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Review

Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: A structured review

Abdulaziz S. Alobaid[a], Maya Hites[b], Jeffrey Lipman[a,c], Fabio Silvio Taccone[d], Jason A. Roberts[a,c,e,*]

[a] Burns, Trauma & Critical Care Research Centre, The University of Queensland, Brisbane, QLD, Australia
[b] Department of Infectious Diseases, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
[c] Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia
[d] Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
[e] School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

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ABSTRACT

The increased prevalence of obesity presents challenges for clinicians aiming to provide optimised antimicrobial dosing in the intensive care unit. Obesity is likely to exacerbate the alterations to antimicrobial pharmacokinetics when the chronic diseases associated with obesity exist with the acute pathophysiological changes associated with critical illness. The purpose of this paper is to review the potential pharmacokinetic (PK) changes of antimicrobials in obese critically ill patients and the implications for appropriate dosing. We found that hydrophilic antimicrobials (e.g. β-lactams, vancomycin, daptomycin) were more likely to manifest altered pharmacokinetics in critically ill patients who are obese. In particular for β-lactam antibiotics, obesity is associated with a larger volume of distribution (V_d). In obese critically ill patients, piperacillin is also associated with a lower drug clearance (CL). For doripenem, these PK changes have been associated with reduced achievement of pharmacodynamic (PD) targets when standard drug doses are used. For vancomycin, increases in V_d are associated with increasing total body weight (TBW), meaning that the loading dose should be based on TBW even in obese patients. For daptomycin, an increased V_d is not considered to be clinically relevant. For antifungals, little data exist in obese critically ill patients; during fluconazole therapy, an obese patient had a lower V_d and higher CL than non-obese comparators. Overall, most studies suggested that standard dosage regimens of most commonly used antimicrobials are sufficient to achieve PD targets. However, it is likely that larger doses would be required for pathogens with higher minimum inhibitory concentrations.

1. Introduction

Obesity is a growing public health concern and is associated with increased morbidity and mortality compared with non-obese individuals [1–3]. Obesity is a well known risk factor for community- and hospital-acquired infections as well as hospital and intensive care unit (ICU) admission [4–6]. Critically ill obese patients in particular are at a higher risk of infection and commonly require antimicrobial therapy [7,8]. However, delivering optimal antimicrobial therapy in this population is considered to be a great challenge. To date, there are few studies summarising the published data and providing clinical guidance for effective dosing in these patients.

Understanding antimicrobial pharmacokinetic (PK) behaviour is crucial to optimise antimicrobial therapy for critically ill obese patients. However, antimicrobial pharmacokinetics is often altered by the pathophysiology associated with critical illness [9,10] and may be further changed in the presence of obesity. Both antimicrobial volume of distribution (V_d) and clearance (CL) can be highly variable in critically ill and obese patients [11,12]. Standard dosage regimens of antimicrobials, particularly those that are mainly eliminated through the kidneys, may result in fluctuations of plasma concentrations in critically ill patients that may require dosing regimen adjustments to ensure optimal antimicrobial concentrations are achieved [13]. Optimised antimicrobial dosing in the ICU requires an understanding of antimicrobial pharmacokinetics/pharmacodynamics and possible PK changes caused by critical illness.

* Corresponding author. Present address: Burns, Trauma & Critical Care Research Centre, The University of Queensland, Level 3 Ned Hanlon Building, Royal Brisbane and Women's Hospital, Herston, QLD, Australia. Tel.: +61 736464108.
E-mail address: j.roberts2@uq.edu.au (J.A. Roberts).

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1.1. Pharmacokinetic/pharmacodynamic (PK/PD) overview of antimicrobials

Antimicrobials can be categorised into three PK/PD classes according to the relationship between drug exposure, pathogen susceptibility and clinical response to antimicrobial therapy [14,15]:

- time-dependent antimicrobials: the time that the free (unbound) concentration of the antimicrobial remains above the minimum inhibitory concentration ($fT_{>MIC}$) drives bacterial killing;
- concentration-dependent antimicrobials: the ratio of the peak antimicrobial concentration to MIC (C_{max}/MIC) drives bacterial killing; and
- concentration-dependent antimicrobials with time dependency: the ratio of the area under the concentration–time curve of the antimicrobial from 0–24 h to the MIC ($AUC_{0–24}$/MIC) drives bacterial killing.

1.2. Possible antimicrobial pharmacokinetic alterations in critically ill patients

Significant physiological changes occur in critically ill patients, resulting in elevated cardiac output, fluid shifts and/or changes in hepatic or renal function [16]. These changes will result in changes in V_d, protein binding and drug CL, thus resulting in altered antimicrobial pharmacokinetics.

1.2.1. Drug distribution

Significant cardiovascular changes can commonly cause V_d alterations in critically ill patients, in particular in patients with sepsis where endothelial dysfunction and capillary leak can occur [9]. These processes can increase fluid shifts from the vascular system into the interstitial space, possible resulting in lower than usual concentrations of hydrophilic antimicrobials (e.g. β-lactams and aminoglycosides). Fluid resuscitation can further aggravate this phenomenon.

1.2.2. Protein binding

A decrease in plasma albumin concentration (hypoalbuminaemia) occurs in ca. 40% of critically ill patients [17] and is associated with altered protein binding. As a result, a higher unbound concentration of antimicrobials may initially be seen, leading to increased drug distribution from the intravascular to the extravascular compartment, thereby increasing V_d. Furthermore, the higher unbound concentration is available for elimination from the body and as such drug CL is often increased as well [18].

1.2.3. Drug clearance

Significant variability in antimicrobial CL is common among critically ill patients [19]. Hydrophilic antimicrobials are mainly eliminated through the kidneys, thus CL can be decreased in the presence of acute kidney injury [16]. Moreover, lipophilic antimicrobials, which are mainly metabolised by the liver, may have lower CL in hepatic dysfunction such as acute liver failure (Table 1) [16].

Increased drug CL has been described in critically ill patients and has been termed augmented renal clearance (ARC), a condition where renal elimination of circulating solutes is increased [20,21]. ARC is defined as a creatinine clearance (CL_{Cr}) of ≥130 mL/min/1.73 m^2. ARC is associated with subtherapeutic antimicrobial concentrations and worse clinical outcomes in critically ill patients receiving standard doses of antimicrobial therapy [22].

Given this background of acute PK changes caused by critical illness, the challenge for the clinician is how to balance the obesity-related PK effects on antimicrobials on drug dosing regimens in obese critically ill patients.

Table 1
Physiochemical properties, pharmacokinetic/pharmacodynamic (PK/PD) indices and pharmacokinetic (PK) characteristics of antimicrobial agents in obese and non-obese patients.

Physiochemical properties	Example antimicrobial classes [a]	PK/PD index	PK differences between non-obese and obese			Suggested weight-based dosing metric
			PK parameter	Non-obese	Obese	
Lipophilic	Fluoroquinolones	$AUC_{0–24}$/MIC or C_{max}/MIC				LBW
	Glycylcyclines	$AUC_{0–24}$/MIC	V_d [b]	Large	Increased in obesity	
	Oxazolidinones	C_{max}/MIC	CL	Primarily hepatic CL	Increased or decreased CL dependent on hepatic function	
	Macrolides	$AUC_{0–24}$/MIC				
Hydrophilic	β-Lactams	$fT_{>MIC}$				LBW or ABW
	Aminoglycosides	C_{max}/MIC				
	Glycopeptides	$AUC_{0–24}$/MIC				
	Polymyxins	$AUC_{0–24}$/MIC	V_d [b]	Small	Increased in obesity	
			CL	Primarily renal CL, variable according to renal function	Increased or decreased CL dependent on renal function	
	Lipopeptides	C_{max}/MIC or $AUC_{0–24}$/MIC				
	Fluconazole	C_{max}/MIC or $AUC_{0–24}$/MIC				

$AUC_{0–24}$, area under the concentration–time curve over 24 h; MIC, minimum inhibition concentration; C_{max}, peak drug concentration; V_d, volume of distribution; CL, drug clearance; LBW, lean body weight; $fT_{>MIC}$, time that the free concentration or unbound fraction of the antibiotic remains above the MIC; ABW, adjusted body weight.
[a] For some classes, agents with different characteristics may exist (e.g. levofloxacin is more hydrophilic than other fluoroquinolones; ceftriaxone and cefazolin have comparatively much higher protein binding than other β-lactams including meropenem and cefepime).
[b] For conceptual reasons, a small V_d is crudely classified to be <0.7 L/kg and a large V_d as ≥0.7 L/kg.

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