0.5 mg/L<br>[c]1 g IV daily | No activity |

[a]For Central Nervous System infections, 2 g intravenous (IV) 8-hourly (30-min infusion) is recommended [1]

[b]Consider extending the infusion to 4-h infusion in obese patients

[c]Consider increasing the dose to 1 g, 12 hourly in obese patients and/or where the causative pathogen's minimum inhibitory concentration (MIC) 0.25–0.5 mg/L

## Recommendations

Standard carbapenem dosing of meropenem and doripenem should be sufficient for the majority of clinical indications in an obese adult patient, but consideration should be made to further optimize the dosage regimen, i.e. consideration of either a higher dose and/or an extended infusion complemented by therapeutic drug monitoring, if available, if the patient has any of the following conditions:

- Critical illness
- Augmented renal clearance
- Renal replacement therapy
- Infection with less susceptible organism (i.e. high MIC)
- Infection with *Acinetobacter* spp.
- Poor initial clinical response.

Refer to Table 6.1 for guidance for standard dosage regimens for adult patients.

## References

1. Therapeutic guidelines: antibiotic Version 15, 2014.
2. Breilh D, et al. Carbapenems. J Chemother. 2013;25(1):1–17.
3. Schurek KN, et al. Faropenem: review of a new oral penem. Expert Rev Anti Infect Ther. 2007;5(2):185–98.
4. Lodise TP, et al. Application of antimicrobial PD concepts into clinical practice: focus on beta-lactam antibiotics. Pharmacotherapy. 2006;26:1320–32.
5. Polso AK, et al. Review Article. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39:584–608.
6. Kays MB, et al. Comparative pharmacokinetics and pharmacodynamics of doripenem and meropenem in obese patients. Ann Pharmacother. 2014;48(2):178–86.
7. Chen M, et al. Comparative PK and PD target attainment of ertapenem in normal-weight, obese and extremely obese adults. AAC. 2006;50(4):1222.
8. Antimicrobial considerations in obese adult patients: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2007;27:1081–91.
9. Falagas ME, et al. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet. 2010;375:248–51.
10. Hites M, et al. Case-control study of drug monitoring of beta-lactams in obese critically ill patients. AAC. 2013;57:708–15.
11. Kendrick JG, et al. Pharmacokinetics and drug dosing in obese children. J Pediatr Pharmacol Ther. 2010;15:94–109.
12. Hites M, et al. Broad spectrum beta-lactams in obsese non-critically ill patients. Nutr Diab. 2014;4:e119.
13. Borracci T, et al. Use of the parenteral antibiotic Ertapenem as short term prophylaxis in bariatric surgery: a pharmaco-kinetic-pharmacodynamic study in class 3 obese female patients. Minerva Anestesiol. 2014;80(9):1005–11.
14. Udy AA, et al. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. Int J Antimicrob Agents. 2012;39:455–7.

15. Goncalves-Pereira J, et al. Assessment of PK changes of meropenem during therapy in septic critically ill patients. BMC Pharmacol Toxicol. 2014;14(15):21.
16. Goncalves-Pereira J, et al. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care. 2011;15(15):R206.
17. Jamal JA, et al. The impact of variation in renal replacement therapy settings on piperacillin, meropenem and vancomycin drug clearance in the critically ill; an analysis of published literature and dosing regimens. CCM. 2014;42(7):1640–50.
18. Roberts JA, et al. Doripenem population PK and dosing requirements for critically ill patients receiving continuous venovenous haemodiafiltration. J Antimicrob Chemother. 2014;69 (9):2508–16.
19. Eyler RF, et al. Pharmacokinetics of ertapenem in critically ill patients receiving CVVH or hemodiafiltration. AAC. 2014;58(3):1320–6.
20. Roberts JA, et al. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrobial Chemother. 2009;64: 142–50.
21. Langan KM, et al. Pharmacokinetics of short versus extended infusion meropenem dosing in critically ill patients: a pilot study. Crit Care Resusc. 2014;16(3):190–6.
22. Jaruratanasirikul S, et al. Pharmacodynamics of doripenem in critically ill patients with ventilator-associated Gram-negative bacilli pneumonia. Int J Antimicrob Agents. 2012;40 (5):434–9.
23. Stein GE, et al. Pharmacokinetics and monte carlo simulations of doripenem in patients with febrile neutropenia. Ann Pharmacother. 2012;46(10):1281–6.
24. Cheatham SC, et al. Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit. J Clin Pharmacol. 2014;54 (3):324–30.
25. Taccone FS, et al. Optimal meropenem concentrations to treat multi-drug resistant P. aeruginosa septic shock. AAC. 2012;56(4):2129–31.
26. Roberts JA, et al. Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, ARC and decreased bacterial susceptibility. CCM. 2013;41 (2):489–95.

# Chapter 7
# Glycopeptides and Antibiotics for Gram-positive Bacterial Infections

**Syed Tabish R. Zaidi and Brett Janson**

**Abstract** Glycopeptides, lipopeptides and other antibiotics, such as linezolid and quinupristin/dalfopristin, are exclusively used for the treatment of infections caused by Gram-positive bacteria. Limited information is available about the dosing of these antibiotics in obese patients. This chapter aims to summarise the available evidence on the dosing of glycopeptides, lipopeptides, linezolid and quinupristin/dalfopristin in obesity. Specific dosing recommendations are also provided to aid clinical decisions making with regards to dosing of these antibiotics in obese patients.

**Keywords** Vancomycin · Daptopmycin · Glycopeptides · Lipopeptides · Linezolid · Quinupristin/dalfopristin · Obese · Dosing

## Introduction

### *Glycopeptides*

Vancomycin is the only true glycopeptide antibiotic, as it contains two glucose moieties (glyco) on a five aromatic ring (peptide) [1]. Teicoplanin, on the other hand, contains a long chain of acyl (lipid) groups in addition to the glycopeptide and therefore, is better classified as glycolipopeptide [1]. The same is true for all the new members of this class, such as oritavancin, dalbavancin and telavancin, which should chemically be referred to as lipoglycolipopeptides [1]. Nevertheless, all such antibiotics are often grouped together as glycopeptides in clinical practice [2] and therefore, this chapter will discuss them all under one section.

S.T.R. Zaidi (✉)
Pharmacy, School of Medicine, University of Tasmania, Private Bag 26, Hobart, TAS 7001, Australia
e-mail: Tabish.razizaidi@utas.edu.au

B. Janson
Department of Pharmacy, Peter MacCallum Cancer Centre, Melbourne, Australia



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_7

Despite the significant pharmacokinetic (PK) limitations [3] and the emergence of resistance [1, 2], vancomycin is still considered as a first-line agent for the treatment of infections caused by methicillin-resistant Staphylococcus *aureus* (MRSA) [4]. Teicoplanin, though mainly known for its preferable pharmacokinetic profile and once-daily dosing advantage, has been shown to be effective against some of the vancomycin-resistant enterococci (VRE), mainly the vanB subtype [1]. Newer agents, such as dalbavancin and telavancin, are ineffective against vanA-containing VRE, like vancomycin and teicoplanin [1, 5]. Oritavancin is the only newer lipoglycopeptide that is effective against both the vanA and vanB subtypes of VRE [6] and therefore offers a benefit over and above the pharmacokinetic advantages of the newer glycopeptides.

## Pharmacodynamic Target

The ratio of the area under the curve (AUC) and the minimum inhibitory concentration (MIC) (denoted as AUC/MIC) is the preferred pharmacodynamic (PD) index that determines the rate and extent of the bacterial killing capacity of glycopeptides [2]. Most of the available PD data are for vancomycin, and a ratio of AUC/MIC > 350 has been suggested, initially based on data from pneumonia [7]. A number of subsequent studies have questioned the validity of this ratio, suggesting both lower (AUC/MIC > 350) [8] and higher (AUC/MIC > 550) ratios [9]. Needless to say, the differences in MIC measurement methods, the difficulties in accurately measuring AUC, an the increasing incidence of isolates with higher MICs and different susceptibility patterns across hospital organizations pose unique challenges in the routine implementation of targeting the AUC/MIC ratio as a standard practice for individualised dosing [10]. As a result, the trough concentration ($C_{min}$) of vancomycin is in common use as a surrogate measure of the AUC/MIC ratio, even though it is not considered highly accurate. Trough concentrations of 15–20 mg/L are recommended for serious Gram-positive infections where vancomycin is indicated [11]. Attaining the PD target of an AUC/MIC of 400 is challenging, particularly when the pathogen has an MIC of >1 mg/L, even when a $C_{min}$ of 20 mg/L is achieved [10]. This raises the question of whether vancomycin should be used when dealing with bacteria that have an MIC > 1 mg/L.

The AUC/MIC ratio has also been suggested for teicoplanin as the preferred PD index. The recommended target ratio for AUC/MIC (>345 mg h/L) is based on data from febrile neutropenia patients [12]. Further support for this model came from the Hagihara et al. [13] study, which investigated the effects of the recommended target trough concentration of teicoplanin in critically ill patients with an MRSA infection. Patients who failed to respond to treatment had an average AUC of 652 mg h/L, compared to the responders who attained an average AUC closer to 900 mg h/L. Given the susceptibility breakpoint of MIC < 4 mg/L for teicoplanin [14], the targeted AUC/MIC ratio of >345 is most likely unattainable for bacterial strains at the higher end of the susceptibility range, given the current dosing approaches. This

has been objectively confirmed in a Monte-Carlo simulation study where the probability of teicoplanin achieving AUC/MIC > 345 was 50 % for isolates with a MIC of close to 2 mg/L, despite using the higher end of teicoplanin dosing (800 mg/day) [12].

All of the newer synthetic lipoglycopeptides are potently bactericidal compared to vancomycin and teicoplanin, with susceptibility breakpoints for most bacteria under MIC < 0.25 mg/L [2]. The AUC/MIC ratio remains the preferred PD index defining their antimicrobial activity [15]. Target AUC/MIC ratios for dalbavancin, telavancin and oritavancin are 214–331, >404 and >11,982 respectively [15, 16].

## Pharmacokinetic Changes in Obesity

As expected, the majority of studies reporting glycopeptide PK in obese patients are related to vancomycin with little information available on teicoplanin. Three PK parameters have principally been shown to be affected [17]:

- An increased volume of distribution (V)
- An altered vancomycin protein binding
- Changes in renal clearance (CL) [17].

Changes to the volume of distribution are predominantly due to the increase in mass associated with obesity, including the increase in muscle mass and connective tissue required to support and maintain the additional adiposity. These changes will affect loading dose requirements as well as the frequency and dose of maintenance dosing. Changes in plasma proteins, in particular, $\alpha_1$-acid glycoprotein, have the potential to change the free fraction (f) of vancomycin, which may further affect changes in the volume of distribution and the proportion of the drug that is available for renal clearance. Obesity tends to result in an increased renal clearance of drugs, including vancomycin, due to several physiological changes, including an increased glomerular filtration rate and an increased renal plasma flow. The plateau of this increase in renal function is subject to debate, but a point of 100 kg has been suggested.

There is only sparse information about the PK changes of teicoplanin in obese patients. One study that reported the development of an outpatient parenteral antibiotic protocol included patients weighing up to 146 kg [18]. Though the study did not detail changes in V and CL specific to obese patients, the authors stated that Ideal Body Weight (IBW) was better in describing the V of teicoplanin than total body weight (TBW) [18].

Though specific studies investigating PK differences in obese patients are not available for newer lipoglycopeptides, clinical trials investigating the effectiveness of these agents included obese patients, and some data is available on the effects of body weight and height on the V and CL of these agents [19–21]. No significant variation, up and above the expected inter-individual variability, in the V or CL of

oritavancin, was noticed that can be attributed to the weight or body mass index (BMI) of patients [19]. A significant linear relationship between the V and CL of dalbavancin and the weight and body surface area (BSA), respectively, has been noted, suggesting an increase of these parameters in obese patients [21]. Similarly, both CL and V of telavancin increased linearly with increases in weight suggesting a higher V and CL in obese patients [22].

## Review of Existing Literature

### *Vancomycin and Teicoplanin*

A number of studies have investigated the dosing of vancomycin in obese patients, though comparing these is difficult due to the inconsistent definitions of obesity across these studies [17, 23–26]. Despite the uniform approach of defining obesity based on the BMI, only a few studies have used this metric, and others have relied on relative percentages (ranging from >120–190 %) of Lean Body Weight (LBW) or IBW.

The earliest study [24] in 4 normal weight healthy males and 6 morbidly obese post-surgical patients showed a strong correlation between TBW and both V and CL of vancomycin. Mean serum vancomycin concentrations were less than 10 mg/L in obese patients at 4 h post-infusion. The authors recommended patients be dosed on TBW and suggested more frequent dosing of lower maintenance doses (e.g., every 8 h instead of every 12 h) to avoid high transient peak concentrations. The study was limited by the fact that it was a single dose PK study and patients were not treated for any infection, and therefore, no clinical outcomes were applicable. Additionally, there was a significant variation of TBW within the 6 obese patients included in the study (111–226 kg). The study did not utilise mg/kg dose, but calculated the reported dosing requirements based on PK parameters derived from a single dose study.

Bauer et al. [23] studied dosing requirements of vancomycin in 24 morbidly obese patients (165 ± 46 kg), who were receiving antibiotic treatment as in-patients with matching normal weight control patients. A significant increase in vancomycin clearance was observed in obese patients and the authors concluded that a vancomycin dose of 30 mg/kg/day (based on TBW) is needed in obese patients to maintain a mean trough concentration of 7 mg/L [23]. Reynolds et al. [27] compared the performance of a high dose vancomycin protocol with a standard dosing regimen in achieving target therapeutic levels of vancomycin (i.e. 10–20 mg/L) in obese patients as a retrospective cohort study. The high dose was defined as 15–20 mg/kg q8–12 h (30–45 mg/kg/day) whereas the standard dose was defined as 10 mg/kg q12 h or 15 mg/kg q24 h. Standard dosing regimens resulted in better target trough attainment (59 % vs. 36 %) in patients and lower toxic concentration (18 % vs. 55 %) thus maximising the effectiveness and

minimising the potential dose related toxicity. Importantly, a greater proportion of patients also had lower than recommended trough concentration (23 % vs. 9 %). While the above two studies addressed some of the limitations of the Blouin et al. study [24], no clinical outcomes were reported [23, 27].

Kosmisky et al. [28] used a different protocol in morbidly obese patients (defined as >100 kg and >140 % of their IBW). The protocol was developed after an internal audit found that the IDSA protocol was associated with supra-therapeutic trough levels (>20 mg/L) in patients weighing >100 kg. The protocol used a 20–25 mg/kg loading dose (maximum 2.5 g; 25 mg/kg reserved for critically ill) followed by a 10 mg/kg maintenance dose given every 12–24 h depending on renal function ( $\geq$65 mL/min and 35 to <65 mL/min, respectively). More than half of the patients did not reach recommended trough concentration of >10 mg/L, and only one third of the patients achieved a trough level of 10–20 mg/L.

Hong et al. [29], in their most recent study of 150 patients, have examined the effect of a two sample (peak and trough concentration) vs. a traditional single sample (trough concentration) strategy on the attainment of target trough concentrations in morbidly obese patients. The percentage of patients who attained the recommended trough concentration on the first measurement was similar between the two groups. However, significantly more patients attained the recommended trough concentration of >10 mg/L (31 % vs. 65 %) in the group dosed according to the two sample measurement [29]. The average loading dose used in the two sample group was 20 mg/kg, the average maintenance dose was 15 mg/kg, and the most common frequency was every 12 h. Importantly, 25 % of patients in the single measurement group and 30 % of the patients in two sample measurement group had a first trough concentration that was more than 20 mg/L (i.e. supra-therapeutic or undesirably high) [29]. The authors reported that the use of TBW for the initial dose calculation was likely to be the source of this overestimation of the initial loading dose, resulting in a higher than accepted trough concentration. This was further supported by their regression analysis, where the V did not show a linear relationship with TBW (R = 0.01). It is important to note that this regression analysis was based on actual two-level measurements and not on population PKs.

Compared to vancomycin, there is a scarcity of published data on teicoplanin dosing in obese patients. Hagihara et al. [13] investigated 33 patients (34–101 kg) and showed that patients with a higher exposure to teicoplanin had a better outcome, and recommended a target AUC (0–24) on the third day of treatment of 800 mg h/L. A variety of loading schedules were used, with higher doses having higher rates of achievement of the target AUC. Brink et al. [30] recommended a loading dose of 6 mg/kg every 12 h for 48 h, followed by once daily doses for infections other than infective endocarditis, septic arthritis and osteomyelitis, for which they suggested that higher doses might be warranted. Pea et al. [31] compared a standard loading dose (400 mg every 12 h for 3 doses followed by 400 mg daily) with a more aggressive approach (800 mg then 400 mg Day 1, 600 mg then 400 mg Day 2, then 400 mg every 12 h thereafter) and found that in the higher dosed group, $C_{min}$ averaged >10 mg/L within 24 h, and 21 out of 22 patients had achieved $C_{min}$ > 10 mg/L at 48 h. When using the standard dosing, only 1 out of

11 patients had a $C_{min}$ > 10 mg/L at 96 h. Higher doses of teicoplanin (12 mg/kg every 12 h for 4 doses followed by daily dosing) were also required in a critically ill population (ventilator-associated pneumonia) to achieve adequate levels [32].

## *Newer Lipogycopeptides*

Similar to teicoplanin, limited published data is available on the use of newer lipoglycopeptides in obese patients. Buckwalter et al. [21] reported a two compartmental PK model for dalbavancin, based on 532 patients receiving the antibiotic for systemic infections. Patient weight in this study ranged from 42 to 320 kg. The authors found a significant linear relationship between V and BSA, and that dalbavancin clearance was influenced by renal function (CrCl) and BSA [21].

A study by Rubino et al. [19] reported the PK of oritavancin in a pooled data from two trials (SOLO I and SOLO II) investigating its effectiveness in skin and skin structure infections using a single dose of 1200 mg. The maximum BMI and weight in the study were 67.4 kg/$m^2$ and 178 kg. No significant variation that could be attributed to the weight or BMI of patients, up and above the expected inter-individual variability, was noticed in the V or CL of oritavancin [19]. Height was considered a more significant influence on oritavancin clearance. This is contrary to an earlier study by the same investigators, where they found a significant increase in CL in patients weighing above 110 kg [20]. This study included 46 patients >110 kg, including 7 with a weight between 150 and 200 kg and 3 patients above 200 kg (max 227 kg). However, it is important to note that this study investigated much lower doses (200 mg for $\leq$110 kg and 300 mg for >110 kg) [20] compared to the 1200 mg dose used in the most recent study [19]. Other earlier studies [33] also suggested that higher doses may be required for obese patients, however, since the adoption of the single high dose, this appears unnecessary. Interestingly, this paper also noted a clinical and microbiological failure in a patient with morbid obesity (>2× IBW); this patient also had a host of comorbidities and was treated using a daily dose [33].

Telavancin pharmacokinetics from a number of previous studies were retrospectively described using a PK model [34]. In obese patients, mg/kg dosing was still considered appropriate, as telavancin is distributed into extracellular fluids. Renal clearance, the main clearance route of telavancin, is also increased in obese patients, resulting in a mildly increased AUC (34 % from 627.4 mg h/L in non-obese patients to 838.0 mg h/L in obese patients (defined as BMI $\geq$ 35 kg/$m^2$)) [34]. In this study, the heaviest patient weighed 314 kg. There were no other details of a number of obese patients, etc. Obese patients (BMI > 35) receiving 10 mg/kg intravenous (IV) q24 h had similar rates of clinical cure compared to non-obese patients (72 % vs. 78 %, significance not reported), similar results were reported for vancomycin despite suboptimal dosing (1 g IV every 12 hours) [35].

## Recommendations

The recommendations made below have been developed based on existing PK data with little clinical data currently available to support altered dosing in obese patients. We recommend that the aggressiveness of the treatment course should be tailored to the severity of the infection. It is currently unknown at what weight the below recommendations should be capped (if at all).

Vancomycin—loading dose based on TBW as per IDSA recommendations (15–20 mg/kg, or up to 25–30 mg/kg for severe infections), whether this recommendation should be capped at any particular weight is currently unknown. The maintenance doses and frequency should be tailored to renal function; a maximum starting maintenance dose of 1.5 g every 12 hours is suggested only for those with normal to high renal function (>110 mL/min CrCl). Maintenance doses >2 g should be avoided; if sub-therapeutic levels are observed with doses of 2 g, the frequency should be increased, with a concurrent decrease in the individual dose. For example, vancomycin 2 g every 12 hours can be change to 1–1.5 g every 8 hours. If subsequent levels are still sub-therapeutic at 1.5 g every 8 hours, 1 g every 6 hours should be considered. Caution should be exercised in cases where a total daily doses >4 g is used because of the associated increase in nephrotoxicity. Trough level and serum creatinine monitoring should occur prior to the third dose, with subsequent doses modified accordingly. Another important consideration with high doses is the adjustment of administration time to 10 mg/min (instead of standard 1–2 h) to minimise infusion related adverse effects.

Teicoplanin—loading dose of 6–12 mg/kg q12 h for 3 doses should be used—the maintenance doses after this should be tailored to renal function and severity of infection; serum concentration monitoring should be used.

Dalbavancin, oritavancin and telavancin—standard dosing should be used, no alteration appears necessary for obese patients. Reduce doses as recommended for renal dysfunction.

## *Other Antibiotics Used Against Gram-positive Bacteria*

Daptomycin, quinupristin/dalfopristin and linezolid are three other commonly used antibiotics for the treatment of infections caused by Gram-positive bacteria. Given the limited data on these antibiotics in obesity, the following section will briefly summarize the available literature to form dosing recommendations.

## *Daptomycin*

Daptomycin is a relatively new addition to the antibiotic armamentarium. It is the first in a class of cyclic lipopeptides and is active against Gram-positive organisms, including MRSA and VRE. The V is approximately 0.1 L/kg, implying a low concentration in the peripheral tissues. Efficacy is most closely correlating with AUC/MIC and the maximum plasma concentration ($C_{max}$) and MIC ratios ($C_{max}$/MIC) [36].

A single dose (4 mg/kg) PK study of daptomycin in moderately obese, morbidly obese and normal weight matched control subjects showed an increase in the V, AUC and renal clearance [37]. Contrary to these findings, the single dose PK study by Pai et al. [38] found no significant difference between the V and CL of daptomycin in obese and normal subjects. The authors argue that better matching of control subjects made their study more valid, a fact that was also supported by other published data on the PK of normal subjects [38]. Regardless of the differences in V and CL, both studies found a significantly higher exposure of daptomycin in obese subjects with higher AUC and $C_{max}$ values [37, 38]. A unique additional contribution of the Pai et al. study was their comparative assessment of various equations to estimate the CL of daptomycin. Based on their analyses, the authors recommend the use of IBW when estimating renal function for dosing adjustment of daptomycin using the Cockroft-Gault equation [38]. None of the studies reported data related to the clinical outcomes.

Daptomycin is dosed at 4 mg/kg daily for complicated skin and skin structure infections and at 6 mg/kg for bacteraemia or right-sided endocarditis caused by Staphylococcus *aureus* [39], higher doses have been reported [40, 41]. The Australian Product Information for Cubicin™ [39] states that no dose adjustment is required for obese patients. However, the single dose studies mentioned above have unanimously concluded an over-exposure of daptomycin in obese patients, as shown as higher AUC and $C_{max}$, when dosing, is based on TBW [37, 38]. Given the potential dose related elevation in creatinine kinase (CK) and the increase the risk of myopathy with higher doses [39], higher AUC and $C_{max}$ associated with dosing daptomycin based on TBW is not free from additional risks. Ng et al, in their first comparative study of daptomycin dose based on TBW and IBW, examined the records of 308 patients who had received daptomycin for at least 72 h [42]. A total of 185 and 123 patients were dosed based on TBW and IBW, respectively. No significant differences were observed between patients who received TBW- and IBW-based dosing on a microbiological or clinical cure. Additionally, no differences were observed in patients with regards to their BMI and dosing based on either IBW or TBW. Although patients in the TBW group had a higher incidence of elevated CK levels than patients in the IBW group, such differences did not reach statistical significance [42].

An excellent review article [43] has recently summarised the disparity surrounding dosing recommendations between different sources of information and highlighted both the increased risk of myopathy (as shown by raised creatinine

phosphokinase (CPK) levels) when using adjusted body weight (ABW) and the importance of therapeutic drug monitoring in this population, where available. Interestingly, an ABW (using a factor of 0.4) was used for all patients with a BMI of $\geq$35 kg/m$^2$ [43]. Lastly, at least one paper [40] has discussed withholding HMG-CoA reductase inhibitors (statins) during daptomycin therapy, due to the potential for increased risk of myopathy. The Australian product information similarly states "consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving daptomycin" [39].

## *Linezolid*

Linezolid is an oxazolidinone antibiotic, which is exclusively used for serious Gram-positive infections resistant to first line agents, particularly MRSA and VRE [44]. Linezolid exhibits time dependent PD and it was learned from the animal model that the antibacterial effect of linezolid is at a maximum when the time the antibiotic concentration is maintained above the MIC (T > MIC) is 85 % or above of the dosing duration [44]. Limited human PD studies have further identified that an AUC/MIC ratio of >100 is an additional predictor of the bacterial killing by linezolid [44]. Additional data from the compassionate use program of linezolid further endorsed the importance of an AUC/MIC ratio of 80–120 in maximising the effectiveness of the skin and soft tissues infections, bacteraemia and pneumonia [45]. A recent study revealed that an AUC/MIC value of 280 was associated with a 50 % probability of linezolid-induced thrombocytopenia [46].

Stein et al. [47] found that 7 obese patients (>50 % above IBW, weight 101–195 kg, BMI range 34–73 kg/m$^2$) that were taking oral linezolid q12 h for the treatment of cellulitis, had a lower $C_{max}$ and AUC when compared to normal weight ($C_{max}$ 12.7 mg/L vs. 16.3–24 mg/L, $AUC_{0-12}$ 92 mg h/mL vs. 138 mg h/L); however, no treatment failures were recorded. De Pascale et al. [48] studied the PK/PD of linezolid in 22 critically ill obese patients (BMI 32.3–39.1 kg/m$^2$) that were being treated for ventilator-associated pneumonia. Linezolid was administered as an intermittent infusion of 600 mg twice daily in 11 patients whereas the remaining 11 patients received a loading dose of 600 mg followed by a continuous infusion of 50 mg/hr. As expected, the percentage of T > MIC was significantly improved in the continuous infusion subgroup (100 % (100–100) vs. 82 % (54.8–98.8), p = 0.009 for MIC of 2 mg/L). No comparison was made to normal weight patients and the results should not be generalised to morbidly obese patients (BMI $\geq$ 40 kg/m$^2$). Lastly, two case studies [49, 50] in obese patients (286 kg, 86 kg/m$^2$ and 116 kg, 37 kg/m$^2$) showed lower steady state and trough concentrations, close to or potentially below the $MIC_{90}$; interestingly, both showed successful treatment outcomes. This further highlights the importance of local susceptibility patterns to guide dose adjustment for individual patients.

### *Quinupristin/Dalfopristin*

Quinupristin/Dalfopristin (Q/D) is a 30:70 mixture of semisynthetic antibiotics of streptogramin groups B and A, respectively [51]. Both of these agents are individually bacteriostatic when combined, but exhibit bactericidal activity against MRSA and enterococci resistant to glycopeptide as a 30:70 mixture [51]. AUC/MIC is the PD index that explains the bactericidal activity of Q/D [52]. Limited information is available on the drug dosing of Q/D in obese patients, but no dose adjustment has been recommended either in elderly or obese patients [53].

One study comparing obese and normal weight patients found an approximate 25 % increase in the $C_{max}$ and AUC of Q/D in obese subjects when the dose was based on TBW. Although the authors noted a better correlation with LBW instead of TBW, they recommend using TBW when dosing Q/D. The mean TBW in the study was 108 kg and the findings may not be extrapolated to morbidly obese patients [54].

## Recommendations

Limited evidence supports the use of IBW for dosing daptomycin, although, for morbidly obese patients (BMI > 35 kg/m$^2$), a better approach will be to consider an ABW with a factor of 0.4. Given the possibility of elevated CK levels and associated myopathy with daptomycin, CK levels should be monitored to identify patients at high risk of developing this serious adverse effect. It remains unclear whether dose adjustment is needed for linezolid, although use of a continuous infusion strategy should be considered for morbidly obese patients, due to the lack of data and a strong association between T > MIC and therapeutic effectiveness. Given the limited use of Q/D in clinical practice and the lack of guidance of the effect of obesity on the PK of this drug, other antibiotics should be considered for obese patients.

## References

1. Kahne D, Leimkuhler C, Lu W, Walsh C. Glycopeptide and lipoglycopeptide antibiotics. Chem Rev. 2005;105(2):425–48.
2. Henson KE, Levine MT, Wong EA, Levine DP. Glycopeptide antibiotics: evolving resistance, pharmacology and adverse event profile. Expert Rev Anti-infect Ther. 2015;12:1–14.
3. Nunn MO, Corallo CE, Aubron C, Poole S, Dooley MJ, Cheng AC. Vancomycin dosing: assessment of time to therapeutic concentration and predictive accuracy of pharmacokinetic modeling software. Ann Pharmacother (Research Support, Non-U.S. Gov't). 2011;45(6):757–63.
4. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of

methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis: Off Publ Infect Dis Soc Am (Practice Guideline Research Support, Non-U.S. Gov't). 2011;52(3):285–92.
5. Smith WJ, Drew RH. Telavancin: a new lipoglycopeptide for gram-positive infections. Drugs Today (Barc) (Review). 2009;45(3):159–73.
6. Arhin FF, Draghi DC, Pillar CM, Parr TR Jr, Moeck G, Sahm DF. Comparative in vitro activity profile of oritavancin against recent gram-positive clinical isolates. Antimicrob Agents Chemother. 2009;53(11):4762–71.
7. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet (Clinical Trial Comparative Study). 2004;43 (13):925–42.
8. Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, et al. Vancomycin AUC/MIC ratio and 30-day mortality in patients with Staphylococcus aureus bacteremia. Antimicrob Agents Chemother. 2013;57(4):1654–63.
9. Lodise TP, Drusano GL, Zasowski E, Dihmess A, Lazariu V, Cosler L, et al. Vancomycin exposure in patients with methicillin-resistant Staphylococcus aureus bloodstream infections: how much is enough? Clin Infect Dis: Off Publ Infect Dis Soc Am. 2014;59(5):666–75.
10. Patel N, Pai MP, Rodvold KA, Lomaestro B, Drusano GL, Lodise TP. Vancomycin: we can't get there from here. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2011;52(8):969–74.
11. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis: Off Publ Infect Dis Soc Am (Practice Guideline Research Support, Non-U.S. Gov't). 2009;49(3):325–7.
12. Kuti JL, Kiffer CR, Mendes CM, Nicolau DP. Pharmacodynamic comparison of linezolid, teicoplanin and vancomycin against clinical isolates of Staphylococcus aureus and coagulase-negative staphylococci collected from hospitals in Brazil. Clin Microbiol Infect: Off Publ Eur Soc Clin Microbiol Infect Dis. 2008;14(2):116–23.
13. Hagihara M, Umemura T, Kimura M, Mori T, Hasegawa T, Mikamo H. Exploration of optimal teicoplanin dosage based on pharmacokinetic parameters for the treatment of intensive care unit patients infected with methicillin-resistant Staphylococcus aureus. J Infect Chemother: Off J Jpn Soc Chemother. 2012;18(1):10–6.
14. Campana EH, Carvalhaes CG, Nonato B, Machado AM, Gales AC. Comparison of M.I.C.E. and Etest with CLSI agar dilution for antimicrobial susceptibility testing against oxacillin-resistant Staphylococcus spp. PLoS ONE. 2014;9(4):e94627.
15. Zhanel GG, Calic D, Schweizer F, Zelenitsky S, Adam H, Lagace-Wiens PR, et al. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. Drugs. 2010;70(7):859–86.
16. Wu G, Truong J, Lee S, Elnadoury O, Kuan W, Abraham T, et al. Oritavancin, a single-dose, complete regimen, for the treatment of acute bacterial skin and skin structure infections. Expert Rev Anti-infect Ther. 2015;13(4):409–16.
17. Grace E. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. J Antimicrobial Chemother (Review). 2012;67 (6):1305–10.
18. Lamont E, Seaton RA, Macpherson M, Semple L, Bell E, Thomson AH. Development of teicoplanin dosage guidelines for patients treated within an outpatient parenteral antibiotic therapy (OPAT) programme. J Antimicrobial Chemother (Practice Guideline Research Support, Non-U.S. Gov't). 2009;64(1):181–7.
19. Rubino CM, Bhavnani SM, Moeck G, Bellibas SE, Ambrose PG. Population pharmacokinetic analysis for a single 1,200-milligram dose of oritavancin using data from two pivotal phase 3 clinical trials. Antimicrob Agents Chemother. 2015;59(6):3365–72.

20. Rubino CM, Van Wart SA, Bhavnani SM, Ambrose PG, McCollam JS, Forrest A. Oritavancin population pharmacokinetics in healthy subjects and patients with complicated skin and skin structure infections or bacteremia. Antimicrobial agents and chemotherapy. [Clinical Trial, Phase I Clinical Trial, Phase II Clinical Trial, Phase III Research Support, Non-U.S. Gov't]. 2009 Oct;53(10):4422–8.
21. Buckwalter M, Dowell JA. Population pharmacokinetic analysis of dalbavancin, a novel lipoglycopeptide. J Clin Pharmacology (Clinical Trial, Phase II Clinical Trial, Phase III Multicenter Study). 2005;45(11):1279–87.
22. Lodise TP, Butterfield JM, Hegde SS, Samara E, Barriere SL. Telavancin pharmacokinetics and pharmacodynamics in patients with complicated skin and skin structure infections and various degrees of renal function. Antimicrobial Agents Chemother. [Research Support, Non-U.S. Gov't]. 2012;56(4):2062–6.
23. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol. 1998;54(8):621–5.
24. Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WO Jr. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother. 1982;21(4):575–80.
25. Demirovic JA, Pai AB, Pai MP. Estimation of creatinine clearance in morbidly obese patients. Am J Health-Syst Pharm: AJHP: Off J Am Soc Health-Syst Pharma (Comparative Study). 2009;66(7):642–8.
26. Vance-Bryan K, Guay DR, Gilliland SS, Rodvold KA, Rotschafer JC. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. Antimicrob Agents Chemother. 1993;37(3):436–40.
27. Reynolds DC, Waite LH, Alexander DP, Deryke CA. Performance of a vancomycin dosage regimen developed for obese patients. Am J Health-Syst Pharm: AJHP: Off J Am Soc Health-Syst Pharma. 2012;69(11):944–50.
28. Kosmisky DEG, Griffiths CL, Templin MA, Norton J, Martin KE. Evaluation of a new vancomycin dosing protocol in morbidly obese patients. Hosp Pharm. 2015;50(9):789–97.
29. Hong J, Krop LC, Johns T, Pai MP. Individualized vancomycin dosing in obese patients: a two-sample measurement approach improves target attainment. Pharmacotherapy. 2015;35 (5):455–63.
30. Brink AJ, Richards GA, Cummins RR, Lambson J. Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. Intl J Antimicrobial Agents (Clinical Trial Multicenter Study Research Support, Non-U.S. Gov't). 2008;32(5):455–8.
31. Pea F, Viale P, Candoni A, Pavan F, Pagani L, Damiani D, et al. Teicoplanin in patients with acute leukaemia and febrile neutropenia: a special population benefiting from higher dosages. Clin Pharmacokinet (Clinical Trial Comparative Study). 2004;43(6):405–15.
32. Mimoz O, Rolland D, Adoun M, Marchand S, Breilh D, Brumpt I, et al. Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia. Intensive Care Med (Research Support, Non-U.S. Gov't). 2006;32(5):775–9.
33. Bhavnani SM, Passarell JA, Owen JS, Loutit JS, Porter SB, Ambrose PG. Pharmacokinetic-pharmacodynamic relationships describing the efficacy of oritavancin in patients with Staphylococcus aureus bacteremia. Antimicrobial Agents Chemother. (Comparative Study Research Support, Non-U.S. Gov't). 2006;50(3):994–1000.
34. Samara E, Shaw JP, Barriere SL, Wong SL, Worboys P. Population pharmacokinetics of telavancin in healthy subjects and patients with infections. Antimicrobial Agents Chemother (Clinical Trial, Phase I Clinical Trial, Phase II Clinical Trial, Phase III Randomized Controlled Trial Research Support, Non-U.S. Gov't). 2012;56(4):2067–73.
35. Slover CM, NA, Barriere S, Lu Q. Telavancin (TLV) for treatment of complicated skin and skin structure infections (cSSSI) in obese patients. In: 51th ICAAC Interscience Conference on Antimicrobial Agents and Chemotherapy September 17–20, 2011; Chicago, IL2011.

36. Vance-Bryan K, Larson TA, Rotschafer JC, Toscano JP. Investigation of the early killing of Staphylococcus aureus by daptomycin by using an in vitro pharmacodynamic model. Antimicrobial agents and chemotherapy. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1992 Oct;36(10):2334–7.
37. Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. J. Clin Pharmacol (Clinical Trial Comparative Study Research Support, Non-U.S. Gov't). 2005;45(1):48–56.
38. Pai MP, Norenberg JP, Anderson T, Goade DW, Rodvold KA, Telepak RA, et al. Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. Antimicrobial Agents Chemother. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't). 2007;51(8):2741–7.
39. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(2):155–64.
40. Bookstaver PB, Bland CM, Qureshi ZP, Faulkner-Fennell CM, Sheldon MA, Caulder CR, et al. Safety and effectiveness of daptomycin across a hospitalized obese population: results of a multicenter investigation in the southeastern United States. Pharmacotherapy (Multicenter Study). 2013;33(12):1322–30.
41. Gyssens I. Daptomycin. In: Grayson MLC, McCarthy J, Mills J, Mouton J, Norrby R, Paterson D, Pfaller M, editors. Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal and antiviral drugs. 6th ed. CRC Press; 2010. p. 621–37.
42. Ng JK, Schulz LT, Rose WE, Fox BC, Andes DR, Buhr KA, et al. Daptomycin dosing based on ideal body weight versus actual body weight: comparison of clinical outcomes. Antimicrobial Agents Chemother (Research Support, N.I.H., Extramural). 2014;58(1):88–93.
43. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39(6):584–608.
44. MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. J Antimicrobial Chemother. 2003;51 Suppl 2:ii17–25.
45. Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003;42(15):1411–23.
46. Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrobial Chemother. 2012;67(8):2034–42.
47. Stein GE, Schooley SL, Peloquin CA, Kak V, Havlichek DH, Citron DM, et al. Pharmacokinetics and pharmacodynamics of linezolid in obese patients with cellulitis. Ann Pharmacother (Clinical Trial Research Support, Non-U.S. Gov't). 2005;39(3):427–32.
48. De Pascale G, Fortuna S, Tumbarello M, Cutuli SL, Vallecoccia M, Spanu T, et al. Linezolid plasma and intrapulmonary concentrations in critically ill obese patients with ventilator-associated pneumonia: intermittent vs continuous administration. Intensive Care Med. (Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't). 2015;41(1):103–10.
49. Mersfelder TL, Smith CL. Linezolid pharmacokinetics in an obese patient. Am J Health-Syst Pharm: AJHP: Off J Am Soc Health-Syst Pharm (Case Reports Letter). 2005;62(5):464, 7.
50. Tsuji Y, Hiraki Y, Matsumoto K, Mizoguchi A, Sadoh S, Kobayashi T, et al. Evaluation of the pharmacokinetics of linezolid in an obese Japanese patient. Scandinavian J Infect Dis. 2012;44:626–9.
51. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2003;36(4):473–81.

52. Aeschlimann JR, Rybak MJ. Pharmacodynamic analysis of the activity of quinupristin-dalfopristin against vancomycin-resistant Enterococcus faecium with differing MBCs via time-kill-curve and postantibiotic effect methods. Antimicrob Agents Chemother. 1998;42(9):2188–92.
53. Rubinstein E, Prokocimer P, Talbot GH. Safety and tolerability of quinupristin/dalfopristin: administration guidelines. J Antimicrobial Chemother. 1999;44 Suppl A:37–46.
54. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy (Review). 2007;27(8):1081–91.

# Chapter 8
# Azole Antifungal Agents

**Nicolette R. Holt and Karin A. Thursky**

**Abstract** Azole antifungal agents, primarily the triazoles fluconazole, itraconazole, voriconazole and posaconazole, are in widespread clinical use for the management of systemic fungal infections. Their application in the prophylaxis against and treatment of systemic mycoses continues to evolve, with ongoing advancements in drug delivery, efficacy, monitoring and side effect profiling. Pharmacokinetic changes and dose guidance for these agents in the obese population will be addressed following a review of the available literature.

**Keywords** Triazoles · Fluconazole · Itraconazole · Voriconazole · Posaconazole

## Introduction

Azole anti-fungal agents in common use in clinical practice for the treatment of systemic fungal infections can be classified into two broad groups [1]:

- Imidazoles
  - Ketoconazole
- Triazoles:
  - First generation: fluconazole, itraconazole
  - Second generation: voriconazole, posaconazole, ravuconazole, isavuconaole.

N.R. Holt (✉)
Department of Medicine, Alfred Health, Prahran, VIC, Australia
e-mail: nicholt6@gmail.com

K.A. Thursky
Victorian Infectious Diseases Service, The Doherty Institute for Infection and Immunity, Parkville, VIC, Australia

K.A. Thursky
Department of Infectious Diseases and Infection Control, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_8

Ketoconazole has largely been withdrawn from use in the treatment of fungal infections, as it has been replaced by the newer triazole agents, due to their improved efficacy and reduce toxicity profile.

Topical triazole preparations used for the treatment of superficial fungal infections include clotrimazole, econazole and miconazole.

Several triazoles currently in development include albaconazole, isavuconazole and ravuconazole, which have all displayed potent activity against *Aspergilus* spp. and *Candida* [1, 2].

This chapter will focus on the triazoles in common clinical use, primarily fluconazole, itraconazole, voriconazole and posaconazole, and their application in the treatment of systemic mycoses.

## Pharmacology and Pharmacokinetics

Ergosterol is a sterol essential to the integrity of fungal cellular membranes. Ergosterol is absent from membranes of animals, whichmakes it an interesting molecular target for antifungal agents.

Azole antifungals exhibit their action through the selective inhibition of the cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase, which is essential for the conversion of lanosterol to ergosterol. Disruption of this critical step in the ergosterol biosynthesis pathway produces membrane instability, increased cellular permeability and ultimately induces cellular death [3–5].

The triazole agents are primarily considered fungistatic in nature, however fungicidal activity has also been demonstrated.

The spectrum of activity and clinical applications are detailed further below under the relevant agents. Refer to Table 8.1 for a detailed summary of their pharmacokinetic and pharmacodynamic properties.

### *Fluconazole*

Fluconazole has activity against most yeast pathogens, including potent activity against *Candida* and *Cryptococcus* species, but has no clinical utility for treating mould infections. It is used treat invasive candidiasis where the patient is clinically stable and where the candida species is presumed susceptible to fluconazole (e.g. *C. albicans*) [6], as systemic prophylaxis for yeast infections in immunocompromised patients [7], and in the treatment of cryptococcosis (usually after induction therapy using amphotericin-based regimens) [6].

Fluconazole is available in oral capsules, liquid suspension and intravenous (IV) injection preparations. It has excellent bioavailability (>90 %) and distributes widely into tissues, with excellent cerebrospinal fluid (CSF) penetration (60–80 %), in addition to vitreous, peritoneal fluid, urine and prostatic tissue [8, 9].

**Table 8.1** Summary of pharmacokinetic and pharmacodynamic properties of systemic triazole antifungals in adults

| | Fluconazole | Itraconazole | Voriconazole | Posaconazole |
|---|---|---|---|---|
| Preparations available | PO: capsules, oral liquid<br>IV injection | PO: capsules, oral liquid<br>IV injection[a] (via SAS) | PO: tablets, oral liquid<br>IV injection | PO: oral liquid, tablets[a]<br>IV injection[a] |
| Dose<br>– Prophylaxis<br>– Treatment | Same dose for oral and IV administration<br>200–400 mg PO or IV daily<br>Loading: 12 mg/kg<br>Maintenance: 6 mg/kg | Capsule and oral liquid not bio-equivalent<br>200 mg PO 12 hourly<br>Loading: No<br>Maintenance: 200 mg 12 hourly | Oral preparations bioequivalent<br>200 mg OR or IV, 12 hourly<br>Loading: 6 mg/kg 12 hourly for 24 h<br>Maintenance: 4 mg/kg 12 hourly | Oral liquid in common use only<br>200 mg PO, 8 hourly<br>Loading: No<br>Maintenance: 200 mg PO, 6 hourly |
| Dose adjustments | Loading dose–normal dose for first 48 h regardless of GFR<br>Dose reduce for GFR < 50 mL/min thereafter | No adjustment | IV preparation contraindicated if CrCl is <50 mL/min<br>50 % maintenance dose reduction in Class A and B Child-Pugh cirrhosis | No adjustment |
| Absorption<br>– Oral bioavailability<br>– Practice point | > 90 %<br>Absorption not significantly influenced by oral intake | Variable —liquid > capsule<br>Capsule requires low pH for absorption<br>Capsule: ↑ absorption in taken with food<br>Liquid: ↑ absorption on empty stomach | 96 %<br>Oral: administer on empty stomach, ↓ absorption with high-fat meal | Variable (range 8–47 %)<br>Liquid: ↑ absorption with low pH and high-fat meal |
| Distribution<br>– Hydro/Lipophilic<br>– Protein binding<br>– Volume of distribution (L/kg) | Hydrophilic<br>11–12 %<br>∼0.6 (range 0.7–0.8) | Highly lipophilic<br>99.8 %<br>10.7 | Lipophilic<br>58 %<br>4.6 | Highly lipophilic<br>>98 %<br>Very large (7–25) |
| Tissue penetration<br>– CSF | High (52–90 %)<br>Dose-proportional (Linear) | Low (<1 %)<br>Concentration-dependent (Non-linear) | High (>50 %)<br>Concentration-dependent (Non-linear) | Low<br>Dose-proportional (Linear) |

(continued)

**Table 8.1** (continued)

| | Fluconazole | Itraconazole | Voriconazole | Posaconazole |
|---|---|---|---|---|
| Pharmacokinetics | | | | |
| Elimination:<br>– Half life (h)<br>– Metabolism<br>– Excretion | 24–30<br>Hepatic-minimally metabolised<br>Renal ≫ faecal; 80 % unchanged form | Oral: single dose—16–28<br>Hepatic via CYP3A4<br>Faecal ≫ renal; mainly as metabolites | 6–12<br>Hepatic via CYP2C19 (major)<br>Renal ≫ faecal; <2 % unchanged form | Liquid: 20–35<br>Minimal-hepatic via glucuronidation<br>Faecal ≫ renal; 66 % unchanged form |
| Time to Cmax (serum) | | | | |
| Monitoring:<br>– Therapeutic drug levels (mg/L) | Oral: 1–2 h<br>Rarely performed | Capsule: 2–5 h, Liquid: 2.5 h | Oral: 1–2 h | Liquid: 3–5 h |
| – Parameters of toxicity | Hepatic and renal function, potassium | Recommended–monitor trough levels<br>Prophylaxis: aim >1.0,<br>Treatment: >0.5–1.0, but <10 | Recommended–monitor trough levels<br>Prophylaxis: aim >1.0 but <6.0<br>Treatment: aim >1.0 but <6.0 | If indicated–monitor trough level<br>Prophylaxis: >0.7<br>Treatment:>1.0 |
| Drug interactions | Strong inhibitor of CYP 2C19 and 2C9<br>Moderate inhibitor of CYP 3A4 | LFTs if pre-existing hepatic dysfunction and in all Pts treated for >1 month | Hepatic and renal function, serum electrolytes. Visual function and skin checks | Renal function—esp if GFR < 50 mL/min, serum electrolytes |
| Pregnancy category | Weak substrate of CYP450 enzymes<br>Substrate of p-glycoprotein<br>D | Strong inhibitor of CYP 3A4<br>Major substrate of CYP 3A4<br>Substrate and inhibitor of p-glycoprotein<br>B3 | Strong inhibitor CYP 3A4<br>Moderate inhibitor CYP 2C19 and 2C9<br>Major substrate of CYP 2C19 and 2C9<br>Minor substrate of CYP 3A4<br>B3 | Strong inhibitor of CYP 3A4<br>Substrate and inhibitor of p-glycoprotein<br>B3 |

[a]Limited availability

Dosing is the same for IV and oral preparations and is dependent on the clinical indication. Dose adjustments are recommended in renal impairment if the estimated glomerular filtration rate (eGFR) < 50 mL/min, however, the loading dose for the first 48 h remains the same, irrespective of renal function. Greater than 80 % of the drug is excreted unchanged in the urine [10, 11].

Fluconazole has a wide therapeutic index and toxicity is generally low. As such, drug concentration monitoring is infrequently required. Mild elevation of transaminases occur at rates between 1 and 18 %, depending on the population, with normalization upon drug cessation [12, 13]. Reversible alopecia and Stevens-Johnson syndrome have also been reported [14, 15]. The most common adverse effects are gastrointestinal upset (diarrhoea, nausea, abdominal pain) [16].

Fluconazole has the potential for causing adverse drug reactions due to its metabolism via the hepatic cytochrome P450 (CYP) enzyme system, however these are minimal at doses below 200 mg/day [17].

## *Itraconazole*

Itraconazole has an extended spectrum compared to fluconazole, including activity against *Aspergillus* spp. and other moulds. It can be used as an alternative prophylactic agent in immunocompromised patients, as sequential therapy for invasive aspergillosis, and as an alternative agent against histoplasmosis, *Scedosporium*, and vulvovaginal candidiasis after failed topical therapy [18].

Itraconazole is available in oral capsule and liquid forms and as an IV injection with limited availability. Importantly, the capsule and oral suspension preparations are not bioequivalent—the bioavailability of the oral liquid is 30–60 % higher than the capsule. Furthermore, itraconazole capsules require an acidic stomach pH for absorption, meaning that absorption is impaired if taken with proton pump inhibitors [19, 20]. Absorption of the oral liquid is not altered by gastric pH, and optimal absorption occurs on an empty stomach [21].

Due to its lipophilic nature, itraconazole distributes extensively throughout the body, with tissue levels significantly greater than plasma. Itraconazole has a high affinity for keratinous tissues, with high levels occurring in adipose tissues, bone, liver, spleen and lungs, however only trace amounts in the CSF due to its high protein binding (>99 %) [9, 22, 23]. Itraconazole undergoes extensive hepatic metabolism, mainly via CYP 3A4, and inactive metabolites are excreted primarily in the feces [18].

Gastrointestinal side effects can occur in up to 10 % of users (dyspepsia, anorexia, diarrhoea) and are more common with the liquid preparation [24, 25]. The utility of itraconazole is limited by its large variability in plasma concentrations between preparations, in addition to marked intra- and inter-patient variability in itraconazole plasma levels, and hence the need for monitoring of serum concentrations to assure therapeutic levels (range >0.5–1 μg/mL but <10 μg/mL,

measured >7 days after therapy initiation) [20, 26, 27]. Itraconazole has largely been superseded by voriconazole and posaconazole, due to their increased and more predictable bioavailability and a decrease in the number of side effects.

## *Voriconazole*

Voriconazole is an extended spectrum triazole, active against yeasts, moulds, including *Aspergillus* spp., *Fusarium* and *Scedosporium* spp., and fluconazole-resistant *Candida* infections. Voriconazole is considered the first line agent for treatment of invasive aspergillosis, with a loading dose of 6 mg/kg IV 12-hourly for 24 h, followed by 4 mg/kg IV 12-hourly [28, 29]. It is used as a fungal prophylaxis in immunocompromised patients at high risk of fungal infection (acute leukemia, and allogeneic stem cell transplant) [7].

Preparations of voriconazole include oral tablets and liquid forms and IV injection. The IV preparation is considered contraindicated if renal function (CrCl) is below 50 mL/min and a 50 % maintenance dose reduction is recommended in Class A and B Child-Pugh liver cirrhosis [30]. Voriconazole has the highest oral bioavailability of the triazole agents, exceeding 90 %, and the oral liquid and tablets are considered bioequivalent. Absorption is improved if administered on an empty stomach [28, 31]. Voriconazole has a large volume of distribution (4.6 L/kg) and penetrates well into the CSF and brain tissues, due to its lipophilic properties [9, 32].

Because voriconazole displays a non-linear pharmacokinetic profile, any dose escalation should be carefully considered due to unpredictable increases in serum levels and half-life [33]. Furthermore, voriconazole plasma concentrations can be highly variable between individuals, due to CYP2C19 genotype polymorphisms. The CYP2C19 enzyme is the primary enzyme responsible for the metabolism of voriconazole. Slow metabolisers (3–5 % of Caucasians and 15–20 % of Asians) will have supratherapeutic serum levels and will be at risk of dose-related toxicity. Conversely, approximately 75 % of Caucasians are homozygous extensive metabolisers, resulting in lower voriconazole exposure [34–36]. Whilst CYP2C19 genotype testing is available, it is currently not routinely utilised. These factors, in addition to clinical parameters such as age, gender and drug interactions, necessitate therapeutic drug monitoring, with a target range recommended between 1 mg/L and 5.5 mg/L 5 days after therapy initiation [27, 37].

Voriconazole has several unique toxicities, including transient visual disturbance in ~30 % of patients, neurologic toxicity, manifesting as hallucinations, photosensitive rash, and it may increase the risk of skin malignancies, especially squamous cell carcinoma. Nail changes and alopecia can also result from long-term exposure. A rise in hepatic transaminases is also common [27, 38, 39].

Voriconazole is both a substrate and an inhibitor of the CYP2C19 and CYP2C9 liver enzymes, resulting in many potential drug-drug interactions, including immunosuppressive agents (cyclosporine A and cyclophasphamide) and antibiotics (rifampicin and erythromycin) [33, 40].

## *Posaconazole*

Posaconazole has a similar antifungal profile to voriconazole, being active against yeasts, *Aspergillus* spp. and *Scedosporium* spp., but has an expanded spectrum to also be active against Mucormycetes [41]. Posaconazole can be used as a salvage therapy or as an alternative in patients who are intolerant of voriconazole in the treatment of invasive aspergillosis. The IV preparation may become increasingly utilised as a first-line therapy instead of liposomal amphotericin B (L-AMB) for murcormycosis [29]. It is used as prophylaxis in patients at high risk of invasive mould infections (primarily AML, SCT and some solid organ transplants) [7].

Posaconazole is available as an oral liquid, with delayed-release tablets and an IV preparation approved for use in some countries. The absorption profile of the oral suspension is highly variable, and is enhanced (up to four times) if taken with a meal, especially with a high-fat content, and an acidic pH [42, 43]. Importantly, sub-therapeutic serum levels can result if absorption is impaired (e.g. mucositis). Therapeutic drug monitoring should be considered in critically ill patients, where either mucosal integrity or limited caloric intake may lead to reduced serum concentrations [37, 44]. The distribution volume of posaconazole is very large at 7–25 L/kg, greater than voriconazole. It is extensively protein bound (>98 %), predominantly to albumin [41, 45]. Posaconazole has negligible penetration into the CSF [9].

The tablet preparation of posaconazole has less variation in its pharmacokinetic profile, with increased bioavailablity and a reduced interaction with food, however, it currently has limited availability [46].

Current recommended dosing of posaconazole therapy is 200 mg orally 8-hourly for prophylaxis and 200 mg orally, 6-hourly for treatment of invasive fungal infections [7, 29]. Dosing above 800 mg/day yields no increase in efficacy with pharmocokinetics appearing saturated [33].

Adverse effects from posaconazole administration are generally mild, and include gastrointestinal complaints (nausea and diarrhoea), rash and headache. Therapeutic drug monitoring can be performed with a trough concentration sampled after 5–7 days to ensure adequate absorption and therapeutic levels. It has been recommended in patients requiring posaconazole prophylaxis or treatment, especially if there is potential malabsorption due to lack of mucosal integrity or in the paediatric setting due to variable gastrointestinal absorption, to ensure efficacy [27, 40, 47, 48].

Posaconazole is not significantly metabolized, with 15 % undergoing non-cytochrome P450 hepatic metabolism, primarily via the glucuronidation, with

the remainder of the unchanged parent drug excreted via the fecal route (77 %), and minimally via the urine. Hence, adjustment in renal or hepatic insufficiency is not required [41, 49]. Posaconazole predominantly inhibits CYP3A4, and is associated with comparatively less drug interactions than the other triazole agents, as it is not a substrate for the P450 hepatic enzyme system [33].

## Pharmacokinetic Changes in Obesity

Increased body fat composition compared to the proportion of lean body weight and total body water can result in alterations in the pharmacokinetic parameters of the triazole antifungals. This may have an impact on the efficacy of these agents, with the consequence of therapeutic failure and antifungal resistance secondary to sub-optimal dosing or drug-related toxicity at supratherapeutic levels [50, 51].

Unfortunately, dosing of the triazole agents cannot accurately be directed by a presumed relationship between their degree of lipophilicity and their subsequent expected propensity to disperse into the increased adipose tissue in the obese patient.

For example, it cannot be assumed that lipophilic triazole agents (itraconazole, voriconazole and posaconazole) will all have an increased volume of distribution in the obese patient, nor can we rely on the hydrophilic agent fluconazole having a lower volume of distribution and subsequently requiring a different approach to dose adjustment in order to achieve therapeutic concentrations.

### *Review of Existing Literature*

Limited published data is available detailing the pharmacokinetic changes in obese patients (body mass index [BMI] $\geq$ 30 kg/m$^2$) to guide the dosing of triazole agents in this population.

Most available information exists for voriconazole, with three case reports [52–54], two retrospective studies [55, 56], and one randomized trial [57]. There are two case reports detailing the pharmacokinetics of fluconazole in an obese patient [58, 59]. Posaconazole dosing has been examined in the obese patient group in two studies, in hematopoietic stem cell transplant (HSCT) recipients [60] and in cardiothoracic transplant recipients [61], and in a recent case report [62].

Currently, there is no data on the pharmacokinetics of itraconazole in obese patients.

Please refer to Table 8.2 for a detailed summary and Table 8.3 for a brief overview of recommendations for dosing of systemic triazole agents in the obese population based on a review of available published literature.

**Table 8.2** Summary of available data and recommendations to guide dosing of triazole antifungal agents in the obese patient

| Triazole agent | Literature source | Study design | Results | Dose recommendation in obesity |
|---|---|---|---|---|
| Fluconazole | Cohen et al. [58]<br>Lopez and Phillips [59] | Case report<br>– 39-year-old male, BMI 48.3 kg/m$^2$<br>– Dosage: TBW<br>– Dosed IV 1200 mg daily (6 mg/kg per dose) for 14 days, no loading dose<br>Case report<br>– 48-year-old male, BMI 84 kg/m$^2$ receiving RRT<br>– Dosage: LBW<br>– IV 1200 mg (12 mg/kg LBW), then 600 mg daily (6 mg/kg LBW) | – $C_{ave}$ significantly reduced at 23.9 mg/L,<br>– $AUC_{0–24}$ decreased two-fold at 574.9 mg/L h<br>– Cl increased at 139.4 mL/min<br>– $C_{max}$ 9.64 mg/L<br>– $C_{min}$ of 5.98 mg/L<br>– $AUC_{0–24}$ of 184.75 mg/L h<br>– Cl 3.25 L/h | Recommended dosing at the higher end of 6–12 mg/kg dosing range<br>Dosage based on LBW produces an AUC:MIC ratio >25, resulting in clinical efficacy |
| Itraconazole | – | | | Data lacking |
| Voriconazole | Pai and Lodise [57] | Randomised, crossover study<br>– 8 healthy volunteers, median weight 133 kg, median BMI 46.3 kg/m$^2$<br>– Regimen 1: 400 mg PO q12 h × 2 doses, then 200 mg PO q12 h × 7 doses<br>– Regimen 2: 400 mg PO q12 h × 2 doses, then 300 mg PO q12 h × 7 doses | V similar for both regimens between obese and non-obese patients<br>– Regimen 1: $AUC_{0–12}$ > in obese patients (14.6 Vs 9.76 mg h/L). Cl 13.4 Vs 20 L/h in obese compared to non-obese patients, respectively | Higher correlation of AUC with LBW compared to TBW<br>– Patient weight not a significant covariate in pharmacokinetic profile of voriconazole<br>– Recommend against dosing of oral voriconazole based on TBW in obese patients |

(continued)

**Table 8.2** (continued)

| Triazole agent | Literature source | Study design | Results | Dose recommendation in obesity |
|---|---|---|---|---|
| | Koselke et al. (2012 | Retrospective review<br>– Comparison of voriconazole $C_{min}$ in obese (BMI $\geq$ 35 kg/m$^2$ Vs non-obese patients) | – Regimen 2: $AUC_{0-12}$ and Cl similar between the two groups<br>– Mean $C_{min}$ greater in obese compared to non-obese patients (6.2 Vs 3.5 mg/L respectively)<br>– Neurotoxicity and hepatotoxicity similar between groups | – Higher incidence of supratherapeutic voriconazole concentrations in obese patients dosed based on TBW<br>– Recommend use of ABW or IBW when dosing voriconazole in obese patients |
| | Davies-Vorbrodt et al. [56] | – Dosage: TBW<br>– IV or PO 4 mg/kg q12 h | | – Dosing based on ABW more appropriate in obese patients |
| | Dickmeyer and Kiel [52] | Retrospective review<br>– 92 haematology patients, stratified based on BMI ($\geq$ or <25 kg/m$^2$)<br>Case report<br>– 30-year-old male, BMI 84.5 kg/m$^2$<br>– Dosage: ABW | – Median random serum concentrations significantly higher for IV preparation in patients with BMI $\geq$ 25 kg/m$^2$ (6.4 Vs 2.8 mg/L, respectively)<br>– Steady state AUC 41.85 mg h/L, similar to values in reference non-obese allogenic HSCT recipients (14.75–47.82 mg h/L) | – ABW dosing obese patients receiving stem cell transplants |
| | Moriyama et al. (2011) | – PO 6 mg/kg q12 h × 2 doses, then 4 mg/kg q12 h<br>Case report<br>– 41-year-old male, BMI 36 kg/m$^2$, CYP2C19 poor metaboliser<br>– Dosage: ABW | – $AUC_{1-12}$ 77.79 mg h/L, steady state $C_{min}$ of 6.1 μg/mL | – Due to prolonged $t_{1/2}$ and reduced drug Cl, discontinued 3 days prior to vincristine chemotherapy<br>– Recommend TDM and genotyping be utilised |

(continued)

**Table 8.2** (continued)

| Triazole agent | Literature source | Study design | Results | Dose recommendation in obesity |
|---|---|---|---|---|
| | Moriyama et al. [53] | – IV 6 mg/kg q12 h × 2 doses, then 4 mg/kg q12 h<br>Case report<br>– 17-year-old male, BMI 35 kg/m$^2$<br>– Dosage: TBW initially, 4.9 mg/kg IV q12 h × 2, then 4.1 g/kg IV q12 h<br>– Decreased to 4 mg/kg IV q12 h via ABW due to hepatotixicity | – After 2.5 days of dosing at 4 mg/kg on ABW, $AUC_{0–12}$ of 86.1 mg h/L and $C_{min}$ of 6.2 μg/mL<br>– Patients genotype: CYP2C19 homozygous poor metaboliser<br>– Drug discontinued due to QTc prolongation | – Voriconazole does not distribute extensively into adipose tissue, and obese patients should be dosed on ABW<br>– Further elevations in voriconazole concentrations if an obese patient dosed on TBW is also a CYP2C19 poor metaboliser |
| Posaconazole | Krishna et al. [60] | Randomised, double blind study<br>– 246 HSCT with GVHD<br>– Patient characteristics analysed: age, gender, weight, race, GVHD status<br>– Dose: oral, 200 mg three times daily | – 28 % reduction in median serum concentration between patients <65 kg compared to >80 kg, 1128 ng/mL compared to 814 ng/mL respectively | – Minimal clinical correlation with plot of concentration versus body weight as a continuous variable |

(continued)

**Table 8.2** (continued)

| Triazole agent | Literature source | Study design | Results | Dose recommendation in obesity |
|---|---|---|---|---|
| | Shields et al. [61] | Retrospective review<br>– 17 cardiothoracic transplant patients<br>– Patient characteristics analysed: age >65 years, gender, weight, race<br>– Modifiable factors analysed: oral administration, concomitant $H_2$ antagonist or proton pump inhibitor<br>– Dose: oral, between 600 and 800 mg daily in divided doses | – Median initial concentrations lower in obese patients compared to non-obese, 0.43 and 0.66 μg/mL respectively<br>– Dose escalation from 800 to 1200 mg daily ineffective at increasing posaconazole levels, with only 29 % of patients (2/7) achieving $C_{min} > 0.5$ μg/mL<br>– Higher levels achieved at 1600 mg/day dosage, but increased gastrointestinal and hepatic toxicity | – Doses beyond 800–1200 mg daily unlikely to correlate with increased serum drug concentrations given saturation of absorption above this dose range |
| | Pettis et al. [62] | Case report<br>– 52-year-old male, BMI of 35.6 kg/m$^2$<br>– Dose: 400 mg oral twice daily<br>– Note: concomitant use of proton pump inhibitor as a cofounder | – Serum concentrations significantly lower compared to referenced published data | – Increase in dose or frequency may not correlate with target serum concentrations in obese patient<br>– Recommend the use of TDM in obese patients, especially in monitoring for suboptimal drug exposure |

Adapted from Polso et al. [51]

*ABW* adjusted body weight, *AUC* area under the curve, *C* concentration, *Cl* clearance, *GVHD* graft versus host disease, *HSCT* hematopoietic stem-cell transplant, *IBW* ideal body weight, *IV* intravenous, *LBW* lean body weight, *MIC* minimum inhibitory concentration, *PO* oral, *TBW* total body weight, *TDM* therapeutic drug monitoring, *V* volume of distribution

**Table 8.3** Summary of recommendations to guide dosing of triazole antifungal agents in the obese patient

| |
|---|
| Fluconazole<br>• Dosing: based on LBW<br>• TDM: role not established |
| Itraconazole<br>• Data lacking |
| Voriconazole<br>• Dosing: based on AdjBW<br>• TDM: recommended to establish clinical efficacy and to avoid toxicity<br>• Cytochrome P450 2C19 genotype testing in select patients |
| Posaconazole<br>• Limit posaconazole dose to 800 mg per day regardless of BMI<br>• TDM: recommended to establish clinical efficacy and to avoid toxicity |

*AdjBW* adjusted body weight, *AUC* area under the curve, *LBW* lean body weight, *MIC* minimum inhibitory concentration, *TDM* therapeutic drug monitoring

## *Fluconazole*

A case report by Cohen et al. [58] detailed a male patient with a weight of 185.5 kg (BMI of 48.3 kg/m$^2$), who was administered 1200 mg daily (6.5 mg/kg total body weight per dose) of intravenous fluconazole over 14 days for the treatment of *Candida albicans* fungaemia. A loading dose was not administered in this case. His creatinine clearance was 124.9 mL/min [58]. The pharmacokinetic profile demonstrated an average steady state plasma concentration for the 24-h dosing interval of 23.9 mg/L, a 24-h area under the serum concentration-time curve of ($AUC_{0–24}$) of 574.9 mg/L h, and a drug clearance of 139.4 mL/min. Values for the maximum plasma concentration ($C_{max}$) and the maximum plasma concentration ($C_{min}$) could not be determined due to minimal fluctuations in fluconazole serum concentration.

Compared to published values in both healthy and critically ill patients, the average concentration was significantly reduced (compared to a $C_{max}$ of 70 mg/L from studies in normal range BMI patients given the same dose of fluconazole), the $AUC_{0–24}$ was decreased two-fold and the fluconazole clearance was increased.

The authors hypothesized that these changes could be secondary to an increase in the apparent volume of distribution of this hydrophilic, renally eliminated drug. They concluded in the obese population, the higher end of the 6–12 mg/kg dosing range of fluconazole should be administered based on total body weight.

A more recent case report by Lopez and Phillips [59] detailed a 48-year-old man with a weight of 272 kg (BMI of 84 kg/m$^2$) who was critically unwell and received support through continuous venous hemofiltration. He was treated with intravenous fluconazole, dosed according to lean body weight (LBW), received a loading dose of 1200 mg (12 mg/kg of LBW), which was followed by a maintenance dose of 600 mg daily (6 mg/kg LBW) [59]. The pharmacokinetic values for fluconazole achieved were a $C_{max}$ of 9.64 mg/L, a $C_{min}$ of 5.98 mg/L, an $AUC_{0–24}$ of 184.75 mg h/L, and a drug clearance of 3.25 L/h.

Whilst there are currently no consensus guidelines regarding a therapeutic range for fluconazole, an $AUC_{0–24}$ to minimum inhibitory concentration (MIC) ratio that exceeds 25 is thought to achieve pharmacodynamic efficacy. Given the lack of a consistent relationship with dose-to-AUC, Lopez and Phillips recommended against using such a relationship to estimate the required drug dosage in the obese population. They recommended that dosing of fluconazole using LBW enabled an AUC: MIC ratio of greater than 25 to be achievable in the morbidly obese patient.

This highlights that further investigation of fluconazole pharmacokinetics in the obese population is warranted. However, until further data emerges, dosing fluconazole in accordance to LBW should enable maximal efficacy in the obese population.

## *Voriconazole*

In 2011, Pai and Lodise studied the pharmacokinetic profile of oral voriconazole administered at either 200 mg 12-hourly or 300 mg 12-hourly, in 8 healthy volunteers with a median weight of 133 kg (105–155 kg) and a median BMI of 46.2 kg/m$^2$ (38.4–53.7 kg/m$^2$), they compared the results to a non-obese reference group. The mean $AUC_{0–12}$ in the obese group was 14.6 and 29.2 mg h/L in the 200 mg and 300 mg doses, respectively, compared to 9.76 and 30.9 mg h/L in the non-obese group. A higher average $C_{min}$ was observed in the obese patient group, 0.81 versus 0.35 mg/L for the 200 mg dose and 1.76 versus 1.43 mg/L for the 300 mg dose, respectively. The volume of distribution was similar between the obese and non-obese patients for both dosing regimens. A strong linear relationship was observed between the $C_{min}$ and area under the curve $AUC_{0–12}$ values. The authors concluded that patient weight was not a significant covariate for the voriconazole pharmacokinetic profile and recommended voriconazole dosing based on either LBW or adjusted body weight (ABW) in the obese group [57].

Two retrospective studies were conducted that recommended ideal or adjusted weight based dosing of voriconazole in obese patients [55, 56].

Koselke et al. [55] evaluated voriconazole serum concentrations in 21 obese (BMI $\geq$ 35 kg/m$^2$) and 66 normal-weight patients, who were administered IV or oral voriconazole at 4 mg/kg 12-hourly based on total body weight (TBW) [55]. The mean serum voriconazole trough concentration was significantly higher in the obese group dosed on TBW compared to the non-obese group (6.2 vs. 3.5 mg/L), and there was greater incidence of supratherapeutic levels when dosed on TBW. Furthermore, mean concentrations varied significantly among obese patients, depending on if the 4 mg/kg dose was administered according to actual, ideal or adjusted body weight, with values of 6.2, 4.0 and 3.3 mg/L, respectively.

Davies-Vorbrodt et al. [56] performed a retrospective analysis of serum voriconazole concentrations stratified based on BMI in 92 haematology patients. With the intravenous formulation, significantly higher random voriconazole concentrations were observed in patients with a BMI $\geq$ 25 kg/m$^2$ (6.4 mg/L)

compared to <25 kg/m$^2$ (2.8 mg/L). This difference was less marked with the oral preparation. Increased derangement in hepatic transaminases was observed with increasing voriconazole concentrations [56].

A case report by Dickmeyer and Kiel [52] described a 30-year-old male weighing 225 kg (BMI 84.5 kg/m$^2$) who received a course of empiric voriconazole therapy in the context of neutropenic fever on day 8 post allogenic HSCT. Voriconazole dosing was based on an adjusted body weight, and a dose of 6 mg/kg followed by 4 mg/kg PO 12-hourly was administered. The calculated AUC was 41.9 mg h/L, which the authors reported as being similar to values in non-obese allogenic HSCT recipients (range: 14.8–47.8 mg h/L). Hence, they recommend adjusted weight based dosing in obese patients receiving stem cell transplants [52].

Two case reports described the pharmacokinetics of voriconazole in obese patients found to be CYP2C19 homozygous poor metabolisers [53, 54]. In both reports, the authors suggested that as voriconazole distributes primarily into lean body tissue, obese patients should receive IV voriconazole therapy based on an adjusted body weight.

Moriyama et al. [53] studied a 41-year-old male with peripheral T-cell lymphoma, a BMI of 36 kg/m$^2$ and known chronic renal insufficiency. He was administered IV voriconazole for pulmonary *Aspergillus fumigatus* at a loading dose of 605 mg (6 mg/kg) 12-hourly for 2 doses, followed by a maintenance dose of 405 mg (4 mg/kg) 12-hourly [53].

The $AUC_{0–12}$ was measured at 77.8 mg h/L and the steady state $C_{min}$ at 6.1 mg/L. Due to a prolonged half-life and a reduced clearance, voriconazole was ceased 3 days prior to commencement of planned vincristine chemotherapy.

In a 2013 case report, Moriyama et al. administered IV voriconazole for the management of suspected pulmonary aspergillosis in a 17-year-old Hispanic man weighing 102 kg (BMI 35 kg/m$^2$). Initially, a dose based on TBW at 500 mg (4.9 mg/kg) IV 12-hourly for 2 doses, then 420 mg (4.1 mg/kg) IV 12-hourly. This was subsequently dose reduced to 340 mg IV 12-hourly based on an ABW of 85 kg (4 mg/kg) due to an elevation in transaminases [54].

Voriconazole pharmacokinetic values after 2.5 days of dosing at 4 mg/kg on ABW were calculated, with an $AUC_{0–12}$ of 86.1 mg h/L and a $C_{min}$ of 6.2 mg/L. The drug was subsequently ceased due to QTc prolongation.

Voriconazole is considered to be moderately lipophilicity, compared to the highly lipophilic itraconazole and posaconazole and thus, its volume of distribution is not as large. However, voriconazole does have a larger volume of distribution than the hydrophilic fluconazole [39].

The non-linear pharmacokinetic characteristic of voriconazole means that dose escalation in accordance to a weight-based approach in obese patients can result in a disproportionately large increase in drug level [63, 64]. Hence, voriconazole dosing should be based on either lean body weight or adjusted body weight, rather than on actual body weight. Therapeutic drug monitoring should be utilised to ensure clinical efficacy, aiming for trough voriconazole concentrations >1.0 mg/L, but <6.0 mg/L to avoid toxicity [27].

### *Posaconazole*

Posaconazole pharmacokinetics was described in a case report of an obese 52-year-old male with a BMI of 35.6 kg/m$^2$ with graft versus host disease (GVHD) by Pettis et al. [62]. The patient was administered 400 mg oral posaconazole twice daily for the management of a presumed invasive fungal infection. Posaconazole serum concentrations were monitored and found to be significantly lower when compared to healthy volunteers. However, this particular patient was also receiving a proton pump inhibitor, which is known to decrease bioavailability of posaconazole by 25–30 % [62].

In a study of 17 cardiothoracic transplant recipients by Shields et al. (2011), median initial posaconazole concentrations were lower in the overweight patients, measured at 0.43 mg/L compared to 0.66 mg/L in normal weight patients [61].

Similarly, in a study of 246 HSCT recipients with GVHD receiving 200 mg oral suspension of posaconazole three-times daily, the median the average plasma concentration ($C_{ave}$) levels decreased as the patient's BMI increased, with readings of 1.13 mg/L (<65 kg), 0.88 mg/L (65–80 kg) and 0.81 mg/L (>80 kg). The authors concluded that minimal clinical correlation was present with a plot of concentration versus body weight as a continuous variable [60].

Because of the high lipophilicity of posaconazole, there may be a corresponding decrease in plasma drug concentration in obese patients, risking subtherapeutic drug exposure. However, dose escalation to account for this may not be straight forward, as posaconazole demonstrates saturation in absorption at doses exceeding 800 mg per day, hence, an increase to 1200 mg daily may be ineffective but confer increased side effects [33, 45].

Further investigations are warranted regarding the impact of body weight on posaconazole concentrations.

## Recommendations

See Tables 8.1, 8.2 and 8.3.

## References

1. Grayson MCS, McCarthy J, Mills J, Mouton J, Norrby S, Paterson D, Pfaller M. Kucers' the use of antibiotics. 6th ed. Boca Raton: CRC Press;2010.
2. Pasqualotto AC, Denning DW. New and emerging treatments for fungal infections. J Antimicrob Chemother. 2008;61(Suppl 1):i19–30.
3. Georgopapadakou NH, Walsh TJ. Antifungal agents: chemotherapeutic targets and immunologic strategies. Antimicrob Agents Chemother. 1996;40(2):279–91.

4. Ghannoum MA, Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. Clin Microbiol Rev. 1999;12(4): 501–17.
5. Zonios DI, Bennett JE. Update on azole antifungals. Semin Respir Crit Care Med. 2008;29 (2):198–210.
6. Chen SC, Sorrell TC, Chang CC, Paige EK, Bryant PA, Slavin MA. Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care setting. Intern Med J. 2014;44(12b):1315–32.
7. Fleming S, Yannakou CK, Haeusler GM, Clark J, Grigg A, Heath CH, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation. Intern Med J. 2014;44(12b):1283–97.
8. Brammer KW, Farrow PR, Faulkner JK. Pharmacokinetics and tissue penetration of fluconazole in humans. Rev Infect Dis. 1990;12(Suppl 3):S318–26.
9. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev. 2014;27(1):68–88.
10. Debruyne D, Ryckelynck JP. Clinical pharmacokinetics of fluconazole. Clin Pharmacokinet. 1993;24(1):10–27.
11. Berl T, Wilner KD, Gardner M, Hansen RA, Farmer B, Baris BA, et al. Pharmacokinetics of fluconazole in renal failure. J Am Soc Nephrol: JASN. 1995;6(2):242–7.
12. Gearhart MO. Worsening of liver function with fluconazole and review of azole antifungal hepatotoxicity. Ann Pharmacother. 1994;28(10):1177–81.
13. Sinnollareddy M, Peake SL, Roberts MS, Playford EG, Lipman J, Roberts JA. Pharmacokinetic evaluation of fluconazole in critically ill patients. Expert Opin Drug Metab Toxicol. 2011;7(11):1431–40.
14. Pappas PG, Kauffman CA, Perfect J, Johnson PC, McKinsey DS, Bamberger DM, et al. Alopecia associated with fluconazole therapy. Ann Intern Med. 1995;123(5):354–7.
15. Thiyanaratnam J, Cohen PR, Powell S. Fluconazole-associated Stevens-Johnson syndrome. J Drugs Dermatol: JDD. 2010;9(10):1272–5.
16. Anaissie EJ, Kontoyiannis DP, Huls C, Vartivarian SE, Karl C, Prince RA, et al. Safety, plasma concentrations, and efficacy of high-dose fluconazole in invasive mold infections. J Infect Dis. 1995;172(2):599–602.
17. Andes D. Optimizing antifungal choice and administration. Curr Med Res Opin. 2013;29 (Suppl 4):13–8.
18. Lestner J, Hope WW. Itraconazole: an update on pharmacology and clinical use for treatment of invasive and allergic fungal infections. Expert Opin Drug Metab Toxicol. 2013;9(7): 911–26.
19. Van Peer A, Woestenborghs R, Heykants J, Gasparini R, Gauwenbergh G. The effects of food and dose on the oral systemic availability of itraconazole in healthy subjects. Eur J Clin Pharmacol. 1989;36(4):423–6.
20. Poirier JM, Cheymol G. Optimisation of itraconazole therapy using target drug concentrations. Clin Pharmacokinet. 1998;35(6):461–73.
21. Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH, et al. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. Pharmacotherapy. 1998;18(2):295–301.
22. Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs. 1989;37(3): 310–44.
23. Kethireddy S, Andes D. CNS pharmacokinetics of antifungal agents. Expert Opin Drug Metab Toxicol. 2007;3(4):573–81.
24. Girois SB, Chapuis F, Decullier E, Revol BG. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. Eur J Clin Microbiol Infect Dis: Off Publ Eur Soc Clin Microbiol. 2006;25(2):138–49.

25. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. New Engl J Med. 2007;356(4):348–59.
26. Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, Hope WW. Toxicodynamics of itraconazole: implications for therapeutic drug monitoring. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2009;49(6):928–30.
27. Chau MM, Kong DC, van Hal SJ, Urbancic K, Trubiano JA, Cassumbhoy M, et al. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy. Intern Med J. 2014;44 (12b):1364–88.
28. Mikulska M, Novelli A, Aversa F, Cesaro S, de Rosa FG, Girmenia C, et al. Voriconazole in clinical practice. J Chemother. 2012;24(6):311–27.
29. Blyth CC, Gilroy NM, Guy SD, Chambers ST, Cheong EY, Gottlieb T, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation. Intern Med J. 2014;44(12b):1333–49.
30. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet. 2006;45(7):649–63.
31. Purkins L, Wood N, Kleinermans D, Greenhalgh K, Nichols D. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. Br J Clin Pharmacol. 2003;56(Suppl 1):17–23.
32. Weiler S, Fiegl D, MacFarland R, Stienecke E, Bellmann-Weiler R, Dunzendorfer S, et al. Human tissue distribution of voriconazole. Antimicrob Agents Chemother. 2011;55(2):925–8.
33. Sandherr M, Maschmeyer G. Pharmacology and metabolism of voriconazole and Posaconazole in the treatment of invasive aspergillosis: review of the literature. Eur J Med Res. 2011;16(4):139–44.
34. Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J, et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol. 2009;49(2):196–204.
35. Owusu Obeng A, Egelund EF, Alsultan A, Peloquin CA, Johnson JA. CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? Pharmacotherapy. 2014;34(7):703–18.
36. Zonios D, Yamazaki H, Murayama N, Natarajan V, Palmore T, Childs R, et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis. 2014;209(12):1941–8.
37. Lewis RE. Antifungal therapeutic drug monitoring. Curr Fungal Infect Rep. 2010;4(3): 158–67.
38. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. New Engl J Med. 2002;347(6):408–15.
39. Thompson GR 3rd, Lewis JS 2nd. Pharmacology and clinical use of voriconazole. Expert Opin Drug Metab Toxicol. 2010;6(1):83–94.
40. Laverdiere M, Bow EJ, Rotstein C, Autmizguine J, Broady R, Garber G, et al. Therapeutic drug monitoring for triazoles: A needs assessment review and recommendations from a Canadian perspective. The Canadian journal of infectious diseases & medical microbiology. J Canadien des Maladies Infectieuses et de la Microbiologie Medicale/AMMI Can. 2014;25 (6):327–43.
41. Lipp HP. Clinical pharmacodynamics and pharmacokinetics of the antifungal extended-spectrum triazole posaconazole: an overview. Br J Clin Pharmacol. 2010;70(4):471–80.
42. Ezzet F, Wexler D, Courtney R, Krishna G, Lim J, Laughlin M. Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet. 2005;44(2):211–20.

43. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother. 2009;53(3):958–66.
44. Vaes M, Hites M, Cotton F, Bourguignon AM, Csergo M, Rasson C, et al. Therapeutic drug monitoring of posaconazole in patients with acute myeloid leukemia or myelodysplastic syndrome. Antimicrob Agents Chemother. 2012;56(12):6298–303.
45. Li Y, Theuretzbacher U, Clancy CJ, Nguyen MH, Derendorf H. Pharmacokinetic/pharmacodynamic profile of posaconazole. Clin Pharmacokinet. 2010;49(6):379–96.
46. Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. J Antimicrob Chemother. 2012;67(11):2725–30.
47. Dolton MJ, Ray JE, Marriott D, McLachlan AJ. Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56(6):2806–13.
48. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother. 2014;69(5):1162–76.
49. Nagappan V, Deresinski S. Reviews of anti-infective agents: posaconazole: a broad-spectrum triazole antifungal agent. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2007;45(12):1610–7.
50. Amsden JR, Slain D. Antifungal dosing in obesity: a review of the literature. Curr Fungal Infect Rep. 2011;5(2):83–91.
51. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39(6):584–608.
52. Dickmeyer NJ, Kiel PJ. Dosing voriconazole in an obese patient. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2011;53(7):745.
53. Moriyama B, Falade-Nwulia O, Leung J, Penzak SR, C JJ, Huang X, et al. Prolonged half-life of voriconazole in a CYP2C19 homozygous poor metabolizer receiving vincristine chemotherapy: avoiding a serious adverse drug interaction. Mycoses. 2011;54(6):e877–9.
54. Moriyama B, Jarosinski PF, Figg WD, Henning SA, Danner RL, Penzak SR, et al. Pharmacokinetics of intravenous voriconazole in obese patients: implications of CYP2C19 homozygous poor metabolizer genotype. Pharmacotherapy. 2013;33(3):e19–22.
55. Koselke E, Kraft S, Smith J, Nagel J. Evaluation of the effect of obesity on voriconazole serum concentrations. J Antimicrob Chemother. 2012;67(12):2957–62.
56. Davies-Vorbrodt S, Ito JI, Tegtmeier BR, Dadwal SS, Kriengkauykiat J. Voriconazole serum concentrations in obese and overweight immunocompromised patients: a retrospective review. Pharmacotherapy. 2013;33(1):22–30.
57. Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother. 2011;55(6):2601–5.
58. Cohen LG, DiBiasio A, Lisco SJ, Hurford WE. Fluconazole serum concentrations and pharmacokinetics in an obese patient. Pharmacotherapy. 1997;17(5):1023–6.
59. Lopez ND, Phillips KM. Fluconazole pharmacokinetics in a morbidly obese, critically ill patient receiving continuous venovenous hemofiltration. Pharmacotherapy. 2014;34(9):e162–8.
60. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Pharmacotherapy. 2007;27(12):1627–36.
61. Shields RK, Clancy CJ, Vadnerkar A, Kwak EJ, Silveira FP, Massih RC, et al. Posaconazole serum concentrations among cardiothoracic transplant recipients: factors impacting trough levels and correlation with clinical response to therapy. Antimicrob Agents Chemother. 2011;55(3):1308–11.

62. Pettis JJ. Effects of obesity on posaconazole kinetics in a patient with graft versus host disease. Pharmacol Pharm. 2013;04(02):244–7.
63. Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob Agents Chemother. 2002;46(8):2546–53.
64. Hope WW. Population pharmacokinetics of voriconazole in adults. Antimicrob Agents Chemother. 2012;56(1):526–31.

# Chapter 9
# Echinocandin Antifungals

**Tara Anderson**

**Abstract** Echinocandins are a relatively new class of systemic antifungals with three agents currently commercially available for clinical use; anidulafungin, caspofungin and micafungin. They have broad spectrum activity against the majority of *Candida* and *Aspergillus* species and consensus guidelines recommend echinocandins for the treatment of invasive candidiasis, for salvage therapy for invasive aspergillosis and for prophylaxis for invasive candidiasis in select high risk patient groups. There is limited literature available relating to optimising a dosing strategy in this patient group but the pharmacokinetic data suggests that in obesity, the echinocandin exposure is less than in leaner patients. The clinical significance of this is currently not clear and further studies are warranted to explore the appropriate echinocandin dosage strategies for this patient group with consideration for safety and efficacy and the role of therapeutic drug monitoring in dose optimisation.

**Keywords** Echinocandin · Anidulafungin · Caspofungin · Micafungin · Antifungal · Candidiasis

## Introduction

Echinocandins are a relatively new class of systemic antifungal and are increasingly used in clinical practice because of their fungicidal activity against *Candida* spp., once daily dose administration and limited adverse reactions and drug interactions [1]. Currently, three echinocandins are commercially available for clinical use; anidulafungin, caspofungin, and micafungin. They are semi-synthetic lipopeptide compounds and are only available in parenteral form, owing to their poor oral bioavailability [1].

T. Anderson (✉)
Department of Infectious Diseases, Royal Hobart Hospital,
48 Liverpool Street, Hobart, TAS 7000, Australia
e-mail: tara.anderson@ths.tas.gov.au



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_9

Echinocandins have broad spectrum activity against the majority of *Candida* and *Aspergillus* species [1]. Consensus guidelines [2–4] recommend echinocandins for the following circumstances:

- Candidemia or invasive candidiasis in patients where the organism is unknown and the patient is critically ill, neutropenic or there are risk factors associated with azole resistance
- Candidemia or invasive candidiasis in patients where the organism has been identified to be fluconazole susceptible but the patient is critically ill or neutropenic
- Candidemia or invasive candidiasis due to an azole resistant *Candida* spp.
- Refractory or salvage therapy for aspergillosis
- Prophylaxis for invasive candidiasis in patients undergoing haematopoietic stem cell transplantation (HSCT) or patients who are expected to have neutropenia for $\geq 10$ days.

The licensing of the different echinocandins has varied worldwide and the clinician should be familiar with the prescribing framework within their own clinical setting.

## Pharmacodynamic Target

The echinocandins inhibit the enzyme 1,3-β-D-glucan synthase, blocking the synthesis of β-1,3-D-glucan polymers, which are major components of the cell wall in most fungal cells, disrupting the integrity of the cell wall [1]. They also exhibit a 'post-antifungal effect' (PAFE), i.e. suppression of fungal growth after limited exposure to an antifungal [1, 5].

The echinocandins have also been shown to be active against *Candida* biofilms in both in vitro and in vivo studies. These biofilms can form on indwelling medical devices or mucosal surfaces and may be associated with the development of a spectrum of clinical syndromes, including invasive candidiasis [6–8].

### (a) *Candida* species

Echinocandins exhibit fungicidal activity against *Candida* species, including azole or amphotericin resistant strains. *C. parapsilosis* and *C. lusitaniae* tend to have higher minimum inhibitory concentrations (MICs) (i.e. lowest concentration that inhibits growth) relative to those observed for more susceptible *Candida* spp. In general, however, the three echinocandins display comparable in vitro activities against *Candida* spp. [1].

All three echinocandins exhibit concentration-dependent fungicidal activity against *Candida* spp. For *Candida* spp., the antifungal efficacy has been best correlated with both the ratio of peak plasma concentration ($C_{max}$) to MIC (i.e. $C_{max}$/MIC)

and the ratio of the area under the serum concentration-time curve, $AUC_{0-24}$ to MIC [1, 9] (i.e. $AUC_{0-24}$/MIC).

As described for the echinocandin class, micafungin efficacy for candidiasis is closely linked to the $AUC_{0-24}$/MIC ratio [9–11]. In patients with non-*C. parapsilosis* infections, the micafungin pharmacokinetic-pharmacodynamic (PK-PD) target associated with optimal clinical and microbiological outcomes is AUC/MIC $\geq 3000$. At standard dosing of 100 mg/day, the PK-PD target attainment analyses would suggest that the majority of patients would achieve this goal for organisms with a MIC <0.06 mg/L. For *C. parapsilosis*, the PK-PD target predictive for efficacy is an AUC/MIC ratio of $\geq 285$. This target would be expected to be attained for organisms with MIC values $\leq 0.25$ mg/L [10].

On review of non-clinical data, the PK-PD target is similar among the other echinocandin agents [9].

Interestingly, some *Candida* isolates may exhibit continued growth at echinocandin concentrations well above the MICs for these agents. This has been termed the "Eagle effect" (or paradoxical effect). This effect appears to be a dose-dependent tolerance in response to cell wall stress and damage rather than due to antifungal resistance. The Eagle effect occurs much more commonly with caspofungin than with anidulafungin or micafungin, and has been documented with the use of conventional dosing regimens, but may be more relevant in higher dosage regimens. The clinical significance of this phenomenon remains unknown [12, 13], but needs to be further investigated, particularly as standard dosage regimens may be altered in varying circumstances.

Currently, clinical resistance of *Candida* spp. to echinocandins is rare; however, there are case reports which demonstrated clinical failure in patients receiving echinocandin therapy. This has been described with a number of species, including *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei* and *Candida dubliniensis.* Mutations conferring reduced susceptibility to echinocandins have been mapped to the FKS1 and/or FSK2 genes that encode for the 1,3-β-D-glucan synthase, but additional mechanisms of resistance have not been fully elucidated [5, 6]. In general, resistance to one echinocandin confers resistance to all others, with MICs of resistant isolates of 1 mg/L and above, but there has been variability in cross susceptibility reported [14, 15].

(b) ***Aspergillus* species**

In contrast to *Candida* spp., echinocandins exhibit fungistatic activity against *Aspergillus* spp. Exposure to echinocandins causes the fungal hyphae to grow irregularly, with many branched tips, disrupted hyphae and distended cells. MICs are difficult to determine for echinocandins against *Aspergillus* species and the minimum effective concentration (MEC) (i.e. the lowest concentration that results in the proliferation of filamentous fungi showing aberrant growth), may be a better measure of susceptibility of *Aspergillus*. Echinocandins display comparable in vitro activity against numerous *Aspergillus* spp., although one in vitro susceptibility study demonstrated that the MECs of anidulafungin and micafungin were 2–10-fold

lower than the MEC of caspofungin [16]. Sporadic treatment failures or breakthrough infections have been reported, these have been associated with high MEC isolates [1].

Unlike what is seen in *Candida* spp., the reduction of the fungal burden in aspergillosis has been shown to be most closely linked to the AUC/MIC ratio, not to the $C_{max}$/MEC ratio. A murine model of pulmonary aspergillosis showed that a $C_{max}$/MEC ratio ranging from 10–20 maximized the activity of caspofungin [17].

Similar to *Candida* spp., the "Eagle effect" (or paradoxical effect) has also been described with caspofungin and *Aspergillus* spp. The clinical significance of this phenomenon, however, remains unknown [13].

(c) **Other fungi**

Other fungi that may be susceptible to echinocandins include *Alternaria* spp., *Bipolaris* spp., *Cladophialophora bantiana*, *Phialophora* spp., *Exophiala* spp., *Fonsecaea pedrosoi*, *Paecilomyces variotii* and *Acremonium strictum*. In vitro studies have indicated variable activity against the dimorphic endemic fungi, but current evidence suggests that the use of echinocandins should be avoided for their treatment. Echinocandins do not have any activity against *Cryptococcus, Trichosporon, Fusarium*, zygomycetes or other filamentous fungi [15].

Limited data is available in relation to the pharmacodynamics properties of echinocandins against other fungal pathogens and no pharmacodynamic target has been identified for these pathogens.

## Pharmacokinetic Changes in Obesity

Although the echinocandins have similar antifungal activities, they have substantially different pharmacokinetic properties, which is important to understand when tailoring dosing regimens for individual patients [1, 18]. A summary of the steady-state PK parameters of the echinocandins in healthy adult volunteers with standard therapeutic dosing [1, 12], are summarized in Table 9.1.

Echinocandins distribute well into the majority of tissues, including the lung, liver and spleen. There is minimal distribution into the central nervous system (CNS) tissues, including the eye, due to their high plasma protein binding and large molecular weight. There is emerging evidence suggesting that therapeutic CNS levels may be achieved, provided that high plasma concentrations are obtained. Echinocandins do not achieve high urine concentrations but they may be effective in treating urinary tract infections due to the high concentrations achieved in tissues [1].

There is limited published literature in relation to PK variability of the echinocandins in critically ill patients. A recent prospective multicenter study demonstrated considerable inter-individual PK variability of both anidulafungin and caspofungin. The observed $AUC_{0–24}$ and $C_{max}$ were lower in the study for both

**Table 9.1** Pharmocokinetic properties of echinocandins

| | Anidulafungin | Caspofungin | Micafungin |
|---|---|---|---|
| Linear or non-linear pharmacokinetics | Linear | Moderate non-linear | Linear |
| Plasma protein binding (%) | 84 | 96–97 | >99 |
| Volume of distribution (L/kg) | 0.5 | 0.14 | 0.22–0.24 |
| Beta elimination half-life (t½β) (hours) | 24–26 | 10–15 | 11–17 |
| Total clearance (mL/min/kg) | 0.16–0.26 | 0.15 | 0.16–0.185 |
| Biotransformation | Slow chemical degradation and metabolism by plasma peptidases | Spontaneous degradation and peptide hydrolysis and N-acetylation | Some involvement of hepatic cytochrome P450 enzymes |
| Elimination | Mainly via biliary excretion with negligible renal clearance | Approximately 40 % of total dose eliminated via urine | Primarily non-renal |

drugs when compared with healthy volunteers [19]. A multi-centre observational PK study of micafungin in adult intensive care unit patients, demonstrated significantly lower micafungin exposure when compared with healthy volunteers, but not when compared with other patient populations [20]. These studies demonstrate that considerable inter-individual PK variability of echinocandins may be seen in patients within the intensive care setting, with the need for further studies to clarify the optimal dosage regimens and to define the role for therapeutic drug monitoring in this patient setting.

There is limited data available relating to the altered pharmacokinetic parameters of echinocandins when administered to obese patients. With an increase in bodyweight, the pharmacokinetic parameters may be altered due to changes in volume of distribution, plasma protein constituents, metabolism and clearance [18], with the potential for lower echinocandin exposure in obese patients.

## Review of Existing Literature

### (a) Micafungin

Pharmacokinetic analyses suggest that micafungin clearance is higher in obese patients compared to non-obese patients. Given that the AUC is inversely

proportional to systemic clearance (i.e. as clearance increases, $AUC_{0–24}$/MIC ratio declines), heavier patients are predicted to attain lower micafungin exposure (and efficacy) than their leaner counterparts [9–11].

An example of this was demonstrated in a case report describing a 40 year old morbidly obese woman with a weight of 230 kg [21]. She was commenced on intravenous micafungin at standard dosage (100 mg daily). Serum concentrations were obtained on day 5, at 4, 13 and 23 h from the start of the infusion and they were 2.93, 1.96 and 1.36 mg/L, respectively. She had a significantly lower AUC, when compared with a patient of normal weight. The authors concluded that clinicians should consider a dosage increase in obese patients with invasive candidiasis in view of the enhanced clearance and significantly decreased exposure observed in obesity.

A prospective study demonstrated a definite relationship between weight and micafungin systemic clearance but a poor correlation between body mass index (BMI) and PK parameters, including clearance. They found that systemic clearance increased as a function of weight, beyond a threshold of 66 kg, at least up to 155 kg, with the relationship accurately expressed by the 3/4 mass ratio expressed by Kleiber's law [22]. This finding suggests that a proportion of obese patients could fail to reach the optimal AUC/MIC ratio at standard micafungin dosages.

For overweight and obese patients, it has been demonstrated to calculate the micafungin clearance point by the following formula:

$$\text{Clearance (L/hour)} = 1.04 * (\text{M}/66.3)^{3/4}$$

where M is the patient's weight in kilograms, starting at 66.3 kg [11, 22].

Pasipanodya et al. recently published micafungin dose rules or formulae for bedside use, which were derived using modelling and simulation information. Rules 1 and 4 were proposed as bedside formulae for use by clinicians to optimize micafungin dosing in the treatment of candidiasis in overweight or obese patients [23].

*Rule 4 is proposed for use at the bedside by clinicians*:

$$\text{Dose (mg)} = \text{patient weight} + 42$$

rounded to the nearest 25 mg, with rounding up starting at 12.

*Rule 1 is proposed for more accurate dose individualization*:

$$\text{Dose (mg)} = 1.03 \times \text{patient weight} + 41.93$$

The formulae are only applicable for patients who are overweight or obese and not for patients less than 66.3 kg.

The current dosage recommendation is the same for all adult patients who weigh over 40 kg, but consideration needs to be given to the possibility that standard dosing may be insufficient in obese patients. When selecting a dose regimen,

consideration needs to be given to the clinical indication, the pathogen, the presence of critical illness and the adequacy of clinical response. The application of the published micafungin dosing formulae may help guide dose modification in the setting of obesity. The safety of micafungin doses up to 250 mg has been demonstrated in the published literature [24]. In these circumstances, however, there may be a role for therapeutic drug monitoring (TDM) to assist with dose modification, although TDM is not routinely available in many centers.

(b) **Caspofungin**

There is conflicting data available on dosage regimens for caspofungin in patients with obesity [15], pharmacokinetic studies suggest that heavier patients may be at risk for lower caspofungin peak and trough concentrations and a lower AUC than leaner patients [25, 26].

A prospective study demonstrated a relationship between weight and both the volume of distribution and the clearance of caspofungin, leading to a decrease in the peak concentration and the AUC. It was identified that systemic clearance increased as a function of weight, with the relationship accurately expressed by the 3/4 mass ratio expressed by Kleiber's law, which is similar to micafungin [25]. BMI was not found to be a significant covariate. The findings suggested that a proportion of obese patients could fail to reach the optimal AUC/MIC ratio at standard caspofungin dosages.

Nguyen et al. conducted a single center prospective study, where patients in a surgical intensive care unit who were receiving caspofungin (70 mg loading dose followed by maintenance dose of 50 mg daily) for suspected or proven fungal infection were enrolled. A linear-mixed effects model was used to identify factors that may have influenced caspofungin plasma concentrations. Caspofungin trough concentration was predicted to be significantly higher in patients with body weight less than 75 kg. The authors concluded that the maintenance dose should be increased in the surgical intensive care unit setting in patients who weigh more than 75 kg [26].

Contrastingly, a retrospective, post hoc analysis of efficacy outcomes in 9 phase 2/3 clinical trials found that caspofungin appeared as efficacious in obese patients and non-obese patients with the use of standard dosing [27]. Criticisms of this study, however, was that the severity of the underlying conditions, concomitant disease or baseline neutropenic status may not have been evenly distributed amongst the patients within the BMI groups, that this study used BMI and not weight when comparisons were made between the patient groups and that the original studies did not pre-specify the intent to examine differences in patient outcomes based on the BMI subgroups [15].

An example of the importance of caspofungin dosing in obesity was illustrated in a prospective cohort study where targeted antifungal prophylaxis was prescribed to 13 heart transplant recipients. The targeted strategy was effective for all patients in the cohort, except for one patient, who had a BMI of 35 $kg/m^2$. Their weight was

not documented. This patient had their dose of caspofungin reduced to 35 mg/day due to liver failure and was receiving haemodialysis. The patient developed pulmonary aspergillosis whilst on caspofungin prophylaxis [28].

The current dosage recommendation for caspofungin in patients weighing more than 80 kg is a maintenance dose of 70 mg daily after a regular loading dose of 70 mg on day 1 [18, 29], recognizing the issue of potential underdosing in obesity. Similar to micafungin, when selecting a dose regimen, consideration needs to be given to the clinical indication, the pathogen, the presence of critical illness and the adequacy of clinical response. If further dose escalation is to be considered, there may be a role for TDM to assist with dose modification, although TDM is not routinely available in many centers.

(c) **Anidulafungin**

There is limited published information describing the influence of obesity on the PKs of anidulafungin. Pharmacokinetic analyses have suggested that an increase in body weight is associated with both an increase in anidulafungin clearance and volume of distribution and a decrease in AUC, but these changes have not been deemed to be of clinical significance [30–32].

In healthy volunteers, an increase in body weight was shown to increase both clearance and volume of distribution, although this was not considered to be clinically important [30].

A population PK-PDs analysis of anidulafungin in adult patients with fungal infections was undertaken. Although the total exposure (AUC) in a typical 150-kg male could be approximately 30 % lower than in a 60-kg male patient, the efficacy did not seem to be affected in patients at the upper end of the weight spectrum, despite their lower exposure [31].

A population PKs analysis of anidulafungin in adult patients with proven or probable invasive aspergillosis identified body weight as the most influential covariate of anidulafungin PKs, with a tendency for anidulafungin AUC to decrease as body size (weight and BMI) increased. The magnitude of the changes in exposure were not considered clinically significant as there was an overlap of the exposure distributions across weight and BMI due to inter-individual variability. Of note however, was that the highest body weight in the analysis was 117 kg [32].

The current dosage recommendation is the same for all adult patients regardless of body weight, but consideration needs to be given to the possibility that standard dosing may be insufficient in the setting of obesity, particularly for patients with extremely high body weights (e.g. weight more than 150 kg) due to the lack of data for this group [31]. Dosage adjustments may need to be considered, particularly if there is a suboptimal clinical response. There are no available formulae for dose modification in the setting of extremely high body weights but in these circumstances there may be a role for TDM to assist with dose modification, although TDM is not routinely available in many centers.

A limited sampling strategy for anidulafungin in selected patients was proposed in a recent publication by van Wanrooy et al, which described obtaining a single sample drawn 12 h after the start of infusion and an estimation of the exposure using either linear regression or a population pharmacokinetics model [33]. In the case of possible insufficient exposure, anidulafungin doses can be increased in a linear manner as the exposure increases proportionally to the dose.

## Dosage Recommendations

Standard recommendations for adult echinocandin dosage for treatment of invasive fungal infection according to the available guidelines [2–4, 29] are as follows: (Table 9.2)

**Table 9.2** Standard echinocandin dosage recommendations

| | Anidulafungin | Caspofungin | Micafungin |
|---|---|---|---|
| Loading dose on day 1 | 200 mg | 70 mg | Nil |
| Maintenance doses | 100 mg daily | *If patient* >80 kg: 70 mg daily [if moderate hepatic impairment, reduce maintenance dose to 35 mg daily] | *If patient* >40 kg: [a]100 mg/day |
| | | *If patient* $\leq$ 80 kg: 50 mg daily [if moderate hepatic impairment, reduce maintenance dose to 35 mg daily] | *If patient* $\leq$ 40 kg: [b]2 mg/kg/day |
| Dosage adjustment required in renal impairment? | No | No | No |
| Dosage adjustment required in renal replacement therapy? | No | No | No |
| Dosage adjustment required in hepatic impairment? | No | 35 mg daily for patients with moderate impairment No recommendation for severe impairment | No recommendation for severe impairment but it is likely that no dose adjustment required [34] |
| Drug interactions | None known | Multiple | Few |

[a]May increase to 200 mg/day if clinical response inadequate (safety data exists for up to 250 mg/day for micafungin [24])
[b]Actual body weight, may increase to 4 mg/kg/day if clinical response inadequate

Clinicians may consider a further dosage increase in obese patients with invasive fungal infection in view of the pharmacokinetics data demonstrating higher clearance and lower drug exposure than leaner patients as previously described. Further studies are warranted, however, to establish the optimal dosing strategy for these patients and to assess the safety and efficacy of higher echinocandin doses in this clinical setting. Therapeutic drug monitoring, if available, would certainly be an important adjunct to assisting clinical management.

## References

1. Aguilar-Zapata D, et al. Echinocandins: the expanding antifungal armamentarium. Clin Infect Dis. 2015;61(S6):S604–11.
2. Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2014 update. Intern Med J. 2014; 44(12):1267–397.
3. Cornely OA, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18(Suppl 7):19–37.
4. Pappas PG, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503–35.
5. Escheunauer G, et al. Comparison of echinocandin antifungals. Ther Clin Risk Manag. 2007;3 (1):71–97.
6. Scott LJ. Micafungin. A review of its use in the prophylaxis and treatment of invasive *Candida* infections. Drugs. 2012;72(16):2141–65.
7. Katragkou A, et al. Role of echinocandins in fungal biofilm-related disease: vascular catheter-related infections, immunomodulation and mucosal surfaces. Clin Infect Dis. 2015;61 (S6):S622–9.
8. Ghannoum M, et al. The role of echinocandins in Candida biofilm-related vascular catheter infections: in vitro and in vivo model systems. Clin Infect Dis. 2015;61(S6):S618–21.
9. Andes D, et al. In vivo comparison of the PD targets for echinocandin drugs against *Candida* species. AAC. 2010;54:2497–506.
10. Andes D, et al. Use of PK/PD analyses to optimize therapy with the systemic antifungal micafungin for invasive candidiasis or candidemia. AAC. 2011;55(5):2113–21.
11. Gumbo T, et al. Population pharmacokinetics of micafungin in adult patients. Diagno Microbiol Infect Dis. 2008;60:329–31.
12. Mayr A, et al. Anidulafungin for the treatment of invasive candidiasis. Clin Microbiol Infect. 2011;17(Suppl 1):1–12.
13. Steinbach WJ, et al. Potential microbiological effects of higher dosing of echinocandins. Clin Infect Dis. 2015;61(S6):S669–77.
14. Walker LA, et al. Fungal echinocandin resistance. Fungal Genet Biol. 2010;47(2):117–26.
15. Song J, Stevens D. Caspofungin: pharmacodynamics, pharmacokinetics, clinical uses and treatment outcomes. Crit Rev Microbiol. 2015.
16. Pfaller MA, et al. In vitro susceptibility of clinical isolates of *Aspergillus* spp. to anidulafungin, caspofungin and micafungin: a head-to-head comparison using the CLSI M38-42 broth microdilution method. J Clin Microbiol. 2009;47:3323–5.
17. Wiederhold NP, et al. PD of caspofungin in a murine model of invasive pulmonary aspergillosis: evidence of concentration dependant activity. J Infect Disease. 2004;190: 1464–71.
18. Muilwijk EW, et al. Impact of special patient populations on the pharmacokinetics of echinocandins. Expert Rev Anti Infect Ther. 2015;13(6):799–815.

19. Sinnollareddy MG, et al. PK variability and exposures of fluconazole, anidulafungin and caspofungin in intensive care unit patients: data from multinational Defining Antibiotic Levels in Intensive Care Unit (DALI) patients study. Crit Care. 2015;4(19):33.
20. Lempers VJ, et al. Altered micafungin PK in intensive care unit patients. AAC. 2015;59 (8):4403–9.
21. Zomp A, et al. Micafungin therapy in a critically ill morbidly obese patient. JAC. 2011; 2678–80.
22. Hall RG, et al. Fractal geometry and the pharmacokinetics of micafungin in overweight, obese and extremely obese people. AAC. 2011;5107–12.
23. Pasipanodya JP, et al. In silico-derived bedside formula for individualised micafungin dosing for obese patients in the age of deterministic chaos. Clin Pharmacol Ther. 2015;97(3):292–7.
24. Sirohi B, et al. A study to determine the safety profile and maximum tolerated dose of micafungin (FK463) in patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplant. 2006;38:47–51.
25. Hall RG, et al. Weight drives caspofungin PK variability in overweight and obese people. AAC. 2013;57(5):2259–64.
26. Nguyen TH, et al. Factors influencing caspofungin plasma concentration in patients in a surgical intensive care unit. JAC. 2007;60:100–6.
27. Ryan DM, et al. Efficacy and safety of caspofungin in obese patients. Med Mycol. 2011; 29(7):748–54.
28. Munoz P, et al. Targeted antifungal prophylaxis in heart transplant recipients. Transplantation. 2013;96:664–9.
29. European Medicines Agency. Cancidas: summary of product characteristics. 2011. Available from: www.ema.europa.eu/humandocs/Humans/EPAR/cancidas/cancidas.htm.
30. Dowell JA, et al. Population PK analysis of anidulafungin, an echinocandin antifungal. J Clin Pharmacol. 2004;44(6):590–8.
31. Liu P. Population PK-PD analysis of anidulafungin in adult patients with fungal infections. AAC. 2013;57(1):466–74.
32. Liu P, Mould D. Population PK analysis of voriconazole and anidulafungin in adult patients with invasive aspergillosis. AAC. 2014;58(8):4718–26.
33. van Wanrooy M, et al. Limited-sampling strategies for anidulafungin in critically ill patients. AAC. 2015;59(2):1177–81.
34. Undre N, et al. Pharmacokinetics of micafungin in subjects with severe hepatic dysfunction. Eur J Drug Metab Pharmacokinet. 2015;40(3):285–93.

# Chapter 10
# Polyene Antifungals

**Janattul-Ain Jamal and Jason A. Roberts**

**Abstract** Determining the optimal polyene antifungal dosing in obese patients is considered highly challenging. Limited data are available to describe the pharmacokinetics of polyene antifungals in these patients. However, polyene antifungals demonstrate widely variable pharmacokinetics in various clinical conditions. In particular, the two main parameters that define dosing requirements, volume of distribution (V) and clearance, can change significantly in obese patients. Therefore, in the absence of robust data to describe optimal polyene dosing in obesity, dosing guided by therapeutic drug monitoring (TDM) remains the best approach, particularly when aggressive dosing is required in the context of poorly susceptible pathogens. Lean body weight appears to be the preferred weight metric to estimate polyene dosing in obesity, in order to prevent inappropriate excessive doses and subsequent adverse events including nephrotoxicity.

**Keywords** Polyene · Dosing · Obesity

J.-A. Jamal · J.A. Roberts (✉)
Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, QLD, Australia
e-mail: j.roberts2@uq.edu.au

J.A. Roberts
Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Butterfield St., Herston, Brisbane, QLD 4006, Australia

J.A. Roberts
Pharmacy Department, Royal Brisbane and Women's Hospital, Butterfield St., Herston, Brisbane, QLD 4006, Australia

J.A. Roberts
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_10

## Introduction

Polyene antifungals, such as amphotericin B, nystatin and natamycin, act as inhibitors of fungal cell membranes by binding to ergosterol in the fungal cell membrane, weakening it and causing a leakage of $K^+$ and $Na^+$ ions that eventually leads to fungal cells death. Amphotericin B is the most commonly used polyene agent in clinical practice, for treatment of systemic fungal infections. It has a broad-spectrum of antifungal activity, which include opportunistic and endemic fungi [1, 2]. Amphotericin B is minimally distributed into tissues such as liver, spleen, lungs, kidney, muscle, skin and adrenal gland [3–7] and has also shown low penetration into the central nervous system (CNS), >4 % [8–11]. Amphotericin B is highly protein binding, >90 % [12, 13]. Biliary elimination accounts for 0.8–14 % of clearance [7], although interestingly, hepatic or kidney failure does not result in any changes to blood concentrations [14, 15].

Lipid formulations of amphotericin B, such as amphotericin B lipid complex, liposomal amphotericin B and amphotericin B colloidal dispersion, are the therapeutic advances in the drug delivery system for this compound in recent years. These formulations enable enhanced amphotericin systemic exposure while minimizing adverse events, such as nephrotoxicity and infusion-related reactions, which appear more common with the conventional formulation, amphotericin B deoxycholate [16].

## Pharmacodynamics Target

Amphotericin B has demonstrated a concentration-dependent fungicidal activity in in vitro studies [17, 18]. The agent has also been shown to have a prolonged post-antifungal effect, which may be as long as 10 h in an in vitro study and even up to 30 h in an in vivo study [19, 20]. The maximum peak concentration ($C_{max}$) to minimum inhibitory concentration (MIC) ratio (i.e. $C_{max}$/MIC) correlated best with the clinical outcome, followed by the time above MIC ($T_{>MIC}$) and finally the area under the concentration-time curve (AUC): MIC ratio, in an animal models [20].

## Pharmacokinetic Changes in Obesity

Limited human data is available describing the pharmacokinetics of amphotericin B in obesity. However, animal studies have shown that obesity could alter the pharmacokinetics [21, 22]. After administration of similar doses of amphotericin B to hyperlipidemic obese rats and lean rats, there was a 2-fold increase in the mean amphotericin B AUC in obese rats compared to the lean rats [21]. In another study, significantly different pharmacokinetics were observed after administration of

liposomal amphotericin B between rabbits with an enriched diet (obese) and normal rabbits, although similar pharmacokinetics were observed in both groups when a conventional amphotericin B formulation (amphotericin B deoxycholate) was administered [22]. These studies have highlighted the possibility that physiological changes due to obesity could affect amphotericin B pharmacokinetics, and that the extent of the changes may vary between different formulations. However, robust human data is required to further identify these changes.

## Review of Existing Literature

Limited data is available describing the pharmacokinetics of polyenes, particularly in obesity. There are presently no completed pharmacokinetics studies available. However, we do look forward to data from clinical trial, NCT02320604, for the pharmacokinetics of liposomal amphotericin.

However some data exist describing the pharmacokinetics of amphotericin B in various clinical conditions (see Table 10.1). This data could be used to help inform treatment in obese patients.

Pharmacokinetic studies of amphotericin B formulations in patients with haematological malignancies demonstrated an elimination half-life of 11–15 h [23]. A larger V and clearance were observed with the administration of amphotericin B in fat emulsion [23]. While data from 51 bone marrow transplant patients treated with amphotericin B colloidal dispersion, showed that drug clearance and V were increased by escalating the dose, with an elimination half-life (t½) of up to 29 h [24].

The pharmacokinetics of various amphotericin B formulations was also evaluated in critically ill patients [25, 26]. Generally, critical illness will lead to unique pathophysiologic changes, such as a hyperdynamic state with an elevated cardiac output and an increased renal and hepatic blood flow, which will lead to supranormal drug clearances. This condition can progress to a more severe condition where patient may develop single or multiple organ dysfunctions that can affect drug clearance and V [27]. Pharmacokinetic alterations of various antibiotics in critically ill patients have been widely discussed [27, 28]. Published data have shown a widely variable amphotericin V after administration of different types of amphotericin B formulations, with V ranging between 30 and 2048 L in critically ill patients [25, 26]. Similarly, total drug clearance was reported between 0.1 and 44.0 mL/min in these critically ill patients. Although higher clearance was observed in critically ill patients receiving continuous renal replacement therapy (RRT), the clearance mediated by the extracorporeal treatment would be considered as minimal, less than 1 % of the total clearance during continuous venovenous haemodiafiltration (CVVHDF) and 20 % of the total clearance during continuous venovenous haemofiltration (CVVH) [26, 29]. This suggests that changes to other elimination pathways are occurring in the presence of RRT which leads to greater amphotericin B clearance.

**Table 10.1** Pharmacokinetic data of amphotericin B in healthy adults and during various clinical conditions

| Ref(s)/patients characteristics | Formulation/dose | Pharmacokinetic parameters[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (mg/L) | t½ (h) | MRT (h) | V (L) | $AUC_{0-24}$ (mg/L.h) | Clearance (L/h) |
| *Healthy adults* | | | | | | | |
| Adedoyin et al. [32] – Healthy adults | Amphotericin B lipid complex ($n$ = 4)—2.5 mg/kg | 3.7 ± 0.8 | 140 ± 67.5 | NA | 676 ± 122 | 47.0 ± 18.6 | 4.9 ± 1.7 |
| *Cancer and/or transplant patients* | | | | | | | |
| Ayestaran et al. [23] – Haematological malignancy, neutropenia | Conventional amphotericin B ($n$ = 8)—1 mg/kg | 2.8 ± 1.2 | 15.2 ± 5.3 | 19.7 ± 7.9 | 35.9 ± 9.7 | 29.0 ± 15.5 | 2.1 ± 0.9 |
| Ayestaran et al. [23] – Haematological malignancy, neutropenia | Fat emulsion preparation ($n$ = 8)—1 mg/kg | 1.5 ± 0.6 | 11.4 ± 5.2 | 19.4 ± 11.1 | 66.4 ± 32.6 | 17.2 ± 11.2 | 4.0 ± 2.3 |
| *Critically ill patients* | | | | | | | |
| Heinemann et al. [25] – Critically ill patients | Conventional amphotericin B ($n$ = 6)—1 mg/kg | 1.7 (1.5–2.1) | 26.8 (9.9–37.0) | NA | 170.6 (79.3–305.9) | 18.7 (9.7–28.3) | 0.07 (0.04–0.1) |
| Heinemann et al. [25] – Critically ill patients | Liposomal amphotericin B ($n$ = 10)—2.8–3.0 mg/kg | 14.4 (6.4–89.0) | 13.05 (8.7–41.4) | NA | 30.2 (3.9–66.9) | 171.0 (53.1–1380.0) | 0.02 (0.0–0.06) |
| Malone et al. [26] – Critically ill patients | Amphotericin B lipid complex (n = 6)—4.5 (4.4–4.8) mg/kg | 0.5 (0.4–0.5) | 32.5 | NA | 2048 (1636–2486) | 11.5 (8.2–13.7) | 43.7 (29.2–55.3) |
| *Critically ill patients receiving renal replacement therapy* | | | | | | | |
| Malone et al. [26] – Critically ill patients, CVVHDF | Amphotericin B lipid complex ($n$ = 8)—4.9 (4.6–5.1) mg/kg | 0.6 (0.5–0.9) | 30.9 | NA | 1476 (783–2403) | 13.9 (8.4–31.6) | 27.4 (11.9–47.9) |
| Bellman et al. [29] – Critically ill on CVVH | Amphotercin B lipid complex ($n$ = 2)—4.9 mg/kg | 0.6 | 13.2 | 18.1 | 678.9 | 7.5 | 36.7 |

$C_{max}$ = maximum concentration; t½ = elimination half-life; MRT = mean residence time; V = volume of distribution; $AUC_{0-24}$ = area under the concentration-time curve from 0–24 h; CVVHDF = continuous venovenous haemodiafiltration; CVVH = continuous venovenous haemofiltration

[a]Data presented as mean ± standard deviation or median (interquartile range)

Comparable data were observed between those derived from the critically ill patients and those with haematological malignancies. The administration of lipid formulations led to higher drug exposure [25], suggesting that aggressive dosing with this formulation should be followed with close drug concentration monitoring. Interestingly, different lipid formulations of amphotericin B (e.g. liposomal amphotericin B versus amphotericin B colloidal dispersion) have resulted in different pharmacokinetics [30], thus confirming a wide interplay of factors contributing to the various levels of amphotericin pharmacokinetic changes.

## Recommendations

More research is required to better understand the precise effects of obesity on polyene pharmacokinetics. Different formulations of amphotericin B are affected differently in various clinical conditions. Therefore, it is expected that obesity would also lead to variable changes in amphotericin pharmacokinetics for the different drug formulations.

In the absence of robust data to describe optimal dosing in obesity, therapeutic drug TDM remains the best tool to guide dosing in these patients. Even though amphotericin is often observed to have a large V, studies in non-obese patients do not report significant distribution into adipose tissue [31], which means that increasing dose based on total body weight is unlikely to result in an equivalent rise of the concentration, as observed in non-obese patients. Given the possible toxicity with inappropriately higher doses, it would be prudent to escalate doses based using a measure of lean body weight in obese patients. If a patient has a very serious infection, then higher doses could be empirically considered, but only with close monitoring of signs of drug toxicity including renal function and electrolytes.

## References

1. Groll AH, Piscitelli SC, Walsh TJ. Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development. Adv Pharmacol. 1998;44:343–500.
2. Groll AH, Walsh TJ. Uncommon opportunistic fungi: new nosocomial threats. Clin Microb Infect (the official publication of the European Society of Clinical Microbiology and Infectious Diseases). 2001;7(Suppl 2):8–24.
3. Pennington JE, Block ER, Reynolds HY. 5-fluorocytosine and amphotericin B in bronchial secretions. Antimicrob Agents Chemother. 1974;6(3):324–6.
4. Lawrence RM, Hoeprich PD, Jagdis FA, Monji N, Huston AC, Schaffner CP. Distribution of doubly radiolabelled amphotericin B methyl ester and amphotericin B in the non-human primate, *Macaca mulatta*. J Antimicrob Chemother. 1980;6(2):241–9.
5. Kerr CM, Perfect JR, Craven PC, Jorgensen JH, Drutz DJ, Shelburne JD, et al. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Ann Intern Med. 1983;99(3):334–6.

6. Christiansen KJ, Bernard EM, Gold JW, Armstrong D. Distribution and activity of amphotericin B in humans. J Infect Dis. 1985;152(5):1037–43.
7. Collette N, van der Auwera P, Lopez AP, Heymans C, Meunier F. Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B-deoxycholate. Antimicrob Agents Chemother. 1989;33(3):362–8.
8. Bindschadler DD, Bennett JE. A pharmacologic guide to the clinical use of amphotericin B. J Infect Dis. 1969;120(4):427–36.
9. Drutz DJ, Spickard A, Rogers DE, Koenig MG. Treatment of disseminated mycotic infections. A new approach to amphotericin B therapy. Am J Med. 1968;45(3):405–18.
10. Utz JP, Garriques IL, Sande MA, Warner JF, Mandell GL, McGehee RF, et al. Therapy of cryptococcosis with a combination of flucytosine and amphotericin B. J Infect Dis. 1975;132 (4):368–73.
11. Dugoni BM, Guglielmo BJ, Hollander H. Amphotericin B concentration in cerebrospinal fluid of patients with AIDS and cryptococcal meningitis. Clin Pharm. 1989;8(3):220–1.
12. Block ER, Bennett JE, Livoti LG, Klein WJ Jr, MacGregor RR, Henderson L. Flucytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. Studies in man. Ann Intern Med. 1974;80(5):613–7.
13. Morgan DJ, Ching MS, Raymond K, Bury RW, Mashford ML, Kong B, et al. Elimination of amphotericin B in impaired renal function. Clin Pharmacol Ther. 1983;34(2):248–53.
14. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. Clin Pharmacokinet. 1983;8(1):17–42.
15. Atkinson AJ Jr, Bennett JE. Amphotericin B pharmacokinetics in humans. Antimicrob Agents Chemother. 1978;13(2):271–6.
16. Hamill RJ. Amphotericin B formulations: a comparative review of efficacy and toxicity. Drugs. 2013;73(9):919–34.
17. Klepser ME, Wolfe EJ, Jones RN, Nightingale CH, Pfaller MA. Antifungal pharmacodynamic characteristics of fluconazole and amphotericin B tested against Candida albicans. Antimicrob Agents Chemother. 1997;41(6):1392–5.
18. Klepser ME, Wolfe EJ, Pfaller MA. Antifungal pharmacodynamic characteristics of fluconazole and amphotericin B against Cryptococcus neoformans. J Antimicrob Chemother. 1998;41(3):397–401.
19. Turnidge JD, Gudmundsson S, Vogelman B, Craig WA. The postantibiotic effect of antifungal agents against common pathogenic yeasts. J Antimicrob Chemother. 1994;34(1):83–92.
20. Andes D, Stamsted T, Conklin R. Pharmacodynamics of amphotericin B in a neutropenic-mouse disseminated-candidiasis model. Antimicrob Agents Chemother. 2001;45 (3):922–6.
21. Vadiei K, Lopez-Berestein G, Luke DR. Disposition and toxicity of amphotericin-B in the hyperlipidemic Zucker rat model. Int J Obes. 1990;14(6):465–72.
22. Ramaswamy M, Peteherych KD, Kennedy AL, Wasan KM. Amphotericin B lipid complex or amphotericin B multiple-dose administration to rabbits with elevated plasma cholesterol levels: pharmacokinetics in plasma and blood, plasma lipoprotein levels, distribution in tissues, and renal toxicities. Antimicrob Agents Chemother. 2001;45(4):1184–91.
23. Ayestaran A, Lopez RM, Montoro JB, Estibalez A, Pou L, Julia A, et al. Pharmacokinetics of conventional formulation versus fat emulsion formulation of amphotericin B in a group of patients with neutropenia. Antimicrob Agents Chemother. 1996;40(3):609–12.
24. Amantea MA, Bowden RA, Forrest A, Working PK, Newman MS, Mamelok RD. Population pharmacokinetics and renal function-sparing effects of amphotericin B colloidal dispersion in patients receiving bone marrow transplants. Antimicrob Agents Chemother. 1995;39 (9):2042–7.
25. Heinemann V, Bosse D, Jehn U, Kahny B, Wachholz K, Debus A, et al. Pharmacokinetics of liposomal amphotericin B (Ambisome) in critically ill patients. Antimicrob Agents Chemother. 1997;41(6):1275–80.

26. Malone ME, Corrigan OI, Kavanagh PV, Gowing C, Donnelly M, D'Arcy DM. Pharmacokinetics of amphotericin B lipid complex in critically ill patients undergoing continuous venovenous haemodiafiltration. Int J Antimicrob Agents. 2013;42(4):335–42.
27. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet. 2006;45(8):755–73.
28. Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit Care Clin. 2011;27(1): 19–34.
29. Bellmann R, Egger P, Djanani A, Wiedermann CJ. Pharmacokinetics of amphotericin B lipid complex in critically ill patients on continuous veno-venous haemofiltration. Int J Antimicrob Agents. 2004;23(1):80–3.
30. Bellmann R, Egger P, Gritsch W, Bellmann-Weiler R, Joannidis M, Kaneider N, et al. Amphotericin B lipid formulations in critically ill patients on continuous veno-venous haemofiltration. J Antimicrob Chemother. 2003;51(3):671–81.
31. Groll AH, Mickiene D, Piscitelli SC, et al. Distribution of lipid formulations of amphotericin B into bone marrow and fat tissue in rabbits. Antimicrob Agents Chemother. 2000;44:408–10.
32. Adedoyin A, Bernardo JF, Swenson CE, Bolsack LE, Horwith G, DeWit S, et al. Pharmacokinetic profile of ABELCET (amphotericin B lipid complex injection): combined experience from phase I and phase II studies. Antimicrob Agents Chemother. 1997;41 (10):2201–8.

# Chapter 11
# Miscellaneous Agents

**Eleanor van Dyk, Rahul P. Patel and Syed Tabish R. Zaidi**

**Abstract** Dosing recommendations for a number of antimicrobial classes are presented in the previous chapters. A number of antimicrobials have very little information on the pharmacokinetics (PK) variability or dosing strategies for obese patients. This chapter will briefly outline the literature and dosing recommendations for other miscellaneous antimicrobials that are not presented elsewhere in this book. Dosing recommendations for these agents in obese patients have been made based on the limited available information. There is an urgent need for robust PK studies of many antibiotics that are commonly used in obese patients to guide dosing recommendations.

**Keywords** Colistin · Lincosamides · Metronidazole · Obesity · Dosing · Guanine antivirals · Oseltamivir

## Introduction

This chapter will collectively discuss the dosing of various antimicrobials that have limited information on dosing in obese patients, and are not covered in the earlier chapters. All of the agents discussed in this chapter have limited clinical indications and do not fall under any of the antimicrobials classes discussed earlier.

1. **Colistin**

Colistin (Polymyxin E) is the most well-known member of the polymyxin group of antibiotics and is commercially available as colistimethate sodium (CMS), which is converted to colistin in the human body. Colistin changes the permeability of the bacterial cell wall, causing the leakage of important intracellular contents, eventually leading to bacterial death [1, 2]. Colistin is a relatively old antibiotic that was

E. van Dyk · R.P. Patel · S.T.R. Zaidi (✉)
Pharmacy, School of Medicine, University of Tasmania, Private Bag 26,
Hobart, TAS 7001, Australia
e-mail: Tabish.razizaidi@utas.edu.au



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_11

previously phased out of clinical use because of its neuro- and nephro-toxicity. The use of colistin has been revived due to the increasing incidence of carbapenem-resistant Gram-negative bacterial infections.

Dosing of colistin has been complicated by the conflicting recommendations provided by the manufacturers of commercially available Colistin (Colomycin® and Colo-Mycin M®). Both of these products contain colistin as a CMS salt, yet differ significantly in their dosing recommendations. The Colomycin® product information sheet recommends a dose of 30–60 mg of Colistin base activity (CBA) every 8 h for patients weighing more than 60 kg and 1.5–2.25 mg of CBA/kg for patients weighing less than 60 kg [3]. Contrarily, the Colo-Mycin M® product information sheet recommends a dose of 2.5–5.0 mg/kg of CBA per day to given as two or three divided doses [3]. This means the lowest recommended dose of Colo-Mycin M® is higher than the maximum recommended dose of Colomycin®. Adjustment in dosing required for obese patients can further complicate dosing calculations and increase the risk of dosing errors. Importantly, dosing based on total body weight (TBW) instead of ideal body weight (IBW) has resulted in significant nephrotoxicity in obese patients [1, 2, 4, 5]. However, the studies investigating various dosing regimens of colistin have shown similar clinical and microbiological cure rates [6–9], questioning the trend of proposing a high dose of colistin in recent studies [7, 10].

Pharmacokinetic/pharmacodynamic (PK/PD) studies have shown that the area under the plasma concentration-time curve (AUC) and the minimum inhibitory concentration (MIC) ratio (i.e. AUC/MIC) is the best PD descriptor (superior to the ratio of peak plasma concentration ($C_{max}$) to MIC (i.e. $C_{max}$/MIC) of antibacterial activity against both *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. This suggests that time-averaged exposure is more important than achieving high peak concentrations, supporting the recommended multiple daily dosing regimen, as opposed to once daily dosing. Multiple daily dosing of colistin also appears to be more effective in minimising bacterial resistance, when compared to once daily dosing [11].

Limited studies have compared the PK of colistin in obese with non-obese subjects [12, 13]. A retrospective cohort study assessing the incidence and risk factors for colistin-associated nephrotoxicity found that 54 patients (43 %) developed dose-dependent nephrotoxicity [12]. DeRyke et al. [12] reviewed 30 patients who received colistin and found that calculating doses using a TBW in obese patients were associated with nephrotoxicity. For example, 47 % of the patients received an excessive dose, and 71 % of these doses were calculated using a TBW in an obese patient [13].

Garonzik et al. [10] performed a study with the aim of developing a population PK model for colistin and CMS. They found that body weight was not a covariate in determining clearance, and, therefore, maintenance dosing should be based on renal function and target concentration. Conversely, they recommended that the loading doses be calculated according to weight, specifically the lower of TBW or IBW [10]. Mohamed et al. [14] found that a weight-based loading dose would have minimal impact on the initial increase in colistin concentration, as CMS is

converted to colistin in the body over time and the concentration of colistin increases over the dosing interval. Given this, it was recommended that only fixed loading doses be used [14].

Based on the above limited evidence, colistin loading doses should be based on the lower of TBW or IBW and maintenance dosing should be based on creatinine clearance and target colistin concentrations. An important consideration in calculating the doses of colistin is the relevant nephrotoxicity associated with a high dose of colistin (5 mg/kg or above). Limited evidence suggested that taking MIC values of causative bacteria into consideration in designing colistin regimens is worthwhile and may prevent high dose exposure and subsequent nephrotoxicity in some patients.

2. **Lincosamides and metronidazole**

Lincosamides and metronidazole are predominantly used to treat infections caused by anaerobic bacteria. Lincosamides refer to a group of antibiotics that closely resemble a natural member of the class, lincomycin [15]. The other two agents in this class are clindamycin and pirlimycin [15]. Clindamycin and lincomycin are the only two agents that are in clinical use for humans, whereas prilamycin is used in the veterinary settings. Lincosamides are effective against infections caused by Gram-positive and anaerobic bacteria with no cover against aerobic Gram-negative bacteria [15]. Metronidazole is a nitro-imidazole antibiotic that is effective against Gram-positive and Gram-negative anaerobic bacteria [16].

Lincosamides are clinically indicated as a second line prophylactic antibiotics for surgical site infections, and, skin and soft tissue infections in penicillin allergic patients. Clindamycin is commonly used in pelvic inflammatory disease and toxic shock syndrome. Additionally, clindamycin has been used in serious uncommon infections such as anthrax, toxoplasmosis and pneumocystis jiroveci pneumonia [15]. Metronidazole is indicated for the treatment of intra-abdominal infections, gut decontamination for surgical procedures, antibiotic associated diarrhea caused by *Clostridium difficile*, antimicrobial prophylaxis for surgical infections, bacterial vaginosis and systemic anaerobic infections [16].

Bouazza et al. [17] studied the pharmacokinetics of oral and intravenously administer clindamycin in 50 patients with osteomyelitis. The mean body weight of patients was 70 kg, and the highest recorded weight was 133 kg. Patients received 600 mg of clindamycin as an intravenous infusion or oral tablets. The authors reported an increase in the clearance of clindamycin proportional to TBW. Subsequent PK modelling revealed that the commonly used dose of 600 mg of clindamycin every 8 h is insufficient in patients weighing more than 75 kg. The authors recommended a higher dose of clindamycin (900 mg every 8 h) in patients weighing more than 75 kg to achieve adequate serum concentrations [17]. Given the lack of information about lincomycin in overweight or obese patients, clindamycin should be the preferred lincosamide in these patients.

A thorough search of the available literature did not lead to any studies regarding metronidazole PK in obese patients. One study assessed the effect of the body mass

index (BMI) on the treatment outcome of patients treated with metronidazole for bacterial vaginosis [18]. The authors randomized 738 patients to metronidazole and found that the treatment response rate was not affected by the degree of obesity as classified by BMI [18]. It is important to note that a substantially large dose of metronidazole (2 g) was used for the treatment of bacterial vaginosis, compared to a 500 mg dose used for most other infections [16]. One study evaluated the relative effectiveness of a quadruple regimen, including metronidazole, for *Helicobacter pylori* infection, found that obese patients are unlikely to achieve 80 % eradication rate associated with the regimen in normal weight individuals [19]. The eradication of *H. pylori* is dependent upon the collective effectiveness of the four individual antibiotics in the regimen and therefore, an observed failure cannot be attributed solely to the ineffectiveness of metronidazole. High dose metronidazole is recommended for the treatment of brain abscesses and serious systemic infections [16]. Given the distribution of metronidazole in most bodily fluids and tissues [20], higher doses may be considered in morbidly obese patients.

## 3. **Guanine antivirals**

Guanine nucleoside analogue antiviral agents inhibit the synthesis of viral DNA. Notable agents in this class are acicolvir, famciclovir, ganciclovir, valganciclovir and valaciclovir. Aciclovir, famciclovir and valaciclovir are commonly used for the treatment and prevention of the infections caused by herpes simplex and varicella-zoster viruses. Ganciclovir and valganciclovir are used for the prevention and treatment of infections caused by the cytomegalovirus. Guanine analogues are activated via phosphorylation by viral and cellular enzymes, they cause inhibition of viral DNA polymerase, thereby blocking viral DNA synthesis [1, 16].

Given the potential for guanine analogues to cause nephrotoxicity, particularly if high doses are administered, it is imperative that IBW is used to calculate doses in order to minimise the risk of significant overdose and renal impairment. Also, neutropenia associated with ganciclovir is dose-dependent and therefore if higher doses are used in obese patients they may be at the significant risk of complications [1, 21].

PK information on guanine analogues in obese subjects is scarce. Available studies have exclusively studied acyclovir, mainly because it is one of the most frequently used antivirals in clinical settings. A single dose PK study in obese and normal weight individuals identified that PK parameters were not significantly different between both groups, including the volume of distribution (V), which was approximately 43 L. This value correlates well with the total body water (48 L/1.73 $m^2$) or lean body weight and consequently, the authors recommended using IBW as a convenient estimation of aciclovir dosing in obese patients to avoid potential overdose and resultant nephrotoxicity [22–24].

Increased risk of nephrotoxicity from unadjusted dosing of aciclovir has been highlighted in many case reports. A 60 year old male with BMI of 37.6 kg/$m^2$ developed acute nephrotoxicity due to an unadjusted aciclovir dose based on TBW. The patient received seven doses of IV aciclovir 1 g (9.2 mg/kg of actual body

weight) 8-hourly for potential herpes encephalitis, the corresponding IBW dose for this patient would have been 650 mg. By the third day his serum creatinine had increased four-fold, aciclovir was ceased (along with concurrent moxifloxacin and doxycycline), and the patient was diagnosed with aciclovir-induced nephrotoxicity [22]. A similar case report of a 23-year old morbidly obese male also highlighted the concerns of renal impairment associated with high doses of aciclovir. This patient had no significant medical history and was administered 10 mg/kg (actual body weight) IV aciclovir 8-hourly for suspected encephalitis/meningitis. Within 48 h his renal function had significantly declined; aciclovir therapy was discontinued, and his renal function returned to baseline [23, 25].

Ganciclovir PK parameters in obese subjects have not been studied in either animals or humans, and prescribing information does not provide any advice regarding dosing in this patient subgroup. Given the hydrophilic nature of ganciclovir, as well as its comparability to aciclovir in terms of small molecular weight, mechanism of action and toxic potential, it may be appropriate to consider calculating ganciclovir doses using IBW or LBW. Aciclovir should be dosed based on IBW or LBW, though a higher dose (10 mg/kg) can be utilised for serious infections and patients who are morbidly obese with appropriate hydration and close monitoring of renal function. No recommendations can be made for other agents though it makes sense to use IBW or LBW based dosing for ganciclovir as well.

4. **Oseltamivir**

Oseltamivir is an antiviral neuraminidase inhibitor. It is available as the prodrug oseltamivir phosphate, which is converted to the active metabolite oseltamivir carboxylate. Oseltamivir selectively inhibits influenza virus neuraminidases, which are glycoproteins found on the virion surface. This prevents the release of newly synthesized viruses from infected cells, thereby reducing replication of the influenza virus and halting the spread of infection. Oseltamivir demonstrates activity against both influenza A and B viruses [1, 2, 16, 26].

Early administration of oseltamivir is imperative, as influenza viral replication peaks at 24–72 h after the onset of illness. Treatment is effective if administered within 24 h of the onset of symptoms. The recommended dosage for the treatment for adults is 75 mg orally twice daily and 75 mg once daily for prevention. Dose reduction is suggested if creatinine clearance (CrCl) is <60 mL/min [1, 2, 4, 16, 26, 27].

Obesity has been identified as a risk factor for experiencing more severe symptoms of influenza with worse outcomes. This was reported after the 2009 pandemic H1N1 influenza outbreak, where obesity was one of the most important risk factors for mortality [23, 28–33]. Given this, there have been suggestions that perhaps the recommended oseltamivir dose is inadequate in obese patients. Obese patients have been administered higher than normal doses previously (particularly if critically ill) [34]. It is also thought that the obese subjects may not have as good a response to the influenza vaccination as non-obese patients, meaning their protection from the vaccination will be reduced [28].

Oseltamivir phosphate is a prodrug that is readily absorbed from the gastrointestinal tract after oral administration and is then extensively and rapidly converted to oseltamivir carboxylate (active metabolite) by hepatic esterases [4, 16, 26]. After administration of oseltamivir, the absolute bioavailability of oseltamivir carboxylate (active form) is 80 % [4, 16, 32]. Several studies have found that obese patients experience reduced total exposure to the active metabolite. However, this is not considered clinically significant [30, 32]. In one randomised PK study with 12 obese and 12 non-obese subjects, PK data of both the pro-drug and the active metabolite were analysed and it was noted that obesity affected the PK of the prodrug. However, it was noted that this is unlikely to have any clinical relevance as there was no clinically significant impact on the PK of the active metabolite [30].

After oral administration of 75 mg twice daily for 5 days and when V was normalised to body weight, the median V of the pro-drug did not differ significantly between the obese and the non-obese. However, the median V of the active metabolite was significantly lower in obese subjects, compared with non-obese subjects (1.8 L/kg versus 3.2 L/kg) [2]. There is no significant difference in median half-life for the pro-drug between obese and non-obese subjects (1.9 and 2.4 h respectively). For the active form, however, the half-life is slightly less in obese subjects (6.9 h) compared with non-obese subjects (8.3 h) [2]. Renal clearance has been found to be higher in obese subjects. When normalised to TBW there was no significant difference between obese and non-obese subjects for total body clearance of the pro-drug, yet median total body clearance of the active form was significantly less in obese subjects (0.18 L/h/kg) compared with the non-obese (0.26 L/h/kg) [2]. One randomised trial found that the clearance of oseltamivir (prodrug) was significantly higher in obese subjects, compared with non-obese subjects, resulting in lower total exposure [30].

A study of single-dose and steady state PK of oseltamivir found that PK data for the active form was not influence by weight, and, therefore, PK in obese patients were comparable to non-obese patients (including systemic exposure to the active metabolite). Given this, it was concluded that the use of a different dose is unlikely to be necessary [31].

The OPTIMO (Oseltamivir PK in morbid obesity) trial was a non-randomised, open-label PK study of single-dose and steady-state oral oseltamivir (both prodrug and active form) in ten healthy morbidly obese (BMI > 40) and ten healthy non-obese subjects. This study found that the morbidly obese group generally experienced lower maximum concentrations and lower systemic exposure to oseltamivir (prodrug) both after the initial dose and at the steady state. The concentrations of oseltamivir carboxylate were modestly lower in obese subjects, compared with non-obese. However, this was not considered clinically relevant. Given that systemic exposure to the active metabolite did not differ significantly between the two groups, the authors of this study concluded that the current treatment dosing recommendations of 75 mg twice daily is sufficient for obese patients [32].

Based on the limited evidence available for dosing oseltamivir in obese patients, no dose adjustment is recommended for the routine prophylaxis and treatment of influenza in obese patients.

## Conclusion

Dosing recommendations for some of the miscellaneous antibiotics are noted in this chapter. We are unaware of any data for other antibiotics such as doxycycline, azithromycin, clarithromycin, erythromycin, co-trimoxazole and trimethoprim. Nevertheless, obesity has been identified as an independent risk factor for antimicrobial treatment failure for these agents in a Canadian study [35]. Therefore, there is an urgent need for PK and clinical studies of these antibiotics in obese patients. Meanwhile, the higher end of normal doses can be safely applied whenever these antibiotics are used in obese patients.

## References

1. Australian Medicines Handbook 2015 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2015. Available from: http://amhonline.amh.net.au/.
2. Micromedex® 2.0 (electronic version). Truven health analytics, Colorado, USA. Available from: http://www.micromedexsolutions.com.acs.hcn.com.au/. Registration and login required.
3. Lim LM, Ly N, Anderson D, Yang JC, Macander L, Jarkowski A 3rd, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. Pharmacotherapy. 2010;30(12):1279–91.
4. DynaMed Plus [Internet]. Ipswich (MA): EBSCO information services; 1995. Available from http://www.dynamed.com. Registration and login required.
5. Therapeutic Goods Administration. Colistin PI. [Internet]: Australian Government Department of Health; 2015 [updated 12 Aug 2015; cited 2015]. Available from: www.ebs.tga.gov.au.
6. Kalin G, Alp E, Coskun R, Demiraslan H, Gundogan K, Doganay M. Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: do we really need this treatment? J Infect Chemother. 2012.
7. Vicari G, Bauer SR, Neuner EA, Lam SW. Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia. Clin Infect Dis. 2013;56(3):398–404.
8. Yilmaz GR, Bastug AT, But A, Yildiz S, Yetkin MA, Kanyilmaz D, et al. Clinical and microbiological efficacy and toxicity of colistin in patients infected with multidrug-resistant gram-negative pathogens. J Infect Chemother. 2013;19(1):57–62.
9. Zaidi ST, Al Omran S, Al Aithan AS, Al Sultan M. Efficacy and safety of low-dose colistin in the treatment for infections caused by multidrug-resistant gram-negative bacteria. J Clin Pharm Ther. 2014;39(3):272–6.
10. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother. 2011;55(7):3284–94.

11. Michalopoulos AS, Falagas ME. Colistin: recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. Ann Intensive Care. 2011;1(30):1–6.
12. DeRyke A, Crawford AJ, Uddin N, Wallace MR. Colistin dosing and nephrotoxicity in a large community teaching hospital. Antimicrob Agents Chemother. 2010;54(10):4503–5.
13. Jm P, Lee J, Marchaim D, Yee V, Zhao JJ, Chopra T, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. Clin Infect Dis. 2011;53 (9):879–84.
14. Mohameda AF, Karaiskosc I, Plachourasc D, Karvanend M, Pontikise K, Janssona B, et al. Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother. 2012;56(8):4241–9.
15. Spizek J, Novotna J, Rezanka T. Lincosamides: chemical structure, biosynthesis, mechanism of action, resistance, and applications. Adv Appl Microbiol. 2004;56:121–54.
16. Katzung BG, Masters SB, Trevor AJ, editors. Basic & clinical pharmacology. 12th ed. USA: McGraw-Hill Companies; 2012.
17. Bouazza N, Pestre V, Jullien V, Curis E, Urien S, Salmon D, et al. Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. Br J Clin Pharmacol. 2012;74(6):971–7.
18. Mastrobattista JM, Klebanoff MA, Carey JC, Hauth JC, Macpherson CA, Ernest J, et al. The effect of body mass index on therapeutic response to bacterial vaginosis in pregnancy. Am J Perinatol. 2008;25(4):233–7.
19. Cerqueira RM, Correia MR, Vilar H, Manso MC. How effective is the quadruple concomitant helicobacter pylori eradication therapy for obese patients undergoing gastric bypass surgery? Obes Surg. 2015.
20. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clin Pharmacokinet. 1999;36(5):353–73.
21. Sweetman S, editor. Martindale: the complete drug reference. London: Pharmaceutical Press (Electronic version); 2015.
22. Hernandez JO, Norstrom J, Wysock G. Acyclovir-induced renal failure in an obese patient. Am J Health-Syst Pharm. 2009;66:1288–91.
23. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39(6):584–608.
24. Wurtz R, Itokazu G, Rodvold K. Antimicrobial dosing in obese patients. Clin Infect Dis. 1997;25:112–8.
25. Seedat A, Winnett G. Acyclovir-induced acute renal failure and the importance of an expanding waist line. Brit Med J. 2012.
26. Therapeutic Goods Administration. Oseltamivir PI. [Internet]: Australian Government Department of Health; 2015 [updated 14 October 2015; cited 2015]. Available from: www.ebs.tga.gov.au.
27. eTG Complete [Internet]. Therapeutic Guidelines Limited. 2014.
28. Beck MA. Influenza and obesity: will vaccines and antivirals protect? J Infect Dis. 2012;205:172–3.
29. Huttunen R, Karppelin M, Syrjänen J. Obesity and nosocomial infections. J Hosp Infect. 2013;85:8–16.
30. Jittamala P, Pukrittayakamee S, Tarning J, Lindegardh N, Hanpithakpong W, Taylor WRJ, et al. Pharmacokinetics of orally administered oseltamivir in healthy obese and nonobese Thai subjects. Antimicrob Agents Chemother. 2014;58(3):1615–21.
31. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy. 2007;27(8):1081–91.
32. Thorne-Humphrey LM, Goralski KB, Slayter KL, Hatchette TF, Johnston BL, McNeil SA. Oseltamivir pharmacokinetics in morbid obesity (OPTIMO trial). J Antimicrob Chemother. 2011;66:2083–91.

33. Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L, Feng L, et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. Clin Infect Dis. 2011;52(4): 457–65.
34. Rodríguez A, Díaz E, Martín-Loeches I, Sandiumenge A, Canadell L, Díaz JJ, et al. Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. J Antimicrob Chemother. 2011;1–10.
35. Longo C, Bartlett G, Macgibbon B, Mayo N, Rosenberg E, Nadeau L, et al. The effect of obesity on antibiotic treatment failure: a historical cohort study. Pharmacoepidemiol Drug Saf. 2013;22(9):970–6.

# Appendix 1
# Clinical Cases

This appendix will include four clinical cases to demonstrate practice-based approach to antimicrobial dosing in obesity.

## Case 1
## Penicillin by Ian Abbott

A 40-year-old man, with history of obstructive sleep apnea, is admitted to hospital following a high-speed motor vehicle accident. He sustained abdominal trauma and multiple ribs fractures with a flail segment. His BMI was estimated at 45 kg/m$^2$. He has no history of diabetes mellitus, has a 20-pack year smoking history and has no drug allergies. His estimated creatinine clearance by Cockcroft-Gault equation was 120 ml/min. He required observation in a high-dependency unit and a thoracic epidural catheter was placed for the administration of epidural analgesic agents to improve tolerance for deep breathing and coughing. However, on day 7 of his admission, he was noted to be febrile, tachycardic, with mild hypotension responding to fluid boluses. Chest X-ray revealed new consolidation at the right lower lobe. Increased volume of purulent sputum was noted and referred to the laboratory for culture. The following day, the culture grew a predominant growth of *Pseudomonas aeruginosa*.

*What would be your empiric antibiotic therapy, if a penicillin class of antibiotic were deemed appropriate, for the suspected hospital acquired pneumonia (HAP) in this man? What dosing schedule would you choose?*

The choice of empiric antibiotic therapy for suspected hospital acquired pneumonia (HAP) should be in-line with local and international published guidelines. Individualised variations would depend on local epidemiology of the hospital microbiology, any pulmonary co-morbidities, and any previous positive cultures in the individual patient. Risk factors for multidrug resistant pathogens, especially in Gram-negative bacilli that are an important cause of HAP, will also influence antibiotic choice. Where a penicillin class of antibiotic is chosen, most commonly oral amoxicillin-clavulanate or intravenous piperacillin-tazobactam would be used.



S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7

This patient has several reasons for an altered PK that would adversely affect penicillin dosing, most importantly the increase in Vd. Together with the early signs of sepsis one would expect further changes in cardiac output, fluid balance, as well as augmented renal clearance risking under-dosing of antibiotics, especially in the initial 24–48 h.

Therefore, empiric antibiotic dosing should follow a front-loading strategy, where antibiotics are given at higher doses initially. For example, if piperacillin-tazobactam was chosen, then dosing should be no less than 4.5 g every 6 h. Oral amoxicillin-clavulanate (875/125 mg) could be dosed 8-hourly, although risking intolerances due to diarrhoea compared to the standard 12-hourly dosing.

*Following the subsequent isolation of P. aeruginosa from the sputum culture, how does this pathogen impact on your choice of agent and dosing schedule? What further information regarding the pathogen would be important to ensure adequate antibiotic target attainment?*

*P. aeruginosa* are intrinsically resistant Gram-negative bacilli that require a penicillin agent with antipseudomonal activity, such as piperacillin-tazobactam. Even among *P. aeruginosa* isolates that test susceptible to an antipseudomonas penicillin, there can be variation in the degree of susceptibility, indicated by the MIC of the organism to the specific antibiotic. Concerns also exist around the rapid emergence of resistance whilst on therapy, especially if the initial antibiotic therapy is inadequate, promoting the growth of a resistant sub-population. In of itself, the isolation of *P. aeruginosa* should prompt aggressive antibiotic dosing, and often consideration for the use of a second non-beta-lactam agent while awaiting formal susceptibility testing results, depending on clinical status.

The combination of obesity, infection and reduced antibiotic susceptibility puts this patient at high risk of treatment failure. In order to obtain optimal individualized antipseudomonal penicillin dosing, assuming the isolate tests susceptible to the penicillin agent, it would be important to draw together the MIC value together with the suspected PK changes in this patient, while also considering drug penetration and early identification of inadequate source control, for example the development of a drainable collection.

Given the relative safety profile of the penicillin antibiotics therapy should ideally be administered at a maximal 24-h dose using an extended or continuous infusion in order to ensure antibiotic target attainment is achieved. For example, piperacillin-tazobactam, following the administration of a bolus dose, could be dosed as an 18 g continuous infusion. Subsequent therapeutic drug monitoring would confirm if target attainment is achieved and provide a means to direct dosing alterations when the MIC information becomes available and to meet the dynamic PK changes seen during the clinical course of infection. Even higher, off-label dosing of penicillin antibiotics could be considered, if close monitoring for adverse reactions is available. Treatment success needs to not only promote clinical cure of the current infection, but also prevent the emergence of resistance.

## Case 2
## Carbapenems by Tara Anderson

A 45 year old man who had recently completed a course of chemotherapy for a haematological malignancy, presented with fever and no obvious source of infection. He was 145 kg in weight. An infusaport was recently inserted although there was no clinical evidence of infection. He was haemodynamically stable. He had a number of investigations performed including blood cultures. His initial blood tests confirm the presence of neutropenia. He was commenced on antimicrobial therapy consistent with the hospital's febrile neutropenia guideline.

At 72 h, it was identified that he had a multi-resistant *P. aeruginosa* (MIC 2 μg/mL) isolated from the initial blood cultures. It was presumed that the patient was likely to have an infusaport-related bacteraemia. He was haemodynamically stable but had ongoing fevers. The clinicians were reluctant to remove the infusaport at this stage. Meropenem was felt to be the most appropriate antibiotic agent to use for this patient.

*What dosage regimen of meropenem would you commence in this patient?*

- 1 g 8 hourly (30 min infusion)

After 24 h of meropenem therapy, the patient was continuing to have fevers and was clinically deteriorating with the development of hypotension and hypoxia on the haematology ward. Urgent removal of the infusaport was being arranged as well as transfer to the intensive care unit.

*What additional considerations may you have in relation to the meropenem dosage regimen in the setting of clinical deterioration?*

- Repeating the blood cultures and if *P. aeruginosa* re-isolated, repeating the MIC measurement to guide appropriate dosage regimen.
- Acknowledge that distribution and clearance are variable and often unpredictable in a critically ill patient. Consideration would be given to undertaking therapeutic drug monitoring to assist appropriate dosage regimen.
- Consideration to be given to either increasing the dose e.g. 2 g 8 hourly (30 min infusion) and/or extending the infusion from 30 min to 3 h.

## Case 3
## Echinocandins by Tara Anderson

A 54 year old woman presented with intra-abdominal sepsis in the setting of a perforated sigmoid diverticulum. She was admitted to the adult intensive care unit. She had a documented *Candida krusei* blood stream infection. She was 100 kg in weight. Her renal and hepatic function was normal.

*What dosage regimen would you commence in this patient?*

a. **Micafungin**

*The usual recommendation for micafungin dosing would be 100 mg daily for this indication. The proposed rules 1 and 4 mentioned above (refer to the corresponding chapter in text) would suggest however that a dose of 150 mg may be more appropriate for this patient:*

*Rule 1*

*Dose (mg) = 1.03 * patient weight + 41.93 = 1.03 x 100 + 41.93 = 144.93 mg, rounded up to 150 mg daily*

*Rule 4*

*Dose (mg) = patient weight + 42 = 100 + 42 = 142 mg, rounded up to 150 mg daily*
*A dose of 150 mg micafungin daily for this patient may be appropriate initially.*

b. **Caspofungin**

The standard recommendation for caspofungin in a patient >80 kg would be 70 mg loading dose followed by 70 mg daily. There are no available formulae for further dose modification in this setting nor routinely available TDM to guide monitoring. Consideration needs to be given, however, to the possibility that standard dosing may be insufficient in the setting of obesity and that dosage adjustments may need to be considered, particularly if there is a suboptimal clinical response.

c. **Anidulafungin**

The standard recommendation for anidulafungin would be 200 mg loading dose followed by 100 mg daily. There are no available formulae for further dose modification in this setting nor routinely available TDM to guide monitoring. Consideration needs to be given, however, to the possibility that standard dosing may be insufficient in the setting of obesity and that dosage adjustments may need to be considered, particularly if there is a suboptimal clinical response.

## Case 4
## Azole Antifungals by Nic Holt

A 55-year-old female undergoing consolidation phase chemotherapy with cytarabine for management of acute myeloid leukaemia (AML) was admitted to an acute medical ward with febrile neutropenia. She had a BMI of 48.1 kg/m$^2$ (height 171.2 cm, weight 141 kg). She had tolerated her chemotherapy relatively poorly, with ongoing issues of nausea and vomiting.

Her past medical history is significant for hypertension, dyslipidaemia, gastro-oesophageal reflux and type II diabetes mellitus for which she is on insulin therapy. Of note, she has been on long term acid suppression with a proton pump inhibitor.

She is commenced on oral posaconazole suspension 200 mg 8-hourly for primary antifungal prophylaxis in the context of her immunocompromised status, in addition to the following primary prophylaxis therapy of valaciclovir for herpes simplex virus (HSV) and trimethoprim-sulfamethoxazole for *P. jirovecii*.

The patient had completed cycle one of cytarabine chemotherapy three days prior to her presentation. At this time, clinical examination could not reveal a septic focus.

Investigations revealed the patient to be pancytopenic (haemoglobin 73 g/L, white cell count 1.2 × 109/L, neutrophils 0.2, and platelets 15 × 109/L). Renal and hepatic parameters were within normal limits.

A full septic screen was unrevealing. She was commenced empirically therapy with IV piperacillin-tazobactam 4.5 g four times daily, in addition to the continuation of her prophylactic antimicrobial agents mentioned previously.

She was persistently febrile after 5 days of therapy with IV piperacillin-tazobactam. Trough plasma posaconazole levels were sample and revealed subtherapeutic levels at 0.1 mg/L, significantly lower than the target of >0.7 mg/L recommended for effective prophylaxis therapy. On further questioning, the patient reports non-compliance with her prescribed prophylactic posaconazole therapy which, in addition to her regular proton pump inhibitor and chemotherapy-induced vomiting and nutritional compromise, contributed to the low serum posaconazole concentrations.

The onset of respiratory distress prompted further investigations. CXR showed segmental areas of opacification in the right upper lobe. Computer tomography (CT) of the chest demonstrated a nodule with surrounding ground-glass infiltrate (the halo sign). *Aspergillus* galactomannan antigen testing and 1,3-Beta-D-glucan assay were both positive, confirming the suspicion of invasive pulmonary aspergillosis. *Aspergillus fumigates* was subsequently isolated on bronchoalveolar lavage (BAL).

*What dosage regimen of voriconazole would you commence in this patient?*

- Voriconazole dosing based on adjusted body weight (AdjBW):
  - Loading dose: Intravenous Voriconazole 6 mg/kg 12-hourly for 24 h.
  - Maintenance dose: Oral Voriconazole 4 mg/kg 12-hourly.
- TDM: recommended to establish clinical efficacy and to avoid toxicity.

High-dose antifungal therapy with voriconazole was initiated, with an intravenous loading dose of 6 mg/kg 12-hourly for 24 h, followed by an oral switch with 4 mg/kg 12-hourly. Dosage was based on total body weight (TBW).

Biochemical parameters were monitored, and on day three of voriconazole therapy, hepatic derangement was detected with elevation in transaminase levels.

Therapeutic drug monitoring was subsequently performed, and a serum voriconazole trough level revealed supratherapeutic levels at 8.6 mg/L (recommended therapeutic voriconazole range: >1.0 mg/L, but <5.5 mg/L). Dose administration was altered to reflect dosage based on an adjusted body weight, however hepatic parameters failed to normalise.

*What additional considerations may you have in relation to the voriconazole dosage regimen?*

- Cytochrome P450 2C19 genotype testing in select patients

Cytochrome P450 2C19 genotype testing was requested, and the patient was found to be a CYP2C19 homozygous poor metaboliser. Subsequently, a further reduction in voriconazole dose was made to reflect the propensity for increased voriconazole exposure and toxicity due to a prolonged half life and decreased clearance associated with a poor metaboliser phenotype.

The patient subsequently had a good clinical response to therapy, and received a total course of voriconazole therapy for 42 days.

# Index





S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7