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Review

Innovative approaches to optimizing the delivery of vancomycin in individual patients☆

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ABSTRACT

The delivery of personalized antimicrobial therapy is a critical component in the treatment of patients with invasive infections. Vancomycin, the drug of choice for infections due to methicillin-resistant *Staphylococcus aureus*, requires the use of therapeutic drug monitoring (TDM) for delivery of optimal therapy. Current guidance on vancomycin TDM includes the measurement of a trough concentration as a surrogate for achieving an AUC to minimum inhibitory concentration (MIC) by broth microdilution (AUC/MIC_{BMD}) ratio ≥400. Although trough-only monitoring has been widely integrated into clinical practice, there is a high degree of inter-individual variability between a measured trough concentration and the actual AUC value. The therapeutic discordance between AUC and trough may lead to suboptimal outcomes among patients with infections due to less susceptible pathogens or unnecessarily increase the probability of acute kidney injury (AKI) in others. Given the potentially narrow vancomycin AUC range for optimal effect and minimal AKI, clinicians need a "real-time" system to predict accurately the AUC with limited pharmacokinetic (PK) sampling. This article reviews two innovative approaches for calculating the vancomycin AUC in clinical practice based on one or two drug concentrations. One such approach involves the use of Bayesian computer software programs to estimate the "true" vancomycin AUC value with minimal PK sampling and provide AUC-guided dosing recommendations at the bedside. An alternative involves use of two concentrations (peak and trough) and simple analytic equations to estimate AUC values. Both approaches provide considerable improvements over the current trough-only concentration monitoring method.

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1. Introduction

Vancomycin is the cornerstone of therapy for patients with invasive infections due to methicillin-resistant *Staphylococcus aureus* (MRSA), the most prevalent multi-drug resistant pathogen in the world [1]. The rising

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rates of MRSA have coincided with a significant increase in the use of vancomycin. In the United States alone, over 20 million days of vancomycin are used annually [2]. Despite its introduction over a half century ago, the optimal dosing strategy for vancomycin remains undefined. Contemporary vancomycin dosing schemes are designed to achieve an area under the curve (AUC) to minimum inhibitory concentration (MIC) (AUC/MIC) ratio ≥400 for serious infections due to MRSA [3,4]. Although an AUC/MIC ratio ≥400 is the prevailing vancomycin exposure target that is based on an MIC determined by broth microdilution (AUC/MIC_{BMD}), AUCs are not determined routinely in clinical practice due to the perceived difficulty in calculating the AUC [3,4]. Historically, a clinician had to collect multiple pharmacokinetic (PK) samples and apply the linear-trapezoidal rule to determine the AUC in a given patient [5]. The perceived difficulties associated with determining vancomycin AUC values in "real-time" have led to the expert guideline committee recommendations to maintain vancomycin trough concentrations between 15 and 20 mg/L as a surrogate marker of an AUC/MIC_{BMD} ratio ≥400 for serious infections due to MRSA [3,4]. This recommendation has been widely integrated into clinical practice. However, the clinical benefits of maintaining higher vancomycin trough values have not been well described [6–11]. In addition, evidence is mounting that intensive vancomycin use to achieve troughs in excess of 15 mg/L with typical intermittent dosing regimens may be associated with increased acute kidney injury (AKI) rates [12].

While trough monitoring is relatively straightforward in most practice settings, there is a high degree of inter-individual variability between a measured trough concentration and the actual AUC value [13,14]. The mathematical discordance between the AUC and trough values is not surprising and is well-described in the literature [13]. In simple terms, the AUC is reflective of the cumulative exposure for a defined time period (e.g., 0–24 h). In contrast, the trough is a single point exposure measurement at the end of the dosing interval. It is unreasonable to expect a single measurement at the end of the dosing interval to be representative of the entire concentration-time profile without incorporating some covariate and parameter assumptions [13,14]. This discrepancy between AUC and trough has clear implications for clinical practice. Trough values of 15–20 mg/L do not guarantee optimal AUC/MIC_{BMD} exposures in patients with infections due to MRSA with vancomycin MIC values in excess of 1 mg/L. Conversely, a trough of 15–20 mg/L may lead to AUC values that have been associated with an increased risk of AKI.

The therapeutic discordance between vancomycin trough concentrations and AUCs has renewed our interest in calculating AUCs in practice. Despite the clear advantages associated with AUC vs. trough-only monitoring for gauging the probability of efficacy while minimizing likelihood of AKI, there has been considerable reluctance by clinicians to move away from trough-only monitoring. Although calculating the AUC by the linear-trapezoidal formula is relatively straightforward [5], it is often too cumbersome to collect multiple levels over one dosing interval in the clinical arena. To address this issue, our group recently identified two simplified approaches for estimating AUC values with low bias and high precision using only one or two antimicrobial concentrations [14,15]. This article will review the contemporary understanding of the pharmacokinetic/pharmacodynamic (PK/PD) profile of vancomycin and describe two innovative methods for computing the AUC in clinical practice based on one or two samples. We will also discuss the additional information required to improve the delivery of vancomycin in future patients.

2. Pharmacodynamic profile of the "15–20 mg/L" target serum vancomycin concentration

Our current understanding of the vancomycin PK/PD profile is best summarized in the 2009 consensus review by the Infectious Diseases Society of America, the Society of Infectious Diseases Pharmacists and the American Society of Health-Systems Pharmacists [4]. Their statement represents the first set of national, evidence-based recommendations for vancomycin dosing and monitoring. While a variety of PK/PD targets have been suggested for vancomycin, they concluded that the AUC/MIC_{BMD} ratio is the optimal predictor of efficacy for vancomycin based on the best available data [4]. The experts proposed that the data—drawn from animal models, in vitro studies, and limited human studies—collectively suggests that microbiologic success is optimized when the vancomycin AUC/MIC_{BMD} ratio exceeds 400 [3,4,16–19].

Since it is difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine the AUC and subsequently calculate the AUC/MIC_{BMD} ratio, the expert guidelines recommend monitoring trough serum concentrations as a surrogate marker for AUC [3,4]. Their conclusion reads as follows: "Based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus*, total trough serum vancomycin concentrations of 15–20 mg/L are recommended"[3,4].

Despite its subsequent widespread integration in clinical practice, the clinical benefits of maintaining higher vancomycin trough values have not been well described. To date, seven published studies of note have evaluated the relationship between vancomycin trough values and clinical outcomes [6–11,20]. No link between clinical success and vancomycin trough values was seen in six of the seven studies that examined this relationship [6–11]. The seventh study by Kullar et al., showed that vancomycin failure (a composite endpoint including duration of bacteremia, recurrence, and mortality) was higher in patients (58–66%) with vancomycin trough concentrations less than 15 mg/L compared to those obtaining trough concentrations between 15 and 20 mg/L (40%). However, at the upper end of the trough continuum, treatment failure again increased in patients with vancomycin trough concentrations >20 mg/L [20].

From a PK/PD perspective, it is not altogether surprising that there is a paucity of clinical data to support the range of 15–20 mg/L for vancomycin serum trough concentrations. The current Clinical Laboratory Standards Institute (CLSI) and Food and Drug Administration (FDA) susceptibility breakpoint for vancomycin against *S. aureus* is ≤2 mg/L [21,22]. However, maintaining vancomycin trough concentrations between 15 and 20 mg/L only ensures a high likelihood (>90%) of achieving an AUC/MIC_{BMD} ratio >400 for *S. aureus* isolates with vancomycin MIC values ≤ 1 mg/L [13,23]. Using vancomycin PK data from patients with hospital-acquired pneumonia, we demonstrated that against *S. aureus* isolates with MIC values of 2 mg/L, the probability of obtaining an AUC/MIC_{BMD} ratio >400 with trough vancomycin concentrations between 15 and 20 mg/was suboptimal and was a function of the total daily dose administered (Fig. 1) [13]. In contrast, the probability of achieving an AUC/MIC_{BMD} in excess of 400 was 100% for MIC values ≤1 mg/L (Fig. 1). Further study is needed, but these data suggest that the current dosing approach of maintaining trough vancomycin concentrations between 15 and 20 mg/L will have a low probability of success for infections due to MRSA with wild-type MIC values by broth microdilution at the upper end of the antibiotic susceptibility range (e.g., 1.5 to 2 mg/L).

3. Mathematical relationship between trough and AUC

As mentioned previously, the trough is a single exposure point estimate at the end of the dosing interval. For vancomycin and most drugs, the trough concentration just prior to the next dose is the lowest concentration observed in the dosing interval. As such, the 24-hour AUC value (AUC_{24}) associated with trough values of 15–20 mg/L will almost always lead to an AUC_{24} in excess of 400 mg∗L/h. As an example, maintaining a vancomycin trough concentration of 17.5 mg/L equates to an AUC_{24} > 420 mg∗L/h (17.5 mg/L × 24 h). Therefore, the probability of achieving an AUC/MIC_{BMD} ratio ≥400 will always be 100% with vancomycin trough values between 15 and 20 mg/L when the MIC value is

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