Review Article

Anti-infective Dosing for Obese Adult Patients: A Focus on Newer Drugs to Treat Methicillin-resistant *Staphylococcus aureus* Acute Bacterial Skin and Skin Structure Infections

Manjunath P. Pai

Pharmacokinetics Core, Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan

ABSTRACT

Purpose: Obesity is recognized to be a risk factor for acute bacterial skin and skin structure infections (ABSSSIs) that are associated with methicillin-resistant *Staphylococcus aureus* (MRSA). Several new antimicrobial agents have been introduced to treat MRSA-related ABSSSI and are dosed with and without regard to weight. This review seeks to explain the pharmacokinetic and pharmacodynamic (PK-PD) rationale for initial and maintenance dosage selection of these newer agents in obese adults.

Methods: A PubMed search was performed using the key words obese or obesity, pharmacokinetics, and the name of each MRSA active drug evaluated in this review. Major themes were identified through a review of this literature. A synopsis of key findings from population PK studies (including reference sources) and independent studies of the PK properties of each new MRSA active agent used to treat ABSSIs were reviewed to derive practical dosing considerations.

Findings: Clinical trials of ABSSSIs have increasingly incorporated individuals across a wide body size spectrum. This inclusion of obese adults has been reflected in population PK analyses that have permitted the evaluation of weight and other body size descriptors. In general, the volume of distribution is higher in obese patients, suggesting the need for higher initial (loading) doses if PK bioequivalence is desired. Less certainty exists with selection of a higher maintenance dose, especially for antimicrobial agents with time-dependent PK-PD properties. Selection of higher maintenance doses through alternate scaling approaches in obese patients can be justified on an individual clinical basis.

Implications: Maintenance dose modification of several MRSA-targeted anti-infective agents is unlikely to be necessary in obese patients and should be capped if dosed on total weight or this higher dose justified with therapeutic drug monitoring. (*Clin Ther.* 2016;38:2032–2044)

Key words: dosing, drug, MRSA, obesity, pharmacodynamics, pharmacokinetics.

INTRODUCTION

Obesity is no longer a "First World" problem with more than half a billion obese adults globally who now outnumber those who are underweight.[1,2] The American Council on Exercise classifies women and men as obese when their proportion of body fat exceeds 32% and 25%, respectively.[3] Easier access to energy-dense and sugar-laden foods coupled with more sedentary lifestyles continues to shift our body compositions toward increased adiposity. In the United States, the average adult today is approximately 25 pounds heavier than his or her grandparents were on average 60 years ago.[4,5] Although

Accepted for publication July 22, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.07.094
0149-2918/$ - see front matter

our definition of obesity has changed over this time period, these trends for increased adiposity are unmistakable.[6]

Historical definitions of obesity in the United States began with the use of weight-for-height tables generated by the Metropolitan Life Insurance Company in the 1940s and 1950s. These tables were used to define "ideal weight" and "desirable weight" for men and women based on height and frame size.[6] Reliance on both height and weight has been central to the quantitative definition of obesity because use of weight alone is less informative of body composition. However, misclassification errors occur with these simple metrics because more athletic individuals have a higher muscle-to-fat ratio. The common definition of obesity today stems from the Quetelet index or body mass index (BMI) that is the weight in kilograms divided by height in square meters with a value ≥ 30 kg/m^2.[6] This definition was adapted by the World Health Organization in 1997 and subsequently adapted by the National Heart, Lung, and Blood Institute expert panel in 1998. This time line is important because our definitions of obesity changed during the era of antimicrobial discovery, knowledge of pharmacokinetic-pharmacodynamic (PK-PD) properties, emergence of pharmacometrics as a discipline, and the regulatory framework to justify antimicrobial dosage selection in clinical trials.[7,8] A plethora of antimicrobial agents targeting methicillin-resistant *Staphylococcus aureus* (MRSA) have been introduced into the marketplace over the past two decades.[9] This pathogen is a common cause of acute bacterial skin and skin structure infections (ABSSSIs), and obesity is a recognized risk factor for this infection.[10–13] Anti-infective agents used to treat ABSSSIs associated with this pathogen span multiple pharmacologic classes, have distinct PK-PD properties, and are dosed by weight and non–weight-based paradigms. As a consequence, this review seeks to inform the reader on empiric and alternate approaches to antimicrobial dosage selection in obese adults using vancomycin and newer agents to treat MRSA-associated ABSSSIs as exemplars.

PK-PD CONSIDERATIONS

The activity of antimicrobial agents can be optimized by selecting dosage regimens that create concentration–time profiles that maximize the rate of bacterial inhibition or killing. Over the past 60 years, we have broadly categorized this PK-PD optimization to be concentration dependent or time dependent.[14] Concentration-dependent antimicrobial agents are optimized by ensuring that the C_{max} and the closely correlated parameter of AUC achieve a certain target value. A classic example of concentration-dependent optimization includes the use of high-dose extended interval aminoglycoside dosing for Gram-negative–related infections. In contrast, time-dependent antimicrobial agents are optimized by ensuring that the concentration profile remains above a concentration threshold for a specified proportion of the dosing interval.[14,15] The β-lactams are a key antimicrobial class in which continuous infusion and extended interval infusion regimens are used to maximize the time above a threshold concentration. The MIC serves as the most common antimicrobial potency threshold value. The activity of concentration-dependent antimicrobial agents is predicted by the C_{max}-to-MIC (C_{max}:MIC) and AUC-to-MIC (AUC:MIC) ratios. Although the activity of time-dependent antimicrobial agents are better predicted by time above the MIC ($T_{>MIC}$) but also correlate with the AUC:MIC ratio because AUC is a mathematical function of both concentration and time.

Figure 1 illustrates the simulated concentration–time profile of an antimicrobial agent administered by variable rates of infusion. This figure serves to illustrate several points about concentration–time profiles relative to an MIC value of 32 mg/L, for example. The first point that can be made is that slower rates of infusion may not achieve the concentration target unless an initial loading dose is administered. This is akin to the effects of obesity on the V_d.[16] Larger adults typically have a larger V_d that is noted by a lower systemic (plasma) C_{max} concentration and may need a loading dose to achieve this. However, maintenance of this larger dose in obese patients may be unnecessary by the third dose for a time-dependent antimicrobial agent because all the illustrated regimens achieve similar $T_{>MIC}$ values. This point of an initial higher but standard maintenance regimen in obese patients is most applicable to agents such as linezolid.[16]

Although not easy to visualize, the second point in this illustration is that all regimens achieve the same AUC over this period of time because the dose is identical in this simulation. The AUC is affected by the dose and clearance (CL) of the agent from systemic circulation.