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AN OVERVIEW APPROPRIATE ADJUSTMENT FOR VANCOMYCIN LEVEL, COMPLICATIONS

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Abstract:
Vancomycin is a glycopeptide antibiotic used to treat grampositive bacterial infections. Consumption has recently grown due to an increase in the incidence of infections caused by methicillinresistant S. aureus (MRSA). Increased use has been linked to increased minimum inhibitory concentration (MIC) levels, a phenomenon known as "MIC." Although the source of this creep is unknown, it has raised clinical concerns about the use of vancomycin. The emphasis on appropriate drug use has increased. Literature search done through the databases, for all published articles up to the beginning of 2022. This narrative literature review's findings strongly show that there is a link between vancomycin trough value and nephrotoxicity. Patients with vancomycin troughs larger than 15 mg/liter had a higher risk of nephrotoxicity than patients with troughs less than 15 mg/liter. Toxicity increased with therapy duration, with the highest rates found in critically sick patients who were in the ICU and receiving concomitant nephrotoxins.

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INTRODUCTION:

Vancomycin has been a cornerstone of therapy for significant Staphylococcus aureus infections since its discovery in the 1950s. Although vancomycin was formerly a second-line therapy, it became a first-line drug for infections caused by methicillin-resistant S. aureus (MRSA) in the 1970s [1]. Because of the expansion of MRSA in both the community and health care settings during the next several decades, its use skyrocketed [2]. Despite the recent availability of other medicines, vancomycin remains the preferred treatment for significant MRSA infections [3].

Despite its extensive usage, there are rising questions about vancomycin's future role, particularly among patients with invasive MRSA infections and vancomycin MICs greater than 1 mg/liter [4]. Although host and pathogen-related factors have been postulated as a cause, inadequate vancomycin dose has been proposed as an alternate reason for these patients' inferior outcomes. To address some of these concerns and increase the chances of achieving a 24-h ratio of area under the curve to MIC (AUC/MIC) of greater than 400, expert guidelines now recommend more intensive vancomycin dosing and maintaining troughs between 15 and 20 mg/liter for serious MRSA infections [5,6].

For serious MRSA infections, the suggestion to keep troughs between 15 and 20 mg/liter has been extensively adopted in clinical practice. Despite its widespread use, there is limited evidence that maintaining vancomycin trough levels between 15 and 20 mg/liter improves outcomes [7,8]. Furthermore, increased reports of vancomycin-induced nephrotoxicity have been linked to the widespread use of the more rigorous vancomycin dose schedules proposed by previous guidelines. Nephrotoxicity is a long-standing, although hotly contested, side effect of vancomycin treatment [1]. Initial reports of vancomycin-induced nephrotoxicity were mostly related to formulation impurities. Following contemporary fermentation and purification technologies, nephrotoxicity was thought to be rare (5 to 7%) and reversible [9,10].

DISCUSSION:

Vancomycin's killing effect is characterized by a sluggish mode of action, which is impeded further by a large bacterial inoculum, a stationary growth phase, and anaerobic conditions [5,6]. Despite the fact that numerous pharmacodynamic measures have been proposed to predict vancomycin activity, data from experimental and clinical investigations have shown the area under the curve (AUC)/MIC ratio as the best parameter to predict vancomycin effectiveness [7,9]. In vitro data, animal models, and clinical studies all support the target consensus of an AUC/MIC ratio of 400 for MRSA infections [7]. It should be noted, however, that the vancomycin MIC for S. aureus varies depending on the testing method employed. Etest produces MICs that are 0.5 to 1.5 log2 dilutions higher than those obtained via broth microdilution (BMD) [10,11]. Unless otherwise stated, all of the AUC/MIC ratios in this review are Etest measurements; Etest is the approved method for evaluating the MIC for MRSA bloodstream infection isolates [11].

Using an experimental mouse model of MRSA pneumonia, our laboratory discovered that an optimal dose of vancomycin (AUC/MIC ratio 400) was more effective than lower doses in clearing bacteria from the lungs and blood, although not demonstrating a greater survival rate [12]. In clinical investigations, an AUC/MIC ratio of 400 or above is associated with the greatest survival rate or clinical success in patients with S. aureus bacteremia, while various thresholds have been seen [10,13]. Using the BMD technique, an AUC/MIC ratio of >373 was identified as the breakpoint substantially linked with lower 30-day mortality (odds ratio [OR], 0.44) in a cohort of 182 patients with S. aureus bacteremia. In a cohort of 35 patients with MRSA-associated septic shock, Zelenitsky et al. [13] discovered that individuals with higher AUC/MIC values had a higher survival rate, reaching 70% when the AUC/MIC ratio was 451 ($P = 0.006$) and 81.8% when the AUC/MIC ratio was 578 ($P = 0.012$). Nonetheless, these findings should be regarded with caution because the AUC was calculated using a population PK model with only one serum level estimate and a MIC of 1 mg/liter was postulated based on surveillance BMD data. A recent retrospective cohort study [11], which used Bayesian methods to estimate the vancomycin exposure profile in 123 patients with MRSA bacteremia, showed that failure (defined as 30-day mortality, bacteremia for ≥ 7 days, or recurrence) was less in those cases achieving an AUC/MICEtest ratio of ≥ 303 and ≥320 (relative risk [RR], 0.5) on day 1 and day 2, respectively or an AUC/MICBMD ratio of ≥ 521 (RR = 0.6) and ≥650 (RR = 0.5) on day 1 and day 2, respectively.

Peak vancomycin serum levels have no relationship with toxicity or efficacy. Trough serum levels at steady-state circumstances, on the other hand, have been recommended as a more accurate and practical technique of monitoring vancomycin. The relevance of therapeutic drug monitoring and the use of the trough concentration as a proxy for the goal AUC is

emphasized in vancomycin therapy guidelines. The primary guidelines include giving 15 to 20 mg/kg body weight every 8 to 12 hours to attain target trough levels of 15 to 20 mg/liter and starting monitoring the vancomycin trough concentration before the fourth dose [4]. This method is founded on numerous assumptions. For starters, vancomycin efficacy and toxicity are both proportional to AUC, with a somewhat narrow therapeutic ratio. Second, establishing the AUC necessitates the collection of numerous serum vancomycin samples, and a different technique is required in the clinical context to facilitate monitoring. However, whether trough values are an adequate surrogate for AUC remains debatable. In the PK/PD investigation involving a series of Montecarlo simulations done by Patel et al. [14], a wide variety of AUC values from different dosing regimens yielding isometric Cmin values, and vice versa, was identified. The simulations also revealed that when the trough was 15 to 20 mg/liter and the MIC was 1 mg/liter, the likelihood of reaching an AUC/MIC ratio of >400 was nearly 100%, but the likelihood steadily diminishes as the MIC increased. The largest population PK model, reported by Neely et al. [15], is built on three earlier data sets from 47 thoroughly sampled individuals receiving vancomycin. Their findings show significant interpatient variability in AUC, trough, and peak values. These authors built a two-compartmental model based on the whole data set that fitted the observed concentrations well (R2 = 0.902). They discovered that the AUCs estimated from the trough and the peak-trough data sets were lower than the AUCs from the entire data sets, with a difference of 341.9 mg/liter (P < 0.001) and 159.3 mg/liter (P < 0,001), respectively. Notwithstanding, up to 60% of persons who reached a therapeutic AUC of >400 mg · h/liter would have had a trough concentration < 15 mg/liter [15]. This emphasizes that for strains having a MIC of 1 mg/liter, trough concentrations of 15 mg/liter may be sufficient to attain the desired AUC/MIC ratio of 400. If the vancomycin MIC is more than 1 mg/liter, an alternate agent should be considered. It should be noted that this guideline does not apply to S. aureus strains that exhibit heteroresistance to vancomycin. Vancomycin MICs of heterogeneous vancomycin-intermediate S. aureus (hVISA) strains are in the susceptible range, but include up to 1/105 to 1/106 bacterial subpopulations with higher MIC. The true prevalence of hVISA is unknown; however, current research indicates that it is increasing. Furthermore, once the vancomycin MIC exceeds 1 mg/liter, the fraction of hVISA increases [15].

Because of the interindividual heterogeneity in vancomycin trough levels and the AUC/MIC ratio, directing vancomycin dose only on trough levels may be insufficient. Linear regression analysis, population PK models, and Bayesian estimate processes have all given a more accurate approach [16].

Linear regression analysis, assuming a one-compartment model, estimates dose based on two serum results. It is a simple procedure, but it is not very precise in changing situations (for example, renal function) [16].

Population approaches build nomograms for determining doses using population PK values, however these methods have significant limitations. They begin by assuming a linear relationship between renal function and vancomycin clearance. Second, they usually aim to achieve target trough levels rather than a goal AUC. Furthermore, just a few nomograms have been produced to meet the present endpoints. Wesner et al. [17] and Kullar et al. [18] studied different trough levels, whereas Revilla et al. [19] built nomograms to attain an AUC/MIC ratio of 400. Application to populations of individuals excluded from the research should be avoided in all situations.
For estimating dosages, the third method, Bayesian estimation processes, combines optimal population information with PK information from the patient. When applied appropriately, it is the most accurate procedure. Vancomycin dosages can be determined using Bayesian approaches to obtain a target AUC/MIC, avoiding the use of trough serum levels as a surrogate target [11]. The key disadvantage is that Bayesian approaches necessitate precise information on numerous characteristics, including age, weight, renal function, and past therapeutic regimen, among others. Another issue is the requirement for trained staff with specialist understanding of pharmacokinetics [16].

LOADING DOSE:

A loading dose of 25 to 30 mg/kg has been proposed as an appropriate strategy in order to avoid subtherapeutic vancomycin levels in the initial stages of therapy. This recommendation is based on one randomized clinical trial (RCT) [20] and on other studies evaluating trough serum vancomycin levels after a loading dose on different types of patients (. The previously mentioned RCT [20] assayed a loading dose of 25 to 30 mg/kg in critically ill patients. Regrettably, it presented the caveat that the authors only determined peak vancomycin levels, despite peak levels not correlating to efficacy [20]. Recently, Rossini et al. [21] performed an RCT on 99 patients

receiving a loading dose of 30 mg/kg of vancomycin or the standard therapy with 15 mg/kg. After 12 h, the proportion of patients achieving a trough level of 15 mg/liter was higher in the group with loading dose (34% versus 3%; $P < 0.01$), without toxicity differences between them. This study included both critically and noncritically ill patients. Truong et al. [22] failed to find differences in the proportion of patients with trough vancomycin levels of ≥15 mg/liter in a pre- and postintervention study when comparing standard therapy with a fixed loading dose of 2 g in 52 critically ill patients. Despite that, the mean (± standard deviation [SD]) trough plasma concentrations were higher in the postintervention group (9.8 ± 6.6 versus 14.9 ± 6.3 mg/liter). However, the sample is lacking statistical power, with just 11 patients receiving the loading dose. Vandecasteele et al. [23] proposed a loading dose for patients undergoing hemodialysis. It was calculated according to dry body weight and the period to the next dialysis session. The usefulness of a loading dose to achieve the targeted trough levels early in other groups of patients has not been assessed. In summary, selected patients with severe disease may benefit from a vancomycin loading dose with the aim of achieving early steady-state levels. Further studies are needed to clarify the clinical impact of applying a loading dose in all kinds of patients.

All efforts to demonstrate differences in the effectiveness of continuous infusion (CoI) and intermittent infusion (InI) have failed [24]. In contrast, there are many reports of a reduced toxicity of CoI with respect to InI. Cataldo et al. [25] performed a meta-analysis comparing these two dosing approaches and concluded that CoI achieved a similar overall mortality rate and less renal impairment. Of note, only six studies, quite heterogeneous (I^2 of 90% for vancomycin exposure, I^2 of 0 for nephrotoxicity and mortality), could be included, and just one was a randomized clinical trial, so results cannot be considered conclusive. Subsequently, Hanrahan et al. [26] found a significant association between InI and nephrotoxicity in a retrospective cohort of 1,430 critically ill patients.

Others have proposed that higher loading dosages, higher dose frequencies, or continuous infusions are required to attain higher success rates [26, 27]. Even with continuous infusion, however, a suitably high loading dosage is required to avoid subtherapeutic concentrations [26]. This could be attributed to an increase in the volume of distribution for hydrophilic medicines like vancomycin in critically ill individuals. Furthermore, creatinine clearance will influence vancomycin serum concentrations during the first days of therapy. Supratherapeutic vancomycin concentrations can occur from low creatinine clearance [27].

We were surprised by the low success rates in our data since we expected subtherapeutic trough serum concentrations to be addressed through the therapeutic drug monitoring (TDM) process. TDM has been the standard clinical approach for monitoring vancomycin therapy for many years. In their comprehensive review, Ye and colleagues concluded that TDM "significantly increases the rate of clinical efficacy" in vancomycin patients [28]. Unfortunately, this study shows that only half of individuals with trough serum concentrations outside the therapeutic range received adequate dose changes. As a result, there is significant opportunity for development. Increased pharmaceutical collaboration and the introduction of a vancomycin dose adjustment methodology to aid in TDM may increase the proportion of appropriate dose modifications. Such a strategy is simply internalizable in modern electronic medical records, ensuring improved followup [28].

Vancomycin is used to treat grampositive infections like Staphylococci and Enterococci. According to Candeloro et al., vancomycin is more typically used as an empiric treatment rather than directed therapy [29]. Only one-quarter of the treatments were targeted. Both units in this study meet with infectious disease practitioners on a regular basis. Rimawi and colleagues found that daily collaboration between infectious disease practitioners and critical care practitioners might "significantly reduce medical ICU antibiotic overuse" while increasing mortality, lowering healthcare costs [30].

COMPLICATIONS:

While the occurrence of nephrotoxicity is alarming, it appears to be largely reversible in the majority of patients with termination of vancomycin [31]. Only about 3% of patients required short-term dialysis, and none required long-term dialysis. Concomitant nephrotoxins were administered to all patients who required dialysis [32]. This finding lends credence to the idea that specific clinical variables exacerbate the severity of vancomycin-induced renal impairment. Although vancomycin-induced nephrotoxicity was often reversible, the nephrotoxic episodes were associated with longer hospital stays and poorer outcomes [33].

When interpreting these results, several factors should be addressed. First, establishing that exposure-

nephrotoxicity correlations exist for medicines that are renally removed is difficult. Because vancomycin is primarily removed through glomerular filtration, any reduction in renal function will result in an increase in vancomycin serum concentrations [34]. Recognizing this, we limited our analysis to research that looked just at first troughs. For patients with initial trough levels of 15 mg/liter, the chances of nephrotoxicity remained elevated, at 3.12 (95% CI, 1.81 to 5.37; P 0.01) [35]. The existence of a vancomycin trough-nephrotoxicity link is further supported by the fact that the majority of nephrotoxic incidents occurred after 7 days of medication. This association between exposure and toxicity is biologically feasible and confirmed by recent animal and human studies indicating vancomycin works as an oxidative stressor in proximal renal tubular cells [35].

Second, the analysis that classified vancomycin into more precisely defined trough strata (10, 10 to 15, 15 to 20, and >20 mg/liter) suggests that vancomycin-induced nephrotoxicity is similar among patients with troughs between 10 and 20 mg/liter and greatest among patients with troughs greater than 20 mg/liter. There was a considerable potential for vancomycin stratum misclassification mistake due to the minor demarcation in trough values between 10 to 15 and 15 to 20 mg/liter, especially as these data were acquired from retrospective cohort studies. While vancomycin trough values of >20 mg/liter may be causing nephrotoxicity in the >15-mg/liter strata, caution should be maintained before drawing final conclusions from these data [35]. Until more data are available to accurately define the vancomycin exposure-toxicity curve, doctors should rely on the findings of the 15 trials included in this meta-analysis, which imply that people with troughs of >15 mg/liter are at increased risk of toxicity [36].

CONCLUSION:

Vancomycin is a glycopeptide antibiotic used to treat grampositive bacterial infections. Consumption has recently grown due to an increase in the incidence of MRSA infections. Increased use has been linked to increased minimum inhibitory concentration (MIC) levels, a phenomenon known as "MICcreep." Although the source of this creep is unknown, it has raised clinical concerns about the use of vancomycin. The emphasis on appropriate drug use has increased. Vancomycin efficacy is linked to proper dose based on appropriate PK/PD characteristics. In patients with S. aureus bacteremia, an AUC/MIC ratio of 400 has been linked to higher survival rates. Although trough vancomycin levels are not a perfect predictor of AUC, obtaining a trough concentration of 15 to 20 mg/liter would be sufficient to treat S. aureus infections with a MIC of 1 mg/liter. Individualized doses are the best option due to relevant interindividual variability, and Bayesian estimate processes are the most accurate way to determine them. Special pharmacokinetic trials, such as those involving obese individuals or renal replacement therapy (RRT), are required. Vancomycin therapy for patients undergoing intermittent RRT should be tailored using validated nomograms, with patient weight, dialyzer type, residual renal function, and interdialysis interval all being taken into account, aided by monitoring levels.

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