Eur J Drug Metab Pharmacokinet
https://doi.org/10.1007/s13318-017-0456-4

CURRENT OPINION

Vancomycin Dosing and Monitoring: Critical Evaluation of the Current Practice

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Abstract After more than six decades of its use as the mainstay antibiotic for the treatment of multidrug-resistant Gram-positive bacterial infections, dosing and monitoring of vancomycin therapy have not been optimized. The current vancomycin therapeutic guidelines recommend empiric doses of 15–20 mg/kg administered by intermittent infusion every 8–12 h in patients with normal kidney function. Additionally, the guidelines recommend trough concentration of 15–20 mg/L as a therapeutic goal for adult patients with severe infections. This review critically discusses the current guidelines considering the basic pharmacokinetics and pharmacodynamics of vancomycin and the recent published reports from clinical studies. More in-depth discussion will be focused on (1) providing evidence of advantages of administering vancomycin by continuous infusion compared to intermittent infusion; (2) revising the current practice of trough-only monitoring versus the area under concentration–time curve (AUC); and (3) assessing the current practice of weight-based dosing versus AUC-based dosing. Using the gathered information presented in this paper, two user-friendly and scientifically based dosing strategies are proposed to improve the efficiency of vancomycin dosing while avoiding the risk of nephrotoxicity and minimizing the cost of therapeutic drug monitoring.

Key Points

This review critically discusses the current guidelines of vancomycin dosing and monitoring, considering its basic pharmacokinetics and pharmacodynamics properties and the recent published reports from clinical studies.

We herein propose two user-friendly and scientifically based dosing strategies (nomograms) to improve the efficiency of vancomycin dosing while avoiding the risk of nephrotoxicity and minimizing the cost of therapeutic drug monitoring.

1 Introduction

Vancomycin is a glycopeptide antibiotic that is widely used for the treatment of serious Gram-positive infections, especially community- and health-care-associated methicillin-resistant *Staphylococcus aureus* (MRSA) in both adult and pediatric patients [1]. Even though it has been used clinically for over 60 years, controversies still exist regarding the optimum dosing regimens and pharmacokinetic/pharmacodynamic properties of vancomycin. The current vancomycin dosing and monitoring guidelines are based on a consensus statement of the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) that was published in 2009 [2]. The main recommendations of these guidelines are (1) patients with normal kidney function receive an

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Published online: 19 December 2017

intermittent infusion of 15–20 mg/kg (based on actual body weight) every 8–12 h; (2) the ratio of the area under the curve for a total daily dose (AUC_{24}) to the minimum inhibitory concentration (MIC) of ≥ 400 should be a target for clinical effectiveness; (3) a total vancomycin trough concentration of 15–20 mg/L is recommended for serious MRSA infections such as bacteremia and pneumonia; and (4) a loading dose of 25–30 mg/kg (based on actual body weight) should be considered to achieve rapid attainment of the target steady-state concentration.

Although these guidelines represent a consensus statement from three major organizations, and despite the role of vancomycin in treating serious MRSA infection, there is still a lack of clear evidence of the need to maintain such high trough concentrations or AUC_{24}/MIC ratios and preference of intermittent infusion over continuous infusion. It should be noted that these recommendations are mostly based on in vitro and animal studies (such as the neutropenic mouse model) [3]. Although limited human studies have demonstrated that AUC_{24}/MIC is a preferred measure for monitoring vancomycin efficacy and AUC_{24}/MIC ≥ 400 correlates with adequate pharmacodynamic exposure and clinical outcomes in adults [4], several other human studies reported different conclusions. For example, Jeffers et al. found no evidence that aggressive vancomycin dosing to achieve high trough concentration (≥ 15) and AUC_{24} (≥ 400) targets results in better clinical outcomes in treating MRSA pneumonia [5].

On this basis, the purpose of this literature analysis is to critically evaluate the current practices of vancomycin dosing and monitoring, as well as offering scientific-based and user-friendly alternative approaches.

2 Continuous Versus Intermittent Infusion

Vancomycin is regularly administered via continuous intravenous infusion in Europe. Intermittent infusion, on the other hand, is the most widely used dosing method in the USA. In general, the published comparative studies failed to demonstrate any clinical superiority of one dosing strategy over the other [6–8]. This makes sense from the pharmacokinetics prospective as long as vancomycin clearance is not altered and the patient receives the same daily dose (AUC = dose/clearance). Therefore, this article will consider other factors to be considered in selecting a dosing method that should simplify and improve the accuracy of dosing and monitoring of vancomycin therapy. One of the most challenging steps in monitoring vancomycin therapy during intermittent infusion is the accuracy of trough concentration sampling time. Ideally, this measurement should be obtained just before the next dose at steady state [2]. Survey data indicate that 40–45% of the reported trough measurements were obtained too early, i.e., more than 30 min before the next dose [9, 10]. To assess the adherence to routine monitoring guidelines, Neely et al. reported that 81% of the first samples that were followed by an additional dose were not obtained within the hour before that dose; i.e., were not actually trough concentrations [11]. Too early measurement of trough vancomycin concentrations is expected to provide values that are misleadingly higher than the true levels, and therefore makes the dosing and monitoring of vancomycin more challenging. Because vancomycin concentration is constant (plateau) at steady state during administration by continuous intravenous infusion, this dosing method eliminates the variability in trough concentrations with intermittent infusion originating from errors in timing of sample withdrawal. Therefore, administration by continuous infusion seems to simplify and enhance the accuracy of therapeutic monitoring of vancomycin.

Another concern with intermittent infusion dosing is the significant inter-individual variability and inconsistencies between trough concentration and AUC_{24} values which refers mostly to the selection of the dose and dosing interval [11]. Administration of vancomycin by continuous infusion at a rate of, for example, 3000 mg/day, i.e., 125 mg/h, to a patient with vancomycin clearance of 5 L/h should achieve a steady-state (plateau) concentration of 25 mg/L. However, if the patient received vancomycin by intermittent infusion using the same dosing rate (3000 mg/day), different peak and trough values will be obtained depending on the dosing regimen. For example, dosing regimens that have larger doses and longer dosing intervals (e.g., 1500 mg every 12 h) produce higher peak and lower trough concentrations compared to dosing regimens that have smaller doses and shorter dosing intervals (e.g., 1000 mg every 8 h and 750 mg every 6 h); Fig. 1. It should be noted that the large fluctuations of vancomycin concentration produced by intermittent infusion may attain

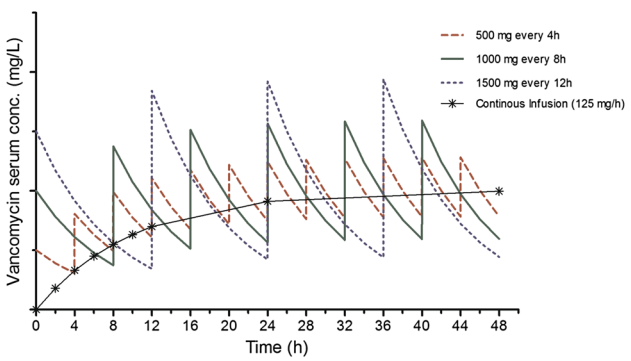

Fig. 1 Simulation of vancomycin serum concentration following administration by intermittent and continuous infusion at the same dosing rate. The highlighted area represents the target trough concentration range (15–20 mg/L)

sub-therapeutic or supra-therapeutic levels for extended periods of time resulting in high risk of developing resistance or nephrotoxicity, respectively. In support of this conclusion, a study by Vuagnat et al. reported a consistent vancomycin steady-state concentration produced by continuous infusion, but highly variable trough vancomycin concentration after administration by intermittent infusion in a group of patients with osteomyelitis, despite the fact that the mean daily vancomycin dosing was the same in the two groups [7].

Recent development of vancomycin-resistant pathogens such as vancomycin-intermediate *S. aureus* (VISA) strains, heteroresistant VISA (hVISA) and vancomycin-resistant *S. aureus* (VRSA) poses a significant challenge to the speed of the bactericidal activity of vancomycin and raises concerns about the clinical utility of this antibiotic. Strong evidence suggests that exposure to trough vancomycin concentrations of < 10 mg/L can produce strains with VRSA-like characteristics [2]. Additionally, the development of staphylococcal resistance to vancomycin has been associated with prolonged exposure to low serum vancomycin concentrations [12]. Administration of vancomycin by continuous infusion maintains a constant plasma concentration at steady state that is above the MIC of the suspected pathogen and therefore significantly reduces the risk of developing resistance [12]. Administration by intermittent infusion, on the other hand, even with similar daily doses, has the risk of producing significant fluctuations between peak and trough levels and prolonged exposure to vancomycin concentrations below the MIC (Fig. 1). Therefore, we expect that the probability of developing reduced susceptibility to vancomycin therapy would be higher for intermittent infusion compared to continuous infusion.

Vancomycin-induced nephrotoxicity (VIN) is the most concerning problem when dosing vancomycin. Although limited data are available to suggest a direct causal relationship between VIN and specific vancomycin concentrations, studies have identified several risk factors for VIN, including high trough concentrations [13, 14]. Consequently, the new recommendations of increasing the target vancomycin trough concentration from 5–10 to 15–20 mg/L to ensure adequate drug exposure and bacterial killing may increase the risk of nephrotoxicity, especially for critically ill patients and patients simultaneously receiving other nephrotoxic agent [2]. Although several studies have investigated the difference in risk of nephrotoxicity between intermittent and continuous infusion, these reports are conflicting and lack the evidence to support one dosing method over the other [15–20]. For example, the systemic reviews by Cataldo et al. [19] and Hao et al. [17] meta-analyzed the available published data and showed a clear trend toward reduced nephrotoxicity when vancomycin was administered by continuous infusion. On the other hand, an updated meta-analysis, inclusive of a recently published large-scale retrospective study, showed a non-significant trend of reduced nephrotoxicity in those patients who received vancomycin by continuous infusion. Although the current guidelines for the treatment of MRSA infections do not recommend the administration of vancomycin by continuous infusion regimen, since an improvement in patient outcome versus intermittent dosing is considered unlikely, this dosing method may be preferable when elevated risk of nephrotoxicity exists, such as coadministration of nephrotoxic agents, in the presence of septic shock, and in patients who need high doses of vancomycin. Authors of one of the largest population pharmacokinetic model of vancomycin in adults with prospectively collected and intensively scheduled samples proposed a steady-state AUC_{24} of 700 mg·h/L as a conservative threshold of vancomycin exposure [11]. Above this upper level, the risk of vancomycin-induced nephrotoxicity would increase more rapidly. In fact, this conclusion is consistent with the published consensus guidelines [2] for pathogens with vancomycin MIC ≥ 2 mg/L, when an AUC_{24} of 800 mg·h/L is required to maintain a therapeutic goal of AUC/MIC of 400. The observation that trough concentrations above 20 mg/L achieved with intermittent infusion are associated with higher risk of nephrotoxicity [21–23] compared to steady-state concentrations between 20 and 30 mg/L achieved with continuous infusion [17, 19] may be explained by the fact that AUC, not trough concentration, should be the correct marker of vancomycin toxicity. The inconclusive nature of the published studies indicates the necessity of a large randomized controlled trial to resolve this issue.

In this increasing cost-conscious environment, questions relating to the cost-effectiveness of drug dosing and monitoring should be justified. Reported data from randomized studies, meta-analyses, pharmacoeconomic studies and systemic reviews in the last two decades indicate reduced cost of vancomycin treatment using continuous infusion compared to intermittent infusion [8, 18, 24]. This cost-saving effect may be attributed to one or more of the following reasons; faster achievement of target vancomycin concentration with a lower AUC variance [8], fewer blood samples needed for monitoring and adjusting the treatment [18], reduced number of samples required for drug-level determination, lower amount of drug required [20], and reduced time and labor cost associated with routine monitoring of vancomycin levels [25].

The two major concerns with administering vancomycin by continuous infusion are its stability in solution for an extended period of time (24–48 h), and compatibility with other ingredients that need to be mixed in the same infusion bag. Studies have shown that vancomycin is stable in 5%

dextrose and 0.9% sodium chloride for at least 48 h at room temperature unprotected from light [26, 27]. Therefore, significant degradation of vancomycin during administration by continuous infusion is not anticipated, even in patients with impaired renal function when it is administered at a slower rate for a longer period. Compatibility studies on the other hand have identified many drugs that are chemically and/or physically incompatible with vancomycin (Table 1). Several sources suggest it is incompatible with alkaline solutions (e.g., aminophylline, aztreonam, dexamethasone, and sodium bicarbonate) and may form precipitate with heavy metals [26]. If the concomitant administration of these agents with vancomycin is deemed therapeutically important, one of the following measures should be implied: (1) use independent lines, (2) use multiple-way catheter, (3) use an alternative therapy such as aminoglycosides (compatible with vancomycin) instead of β-lactams to provide Gram-negative coverage, or (4) temporarily suspend the vancomycin infusion or switch to intermittent infusion method [24, 26].

3 Monitoring Vancomycin Trough Concentration Versus AUC_{24}

Mathematically, AUC is the definite integral of the drug concentration–time curve. In pharmacokinetics, AUC represents the total drug exposure to the given dose over a defined time interval. The current guidelines suggest an AUC_{24}/MIC of ≥ 400 as the target predictive of successful therapy. Because of the difficulty in measuring AUC, the guidelines suggest that vancomycin trough concentrations between 15 and 20 mg/L should be achieved as a surrogate marker for the optimum vancomycin exposure and effect. Several clinical and simulation studies have led to questioning the need for vancomycin trough values of 15–20 mg/L for all patients. Regimens producing trough values in excess of 15 mg/L are not always necessary to provide an AUC_{24}/MIC ratio ≥ 400, especially if the MIC is ≤ 1 mg/L [30]. In a retrospective analysis of vancomycin therapeutic drug monitoring data collected in 95 elderly patients treated with intermittent intravenous vancomycin, only a moderate correlation ($R = 0.51$) was found between AUC_{24} and trough concentration and AUC_{24} values >400 mg·h/L were obtained with trough levels <15 mg/L in more than 30% of the study subjects [31]. The study, through regression analysis, identified a vancomycin trough concentration of 10.8 mg/L as the optimal predictor of $AUC_{24} > 400$ mg·h/L [31]. Therefore, several clinical and simulation studies have led to questioning the need for vancomycin trough values of 15–20 mg/L for all patients. Regimens producing trough values in excess of 15 mg/L are not always necessary to provide an AUC_{24}/MIC ratio ≥ 400, especially if the MIC is ≤ 1 mg/L [30].

The current guidelines indicate that vancomycin efficacy is determined by AUC_{24}/MIC ratio ≥ 400, which correlates to a vancomycin trough of 15–20 mg/L. Assuming vancomycin trough concentrations at steady state is a good surrogate marker for AUC_{24}, trough-only monitoring of

Table 1 Physical compatibility of vancomycin with selected intravenously administered drugs [28]

Physically compatible	Physically incompatible	Compatibility information is not available or not adequate
Acyclovir, amikacin, amiodarone, argatroban, atracurium, bumetanide, calcium gluconate, caspofungin, cisatracurium, clindamycin, dexmedetomidine, dextrose 5% diltiazem, diphenhydramine, dobutamine, dopamine, doripenem, doxycycline, epinephrine, eptifibatide, esmolol, famotidine, fentanyl, fluconazole, gentamicin, hydromorphone, insulin regular, labetalol, levofloxacin, linezolid, lorazepam, magnesium sulfate, mannitol, meropenem, metoclopramide, metronidazole, midazolam, morphine sulfate, nicardipine, nitroglycerin, nitroprusside, octreotide[a], ondansetron, phenylephrine, piperacillin–tazobactam[c], potassium chloride, Ringer's lactated, sodium chloride (0.9%), tigecycline, tobramycin	Albumin human, amobarbital, aztreonam, bivalirudin, daptomycin, dexamethasone, furosemide, heparin, phenobarbital	Ampicillin, ampicillin–sulbactam, cefazolin, cefepime, cefotaxime, cefoxitin, ceftaroline, ceftazidime, ceftriaxone, ciprofloxacin, hydrocortisone, imipenem–cilastatin, methylprednisolone, micafungin, pantoprazole[b], penicillin G, phenytoin, potassium phosphate, propofol, sodium bicarbonate, trimethoprim–sulfamethoxazole

[a]Protected from light

[b]Test was performed with ethylenediaminetetra-acetic acid (EDTA-free formulation

[c]Test was performed with vancomycin 4 mg/mL and piperacillin sodium 30 mg/mL plus tazobactam 3.75 mg/mL or piperacillin sodium 40 mg/mL plus tazobactam 5 mg/mL [29]

vancomycin seems an easy and accurate approach. However, several challenges are associated with this method. Recent studies have documented a high degree of variability as well as therapeutic discordance between AUC_{24} and trough levels [11, 30]. For example, a study by Neely et al. demonstrated that 60% of adult patients who achieved a therapeutic $AUC_{24} > 400$ mg·h/L would have a trough concentration below 15 mg/L, especially for strains with MIC ≤ 1 mg/L [11]. Additionally, the study documented that AUCs estimated from trough data only significantly underestimated the actual AUCs calculated from a full data set, which could normally result in unnecessarily increased doses and higher risk of toxicity [11]. Using a Monte Carlo simulation ($n = 5000$) of vancomycin concentration–time profile based on administration of 1 g every 8 h regimens, Pai et al. found that trough concentrations at steady state cannot explain > 50% of the inter-individual variability in AUC [32]. It is not uncommon to observe a wide range of AUC values from several different dosing regimens that achieve similar trough values and vice versa. This significant inter-individual variability correlating vancomycin trough concentration and AUC makes trough-only monitoring an ineffective approach for vancomycin dosing.

The use of AUC_{24} as a target pharmacodynamic parameter for vancomycin dosing is more appealing and scientifically sound because its bacterial killing activity is concentration independent. Compared to trough-based dosing, AUC-based dosing is much simpler and involves only one step to calculate the daily dose to achieve the desired AUC_{24} as shown in Eq. 1.

$$\text{Vancomycin dose (mg/day)} = CL_V \times AUC_{24}, \quad (1)$$

where CL_V is the vancomycin clearance that can be estimated from creatinine clearance (see below).

The Bayesian approach was proposed to overcome the limitation of trough-only measurement in representing the "true" concentration–time profile [32]. The authors reported that this approach can estimate the "true" vancomycin AUC value with minimal pharmacokinetic sampling and provide AUC-based dosing recommendation at the bedside. Although this approach has the advantage of being adaptive to the dynamic patient conditions, clinician may have several logistic and educational barriers in adopting this approach in clinical practice.

4 Weight-Based Versus AUC-Based Dosing

Estimation of vancomycin volume of distribution (Vd) has been a challenge in general, and in obese patients in particular. Although several studies have shown that Vd of vancomycin is related to patient actual body weight (ABW), a wide range of Vd values (0.26–1.25 L/kg) have been reported [3, 33]. Therefore, large doses are given to obese patients in weight-based dosing because it is assumed that Vd is proportional to ABW. This practice has led to obese patients being treated with higher than needed vancomycin doses [34]. Reynolds et al. reported that using weight-based dosing resulted in trough concentrations of > 20 mg/L in approximately 50% of the obese patients; however, no nephrotoxicity was observed [35]. Physiologically, the relationship between Vd and CL_V (primary pharmacokinetic parameters) is described by the following formula (Eq. 2).

$$CL_V = k \times Vd, \quad (2)$$

where k is the first-order elimination rate constant (a secondary pharmacokinetic parameters). Therefore, if an obese patient (with large Vd) and a normal size patient (with normal Vd) have the same creatinine clearance (i.e., same CL_V), the obese patient should have a smaller k, i.e., slower rate of elimination and longer half-life, compared to the normal size patient. Although both patients should receive equal daily vancomycin doses, the dosing regimen for obese patients should include administration of larger doses every long dosing interval to achieve the same trough concentrations. Administration of vancomycin by continuous infusion would offer a simpler solution to obese patients to avoid variability in trough concentration produced by differences in dose and dosing interval. It should be noted that the optimum target C_{ss} depends on the severity of the infection and the MIC of the causative pathogen. Panday et al. [36] indicated that a continuous serum vancomycin concentration of 20 mg/L is needed to treat *S. aureus* strains with MICs of 1 mg/L. For strains with an MIC > 1 mg/L, however, a vancomycin C_{ss} of 25 mg/L was found to be more appropriate [37]. Similarly, a minimum C_{ss} of 16.7 mg/L was recommended for less severe infections, while a C_{ss} in the range of 22–28 mg/L was found to be more appropriate for serious infections [38].

Jeurissen et al. recommended a high continuous infusion vancomycin dose to achieve a target C_{ss} of 25 mg/L [39]. The authors indicated that this level was clinically effective and has limited risk of nephrotoxicity. Although several meta-analysis studies suggested that the risk of vancomycin-induced nephrotoxicity is lower with continuous intravenous infusion compared to intermittent infusion [16, 17], Ingram et al. [40] reported that nephrotoxicity was associated with vancomycin concentrations > 28 mg/L.

5 New Proposed Dosing Approaches

As discussed above, the current practice of vancomycin dosing is not efficient to achieve and maintain therapeutic levels, especially in the critically ill patients. To improve the efficiency of vancomycin dosing while avoiding the

risk of nephrotoxicity and minimizing the cost of therapeutic drug monitoring, two user-friendly and scientifically based dosing strategies are proposed in this article. Although continuous infusion is considered a preferred dosing method for vancomycin, we provide an intermittent infusion dosing strategy that is based on deriving patient-specific pharmacokinetic parameters is provided.

5.1 Intermittent Infusion

This approach estimates patient-specific pharmacokinetic parameters from two vancomycin levels following the first dose (the loading dose). The first level represents the peak vancomycin concentration after the first infusion (C_{peak1}). It is preferred to withdraw this level at least 1 h after the end of the infusion to allow for completion of the vancomycin distribution phase. The second level (C_t) can be withdrawn at any time before the second infusion (Fig. 2). Vancomycin elimination rate constant (k) and volume of distribution (Vd) are then calculated using Eqs. 3 and 4, respectively.

$$C_t = (C_{peak1})e^{-k(t-t')}, \quad (3)$$

$$C_{peak1} = \frac{K_o}{k\text{Vd}}(1 - e^{-kt'}), \quad (4)$$

where C_t is the vancomycin serum concentration at time t, t' the duration of the infusion, C_{peak1} the peak vancomycin serum concentration following the first infusion, and K_o the vancomycin infusion rate.

Using these pharmacokinetic parameters that are patient specific, vancomycin dosing regimen (dosing interval, τ, and infusion rate, K_o) can be calculated to achieve the desired steady-state peak ($C_{ss,peak}$) and trough ($C_{ss,trough}$) concentrations as shown in Eqs. 5 and 6, respectively:

$$C_{ss,peak} = \frac{K_o(1 - e^{-kt'})}{k\text{Vd}\ (1 - e^{-k\tau})}, \quad (5)$$

$$C_{ss,trough} = C_{ss,peak}e^{-k(\tau - t')}. \quad (6)$$

It should be noted that this method is easy to implement, but not practically accurate in patients with unstable hemodynamics (e.g., changes in the renal function). If significant changes are suspected, both k and Vd should be recalculated using two new serum vancomycin levels as described above.

5.2 Continuous Intravenous Infusion

Infusion rate, K_o (mg/h) required to achieve a steady-state concentration (C_{ss}; mg/L), can be determined if vancomycin clearance CL_V, is known as shown in Eq. 7:

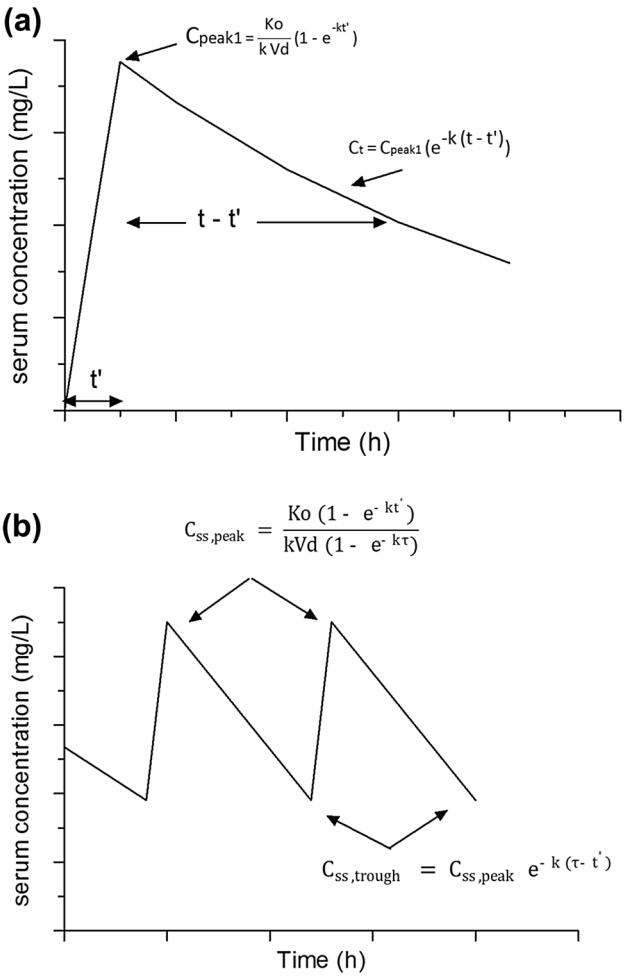

Fig. 2 Vancomycin serum concentration–time graph during and after administration of the first dose (**a**) and after attainment of steady state (**b**) by intermittent infusion at a rate (K_o) over a period of time (t') for every dosing interval (τ). C_t is the vancomycin serum concentration at time t, C_{peak1} is the peak vancomycin serum concentration following the first infusion, and C_{ss} is the vancomycin steady-state serum concentration

$$C_{ss} = \frac{K_o}{k\text{Vd}} = \frac{K_o}{\text{CL}_V}. \quad (7)$$

Due to the fact that vancomycin is mainly eliminated (>80%) by glomerular filtration [41], several investigators have evaluated the correlation between vancomycin clearance and creatinine clearance (CL_{Cr}; mL/min) estimates according to the formula of Cockcroft and Gault [42]. These studies have proposed several regression equations for the prediction of vancomycin clearance. Murphy et al., conducted a study to compare the accuracy of seven published methods to determine which method best predicts vancomycin pharmacokinetic parameters [33]. The authors concluded that the following formula (Eq. 8) performed the best in predicting CL_V from estimated CL_{Cr} (mL/min):

Case study 1

A patient has received the first vancomycin dose of 1000 mg as an infusion over 1 h. The peak serum concentration was measured as 20 mg/L. Another serum level measured 6 h from the start of the infusion was 12.97 mg/L. What is the recommended vancomycin dosing regimen to achieve a steady-state trough and peak levels of 15 and 30 mg/L, respectively?

Solution

1. Calculation of the current infusion rate (K_o):

Infusino rate $(K_o) = \frac{\text{Dose}}{t'} = \frac{1000\text{mg}}{1\text{h}} = 1000$ mg/h.

2. Calculation of the patient-specific vancomycin elimination rate constant (k):

$C_t = (C_{\text{peak1}})e^{-k(t-t')}$; $12.97 = 20e^{-k(6-1)}$; $k = 0.087\ \text{h}^{-1}$ (therefore, half-life = 8 h).

3. Calculation of the patient-specific vancomycin volume of distribution (Vd):

$C_{\text{peak1}} = \frac{K_o}{k\text{Vd}}(1 - e^{-kt'})$; $20 = \frac{1000\ \text{mg/h}}{(0.087\ \text{h}^{-1})(\text{Vd})}(1 - e^{-0.087\times 1})$; Vd = 48 L.

4. Calculation of the dosing interval (τ): assume t' is 1 h, for simplicity:

$C_{\text{ss,trough}} = C_{\text{ss,peak}}e^{-k(\tau-t')}$; $15 = 30e^{-0.087(\tau-1)}$; $\tau \sim 8$ h.

5. Calculation of the desired infusion rate (K_o):

$C_{\text{ss,peak}} = \frac{K_o\ (1-e^{-kt'})}{k\text{Vd}\ (1-e^{-k\tau})}$; $30 = \frac{K_o\ (1-e^{-0.087})}{0.087\times 48\ (1-e^{-0.087\times 8})}$; $K_o \sim 750$ mg.

Vancomycin is normally dosed at a rate not to exceed 1000 mg/h to avoid the red man syndrome [1]. Therefore, the recommended vancomycin dosing regimen is 750 mg administered as a short intravenous infusion over 1 h every 8 h. This regimen is expected to achieve steady-state trough and peak concentrations of 15 and 30 mg/L, respectively.

6. To predict the steady-state peak and trough concentrations from this dosing regimen:

$C_{\text{ss,peak}} = \frac{K_o(1-e^{-kt'})}{k\text{Vd}(1-e^{-k\tau})} = \frac{750(1-e^{-0.087\times 1})}{0.087\times 48(1-e^{-0.087\times 8})} = 29.8$ mg/L,

$C_{\text{ss,trough}} = C_{\text{ss,peak}}e^{-k(\tau-t')} = 30e^{-0.087(8-1)} = 16.3$ mg/L.

$$\text{CL}_\text{V}\ (\text{L/h}) = 0.04\ (\text{CL}_\text{Cr}) + 0.22. \quad (8)$$

Utilization of this formula predicted vancomycin clearance values that were very close to those obtained in recent pharmacokinetic studies [39, 43, 44]. Therefore, this formula is proposed to achieve the desired C_{ss} (e.g., 20–30 mg/L) and AUC_{24} (e.g., 400–700 mg·h/L). Figure 3 shows the proposed nomogram for calculation of vancomycin infusion rate (mg/h) to achieve target steady-state concentrations of 20, 25, and 30 mg/L (Fig. 3a) or their equivalent AUC_{24} values of 480, 600, and 720 mg·h/L (Fig. 3b), respectively, based on different CL_{Cr} estimates. Because steady-state condition will be achieved after at least three half-lives (approximately 24 h in patients with normal kidney function), a loading dose of 20 mg/kg (based on actual body weight) should be administered to achieve a faster approach to steady-state concentration [41]. This loading dose should be immediately followed by the continuous infusion at a rate based on the nomogram in Fig. 3.

Once at steady state, we recommend measuring vancomycin serum concentration (C_{ss}). Due to its linear pharmacokinetics, the infusion rate of vancomycin can be adjusted in proportion to the resulting steady-state concentration to achieve the target level. The AUC_{24} (mg·h/L) can be estimated from the nomogram (Fig. 3b) or calculated by multiplying the measured state concentration by 24 as in Eq. 9:

$$\text{AUC}_{24} = C_{ss} \times 24. \quad (9)$$

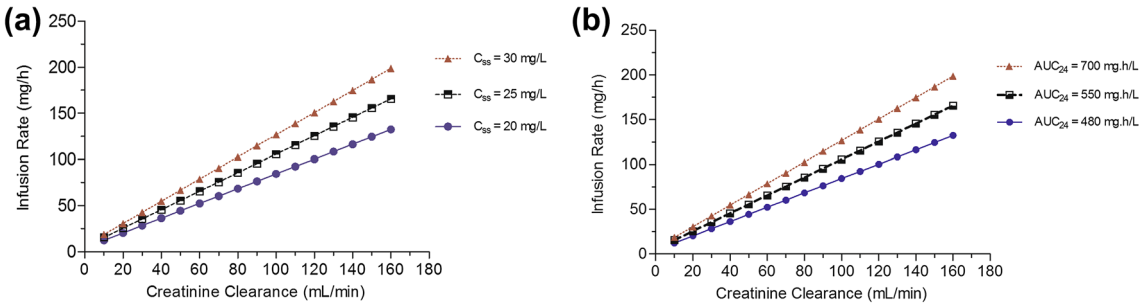

Fig. 3 Nomogram for the calculation of vancomycin continuous infusion rate (mg/h) to achieve target steady-state concentrations (**a**) or equivalent AUC_{24} (**b**) based on different CL_{Cr} estimates

Case study 2:

FE, a 42-year-old, 78-kg (height = 5 feet 10 in.) male patient, was admitted to the intensive care unit for an MRSA wound infection. His serum creatinine is 1 mg/dL, and has been stable for at least 3 days. Pharmacy is consulted to compute a vancomycin dosing continuous infusion regimen for this patient to achieve a steady-state concentration of 25 mg/L.

Solution

1. Estimation of CL_{Cr}:

Calculation of CL_{Cr} using the Cockcroft–Gault equation uses ideal body weight (IBW) unless actual body weight < IBW. IBW (males) = 50 kg + 2.3 kg for each inch over 5 feet = 73 kg. Therefore, it is appropriate to use IBW:

$$CL_{Cr} = \frac{(140-\text{age,years})\ (\text{wt,kg})}{72\ (\text{Cr,mg/dL})} = \frac{(140-42)\ (73)}{72\ (1)} = 99\ \text{mL/min}.$$

2. Calculation of vancomycin clearance (CL_V):

$$CL_V(\text{L/h}) = 0.04\ (CL_{Cr}) + 0.22 = (0.04 \times 99) + 0.22 = 4.18\ \text{L/h}.$$

3. Calculation of vancomycin dose (infusion rate, K_o):

$$K_o\ (\text{mg/h}) = C_{ss} \times CL_V = 25 \times 4.18 = 104.5\ \text{mg/h}.$$

Calculation of the vancomycin continuous infusion rate (mg/h) to achieve a steady-state concentrations of 25 mg/L can also be easily performed using the nomogram shown in Fig. 3 based on the estimated CL_{Cr}. According to the nomogram, an infusion rate should be approximately 105 mg/h (i.e., total vancomycin daily dose is approximately 2500 mg), an answer similar to the one obtained above.

Additionally, a loading dose of 20 mg/kg (i.e., 1500 mg) should be given as an infusion over 90 min followed immediately by the continuous infusion at 105 mg/h.

6 Conclusion

In this article, the current practice of vancomycin dosing and monitoring has been critically revised and assessed. Based on the findings described herein, revising the dosing method (intermittent infusion versus continuous versus), dosing approach (weight-based versus AUC-based), and the pharmacodynamic end point (trough versus AUC) is strongly recommended. Additionally, two user-friendly nomograms based on creatinine clearance estimates are proposed to help in calculating vancomycin dosing by both intermittent and continuous infusion methods. These nomograms are expected to improve the therapeutic efficacy while minimizing the risk of toxicity and cost of vancomycin dosing.

Acknowledgements This work was supported in part by the Faculty Development Grant from Pacific University, Oregon.

Compliance with Ethical Standards

Conflict of interest The author declares no conflict of interest.

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