Antimicrobial Dosing in Obesity

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Outline

Introduction

Managing antimicrobial dosing in obesity can be quite a challenge for clinicians across the spectrum of care. Not only does underdosing patients risk therapeutic failure, but it also has the potential to induce antimicrobial resistance, exposing the microorganism to subtherapeutic concentrations of the drug. In high doses, however, some antimicrobials may be fairly toxic and adverse events may occur if total body weight (TBW) is used for all drugs. As we begin to discuss the dosing of antimicrobials in obesity, let us briefly review the optimization of pharmacokinetic/pharmacodynamic (PK/PD) targets and the impact that alterations in obesity may have on reaching these PK/PD targets.

Activity for antimicrobials can generally be divided into two broad classifications: time-dependent or concentration-dependent. Within those classifications, PK/PD targets that best correlate with efficacy are unique for each antimicrobial class. For example, beta-lactams are optimized when the concentration of the free drug remains above the minimum inhibitory concentration (MIC). In contrast, aminoglycosides are concentration-dependent with dose optimization that targets the maximum concentration (C_{max}) over the MIC (or C_{max}/MIC) and total area under the curve (AUC), AUC/MIC. **Table 2-1** lists PK/PD targets for commonly used antimicrobials.[1-3]

Table 2-1. Activity In Vitro and PK/PD Measures Best Correlated with Efficacy for Commonly Used Antimicrobials

TIME-DEPENDENT	CONCENTRATION-DEPENDENT
Penicillins (T>MIC)	Aminoglycosides (C_{max}/MIC;AUC/MIC)
Cephalosporins (T>MIC)	Fluoroquinolones (C_{max}/MIC;AUC/MIC)
Carbapenems (T>MIC)	Metronidazole (C_{max}/MIC;AUC/MIC)
Monobactams (T>MIC)	Daptomycin (C_{max}/MIC;AUC/MIC)
Linezolid (AUC/MIC)	Amphotericin B (C_{max}/MIC)
Tetracyclines (AUC/MIC)	Echinocandins (AUC/MIC)
Vancomycin (AUC/MIC)	
Azithromycin (AUC/MIC)	
Triazoles (AUC/MIC)	
Clindamycin (AUC/MIC)	

AUC/MIC = area under the curve to minimum inhibitory concentration ratio; C_{max}/MIC = maximum concentration to minimum inhibitory concentration ratio; T >MIC = time above the minimum inhibitory concentration.

As discussed in Chapter 1, obesity can alter a number of PK parameters. Applying these changes to the principles of achieving PK/PD targets, one can easily see the importance of these PK changes in obesity. For example, do the changes in the volume of distribution (V_d) that occur in obesity influence the C_{max} of the drug in question? Does the possibility of increased clearance in obesity reduce the time above the MIC (T >MIC) for a time-dependent antibiotic? The task of the clinician dosing antimicrobials in obesity is to identify dosing strategies that optimize these targets, yet keep drug levels within a safe range without predisposing to adverse effects.

This chapter reviews antimicrobial dosing in three major sections, covering antibiotics, antifungals, and antivirals all broken down into classes. In some cases, fairly consistent opinion exists of the alterations necessary to an antimicrobial regimen in obesity. Unfortunately, many antimicrobial agents may lack human or animal data regarding dosing in obesity. In these cases, we have provided as evidence-based rationale as possible for our recommendations where applicable in these scenarios. The ultimate decision of dosing in obesity must include a careful assessment by the clinician of the institution's antibiogram, MIC of the infecting organism, clinical condition of patient, and ultimately, a risk-benefit assessment with a careful monitoring plan in place for therapeutic efficacy and safety. (See Summary Table: Antimicrobial Drugs.)

Antibiotics

Beta-lactams

The beta-lactams consist of several classes of structurally related agents including the penicillins, cephalosporins, carbapenems, and monobactams. All of these agents are weak organic acids and, with a few exceptions, are relatively hydrophilic in vivo. As such, the V_d tends to correlate to TBW or lean body mass in most individuals (likely until reaching the extremes of obesity). Beta-lactams such as nafcillin and ceftriaxone exhibit moderately high protein binding due to their relative lipophilicity. The V_d of these agents has not been well described in obese individuals; however, it would be expected to be higher than in normal-weight individuals and partially dependent on the available fraction of unbound drug.