Is Trough Concentration of Vancomycin Predictive of the Area Under the Curve? A Clinical Study in Elderly Patients

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Background: Current guidelines suggest that vancomycin trough concentrations (Cmin) between 15 and 20 mg/L should be achieved to optimize vancomycin exposure and effect. The objective of this study was to analyze the correlation between vancomycin Cmin and the area under the concentration–time curve (AUC) and assess the ability to predict an AUC target of 400 mg·h/L based on Cmin.

Methods: A retrospective analysis of vancomycin therapeutic drug monitoring data collected in 95 elderly patients treated with intermittent intravenous vancomycin was performed. For each patient, individual pharmacokinetic parameters of vancomycin and AUC_{24} were estimated from concentration measurements using a Bayesian approach. The relationship between vancomycin Cmin and AUC was studied using global and local correlation analysis as well as logistic regression with Receiver Operating Characteristic curve analysis.

Results: The overall correlation between AUC_{24} and Cmin was significant but moderate ($R^2 = 0.51$). When vancomycin Cmin was greater than 15 mg/L, the corresponding AUC_{24} was >400 mg·h/L in 95% of cases. However, AUC_{24} values >400 mg·h/L were obtained with Cmin < 15 mg/L in more than 30% of the cases. The logistic regression analysis identified a Cmin value of 10.8 mg/L as the optimal predictor of $AUC_{24} > 400$ mg·h/L.

Conclusions: The results of this study indicate that the recommended target range of 15–20 mg/L for vancomycin Cmin seems acceptable for controlling vancomycin exposure, although a value of approximately 11 mg/L appears to be optimal and may be safer.

Key Words: vancomycin, therapeutic drug monitoring, pharmacokinetics, geriatrics

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INTRODUCTION

Vancomycin is a glycopeptide antibacterial that is widely used by intravenous (IV) route in the treatment of severe infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*.[1,2] Vancomycin has long been considered as a concentration-independent or time-dependent antibacterial.[1,3] For this reason, the traditional pharmacokinetic (PK) goal of vancomycin therapy is to maintain vancomycin concentrations well above the minimum inhibitory concentration (MIC) of the suspected or identified bacteria over the entire dosing interval. Several clinical studies have shown that vancomycin trough concentration (Cmin) >10 mg/L,[4] or within the range 15–20 mg/L,[5] was associated with better treatment outcome than lower values.

However, more recent data have shown that the PK/pharmacodynamic index that best correlates with vancomycin killing was not time above the MIC (T_{MIC}) as for typical time-dependent antibacterials such as beta-lactams, but the ratio of the area under the time–concentration curve (AUC) over the MIC (AUC/MIC).[1] USA guidelines for vancomycin therapeutic drug monitoring (TDM),[6] and literature data, have suggested that a ratio of the AUC calculated over 24 hours above the MIC (AUC_{24}/MIC) ≥ 400 mg·h/L should be achieved to optimize the response to vancomycin therapy.[5,7–10] Because AUC is not routinely estimated in clinical practice, the USA guidelines have proposed to use a Cmin interval of 15–20 mg/L as a surrogate target, assuming that AUC_{24} correlated well with Cmin in all patients.[6] However, clinical data supporting this hypothesis are limited.

The objectives of this study were to analyze the correlation between vancomycin AUC_{24} and Cmin and to evaluate whether vancomycin Cmin was a significant predictor of AUC ≥ 400 mg·h/L in the elderly population.

MATERIALS AND METHODS

Study Population and PK Analysis

This was a retrospective analysis of data collected during routine TDM in elderly patients treated with vancomycin. Data from 112 patients (455 vancomycin-measured concentrations) hospitalized between 2002 and 2013 in the geriatric hospitals of the Lyon area were examined. All patients received vancomycin by intermittent IV infusion. Patients who received vancomycin by continuous IV infusion were excluded because in such cases the relationship between AUC_{24} and Cmin at a steady state (SS) is straightforward (Cmin = Css and $AUC_{24} = Css \times 24$). Other exclusion criteria were related to Bayesian estimation of the AUC (see below).

Available data included a full history of vancomycin administration and blood samples for TDM; vancomycin measured concentrations; and the main demographic and

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biological data such as age, weight, and creatinine clearance (CCr). Those data were collected prospectively in each patient as part of a TDM program with Bayesian dose adjustment that has been performed for elderly patients in our institution for many years. Bayesian dose adjustment of vancomycin was performed using the BestDose (formerly MM-USC*PACK) software (Laboratory of Applied Pharmacokinetics, USC School of Medicine, Los Angeles, CA, www.lapk.org). As this was a noninterventional study without any additional procedure, no institutional review board or ethics committee approval was required, in accordance with the French regulation on biomedical research (articles L 1121-1 and R 1121-2 of the French Code of Public Health).

Vancomycin serum concentrations were measured by immunoturbidimetric assay on Abbott Architect C8000 automated analyzer. The assay calibration data, expressed as coefficients of variation, were 6.56%, 2.20%, and 2.41% for control levels of 6.40, 22.26, and 36.08 mg/L, respectively. The lower limit of quantification of the assay was 1.1 mg/L.

In the retrospective analysis, vancomycin individual PK parameters were estimated by a Bayesian, multiple-model approach, as described elsewhere.[11] The Bayesian approach combines individual data (measured concentrations and model covariates) and population data (distribution of PK parameters) to calculate the most likely Bayesian posterior distribution of PK parameters. A good graphical abstract of this method has been recently published elsewhere.[9] Subsequently, the entire individual PK profile can be estimated, including measured concentrations, and the AUC is computed by integration. We used the vancomycin population model for adult patients embedded in the BestDose software. This is a 2-compartment, 5-parameter model, as described previously.[11] The parameters are Vc, the apparent volume of the central compartment (in L/kg); Kcp and Kpc, the intercompartment transfer rate constant (in h^{-1}); Kslope, the renal elimination rate constants (in h^{-1}) per unit of CCr (CCr in mL/min); and Kint, a nonrenal elimination rate constant, this latter is fixed at 0.002043 h^{-1}. The equation of the elimination rate constant, Ke, is as follows: Kel = Kint + (Kslope × CCr). The model is nonparametric, discrete, consisting of 18 support points, that is, 18 sets of values of the 5 parameters, each set having a probability.

As shown in definition of the parameters, individual values of total body weight and CCr were taken into account in the estimation of vancomycin volume of distribution and elimination rate constant, respectively. CCr was estimated using either the Jelliffe equation[12] or the Cockcroft–Gault equation,[13] which have been shown to provide similar clearance and concentration estimates when included in a PK model of vancomycin in elderly patients.[14] To ensure proper estimation of the 4 random parameters of the model and AUC, at least 2 concentrations measured around the same dose, including a trough level, were required. As a result, patients with a single concentration measured postdose were excluded at that step. Also, patients for whom the prediction error, that is, Bayesian predicted minus observed concentration for any measured concentration was ≥25% were also excluded, to avoid large imprecision in the estimation of the AUC. There were 79 measured concentrations (34 trough concentrations and 45 concentrations measured earlier) for which prediction error was ≥25%, from 43 patients. However, more values were eventually excluded because the entire PK profile was discarded in such case, even if the other concentrations of the profile were accurately predicted. The characteristics of patients in whom data were excluded were similar to that of included patients (data not shown). In the final data set used for correlation analysis, there were 323 measured concentrations of vancomycin, including 150 trough levels. For most patients, a peak concentration (measured approximately 30 minutes postdose) and a trough concentration measured just before the next dose were used. A third vancomycin measurement was available in a few patients. Vancomycin TDM was performed on several occasions in some patients. In such cases, PK intraindividual variability may occur and alter the model fitting of all data.[15,16] To optimize the model fit and the estimation of the AUC, the fit was performed sequentially on each occasion, by excluding vancomycin concentrations measured on other occasions. When the inclusion criteria were met, several AUC values could be estimated sequentially and independently for the same patient. As a result, there were more estimated AUC values than the number of patients. The AUC values per dose were obtained from BestDose. In patients who received vancomycin 2 or 3 times daily, the daily AUC was then extrapolated by linear calculation.

Statistical Analysis

First, vancomycin concentrations predicted by the Bayesian approach were compared with the entire initial set of 455 observed concentrations to assess the goodness-of-fit of the model, which was the basis of model-based AUC estimation.

Then, the association between observed vancomycin Cmin ($Cmin_{obs}$) and estimated AUC_{24} was studied in the final data set using 2 approaches. The global association was evaluated using the traditional linear correlation with R^2 coefficient of determination. In addition, we used the Z-score, a nonparametric, local association measure developed by Ducher et al.[17,18] The Z-score quantifies the normalized deviation from independence. Its values may range from −1 to 1. A value of 1 indicates full positive association; a value of −1 indicates full negative association. A value of 0 means independence. This approach is useful to identify areas of strong local association between 2 variables, despite meaningless global association.

Assuming a MIC equal to 1, we compared the numbers and proportions of estimated $AUC_{24} \geq 400$ mg·h/L (so, $AUC_{24}/MIC \geq 400$) associated with 3 usual cutoff values of $Cmin_{obs}$, 10, 15, and 20 mg/L. Sensitivity, specificity, positive, and negative predictive values were calculated for each $Cmin_{obs}$ cutoff value. The AUC target denoted was 400 mg·h/L.

Finally, the influence of $Cmin_{obs}$ on the probability of achieving $AUC_{24} \geq 400$ mg·h/L was evaluated using logistic regression, and the predictive value of that statistical model was assessed by Receiver Operating Characteristic (ROC) analysis. The AUC of the ROC curve was computed and confidence limits were calculated by a bootstrap procedure. The optimal predictive value of $Cmin_{obs}$ was derived from the curve. These analyses were performed within the MATLAB software (version R2011b; MathWorks, Natick, MA).

TABLE 1. Characteristics of Patients Included in the Correlation Analysis (n = 95) and the Main PK Results

Characteristic	Mean ± Standard Deviation
Age, yrs	82.3 ± 6.7
Body weight, kg	61.5 ± 12.4
CCr, mL/min	52 ± 19.4
No. vancomycin administrations per day	2.1 ± 0.5
Observed trough vancomycin concentration, mg/L	13.4 ± 5.8
Predicted trough vancomycin concentration, mg/L	13.1 ± 5.9
AUC_{24}, mg·h/L	480.8 ± 217.5

AUC_{24}, estimated daily vancomycin AUC.

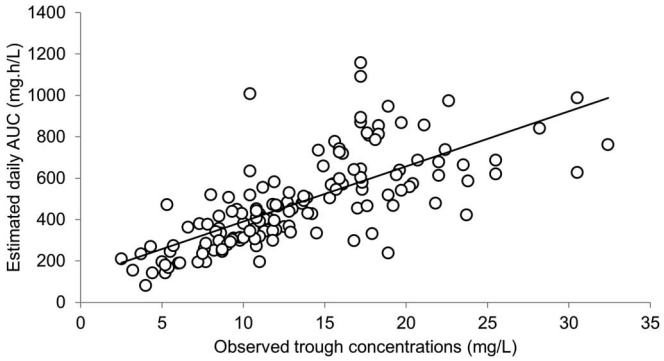

FIGURE 1. Estimated vancomycin daily area under the concentration–time curve (AUC) versus observed trough concentrations.

RESULTS

In the initial data set (n = 455 vancomycin concentrations; range, 2.2–58.9 mg/L), the vancomycin model fitted the observed data very well. The linear regression equation of predicted versus observed concentrations was as follows: $y = 1.07x + 0.1$, $R^2 = 0.86$. The mean prediction error was 1.2 ± 4.5 mg/L; the median absolute prediction error was 10%. Based on this good predictive performance, AUC estimates from the model were deemed to be trustworthy.

For the correlation analysis, 323 vancomycin concentrations, including 150 $Cmin_{obs}$, were available from 95 patients, and 150 corresponding AUC_{24} were estimated with the model. Six, 73, and 16 patients were administered vancomycin once, twice, and thrice daily, respectively. Patients' characteristics and the main vancomycin PK data are shown in Table 1.

Figure 1 shows the linear correlation between vancomycin $Cmin_{obs}$ and estimated AUC_{24}. The correlation appeared to be significant but moderate, $Cmin_{obs}$ explaining only 51% of the variance of AUC_{24}. For $Cmin_{obs}$ between 15 and 20 mg/L, there was a large variability in associated AUC_{24}. Results of the local association assessment (Z-score) are shown in Figure 2. This method indicated that 101 pairs of $Cmin_{obs}$-AUC_{24} were correlated, whereas 49 were independent. The strongest association between $Cmin_{obs}$ and AUC_{24} was observed for the lowest and highest $Cmin_{obs}$-AUC paired values. The association was positive but weaker for paired values within the therapeutic range of interest. For example, the Z-score was 0.349 for $Cmin_{obs}$ and AUC_{24} ranging from 10 to 17.4 mg/L and 351–620 mg·h/L, respectively.

The number and percentages of AUC_{24} less than 400 mg·h/L and those greater than or equal to that value for the 3 $Cmin_{obs}$ cutoff are shown in Table 2. Ninety-five percent of AUC_{24} values were ≥ 400 mg·h/L when $Cmin_{obs}$ was ≥ 15 mg/L. However, about one-third of AUC_{24} values were ≥ 400 mg·h/L when $Cmin_{obs}$ was <15 mg/L. A trough concentration threshold of 20 mg/L was associated with poor sensitivity. A cutoff value of 10 mg/L provided better values of the various predictive indices.

Logistic regression analysis showed that $Cmin_{obs}$ was significantly associated with the probability of achieving AUC_{24} ≥ 400 mg·h/L. The corresponding odds ratio was 1.56 [95% confidence interval (CI), 1.35–1.81, $P < 0.001$]. The area under the ROC curve was 0.89 (95% CI, 0.83–0.94), indicating a good predictive performance. The optimal value of $Cmin_{obs}$ was 10.8 mg/L, which was predictive of AUC_{24} ≥ 400 mg·h/L with a sensitivity of 89% and a specificity of 69%.

DISCUSSION

TDM of vancomycin and achievement of target exposure are key determinants for vancomycin treatment success.[6–10] Although the AUC is the PK index that best correlates with vancomycin antibacterial effect, routine TDM of vancomycin has long been based on the measurement of trough concentrations. While estimating vancomycin

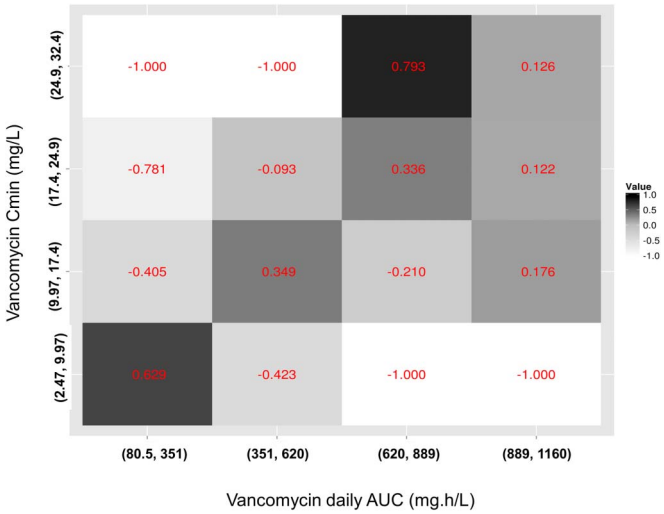

FIGURE 2. Local association between vancomycin trough concentrations and daily area under the concentration–time curve (AUC) values. The values of vancomycin trough concentration ($Cmin_{obs}$) and daily AUC are categorized into 4 intervals of ascending level, resulting in 16 surfaces of paired values. The value indicated in each square is the Z-score quantifying the association. A value of 1 indicates full positive association; a value of −1 indicates full negative association. A value of zero means independence.

TABLE 2. Distribution of AUC_{24} Values for Various Thresholds of Vancomycin Trough Concentration

	$AUC_{24} \geq 400$ mg·h/L, n (%)	$AUC_{24} < 400$ mg·h/L, n (%)	Total
$Cmin_{obs} \geq 15$ mg/L	53 (95)	3 (5)	56
$Cmin_{obs} < 15$ mg/L	35 (37)	59 (63)	94
Se = 60%, Sp = 90%, PPV = 95%, NPV = 63%			
$Cmin_{obs} \geq 10$ mg/L	81 (76)	25 (24)	106
$Cmin_{obs} < 10$ mg/L	7 (16)	37 (84)	44
Se = 92%, Sp = 60%, PPV = 76%, NPV = 84%			
$Cmin_{obs} \geq 20$ mg/L	18 (100)	0 (0)	18
$Cmin_{obs} < 20$ mg/L	70 (53)	62 (47)	132
Se = 20%, Sp = 100%, PPV = 100%, NPV = 41%			
Total	88	62	150

AUC_{24}, estimated daily vancomycin AUC; $Cmin_{obs}$, vancomycin observed trough concentration; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

AUC based on limited PK sampling is feasible and preferable,[9,19] we considered the problem of predicting vancomycin AUC based on trough-only monitoring, which is still a widely used TDM approach in routine clinical practice. In such setting, it is important to evaluate whether vancomycin Cmin is a reliable predictor of the AUC.

The results have shown that a significant linear correlation existed between observed vancomycin Cmin and estimated AUC_{24}. However, this correlation was moderate ($R^2 = 0.51$), and a large variability (up to 5-fold) was observed in AUC_{24} values corresponding to a given $Cmin_{obs}$. The local association analysis confirmed a positive correlation between observed vancomycin Cmin and estimated AUC_{24}, but of limited magnitude in the therapeutic ranges of both variables. Therefore, vancomycin trough concentration is a poor quantitative predictor of the AUC, as one cannot accurately predict the AUC_{24} corresponding to a given $Cmin_{obs}$. This result is consistent with the basic PK principles, as the AUC reflects the overall PK profile, which depends on all parameters of the 2-compartment model, whereas the trough concentration is less dependent on drug distribution. This also is in agreement with simulation results[9] and clinical observations. In neonates, Frymoyer et al reported an R^2 of 0.63 for the linear correlation between vancomycin Cmin and AUC_{24}, whereas Haeseker et al reported an R^2 of 0.38 in adult patients.[20,21] A large variability was also observed in AUC_{24} for a given Cmin in those 2 studies (up to 3-fold). This variability appears to be even greater in elderly patients as observed in this study.

However, our results suggest that vancomycin Cmin can be a reliable categorical predictor of achieving $AUC_{24} \geq 400$ mg·h/L. Ninety-five percent of AUC_{24} values were above this threshold when $Cmin_{obs}$ was ≥ 15 mg/L. This result is logical considering that the SS concentration of a constant infusion of vancomycin (without a peak) corresponding to an AUC_{24} of 400 mg·h/L is approximately 16.7 mg/L. This result may be viewed as supporting the USA guidelines which recommend a target trough of 15–20 mg/L to optimize the exposure.[6] However, based on our data and logistic regression analysis, a lower Cmin target appears to be sufficient to achieve $AUC_{24} \geq 400$ mg·h/L in most elderly patients. A Cmin of approximately 11 mg/L was identified as the optimal predictor of $AUC_{24} \geq 400$ mg·h/L in this study population. To our knowledge, our study is the first that suggests a target Cmin for optimizing AUC for intermittent IV vancomycin therapy for elderly patients.

Our results are consistent with previous findings. Based on PK simulations, Neely et al predicted that 60% of adult patients with normal renal function and $AUC_{24} \geq 400$ mg·h/L would have Cmin < 15 mg/L.[19] In adult patients, Haeseker et al reported that 92% of patients with vancomycin Cmin between 10 and 15 mg/L achieved $AUC_{24} \geq 400$ mg·h/L.[21] High rates of vancomycin AUC target attainment have also been reported for Cmin < 15 mg/L or even 10 mg/L in children and neonates.[20,22]

This lack of sensitivity of Cmin ≥ 15 mg/L for predicting $AUC_{24} \geq 400$ mg·h/L may have important clinical implications in terms of risk/benefit ratio of vancomycin use. There is sound evidence that vancomycin nephrotoxicity correlates with vancomycin Cmin and that Cmin > 15 mg/L is associated with increased risk of toxicity compared with lower Cmin values.[23,24] As a consequence, targeting vancomycin Cmin of 15–20 mg/L may be associated with an increased risk of toxicity, while providing negligible benefits in terms of AUC target attainment, compared with a lower target interval of 10–15 mg/L.

This study has several limitations. It was based on limited data from a special population, that is, elderly patients. We used a 2-compartment model and a Bayesian fitting approach based on at least 2 measured concentrations and 2 covariates (body weight and CCr) to estimate the AUC. The gold standard approach for AUC estimation is noncompartmental analysis of rich PK data. However, this is not possible in clinical practice. Also, the use of a different structural model and different covariate model could have provided different AUC estimates. Of note, Neely et al have shown that Bayesian estimation based on a 2-compartment model, an informative prior and only 2 or even 1 measured concentration, provided precise estimates of vancomycin AUC.[19] However, the results may not be generalized to other patient populations and vancomycin PK models, and therefore, further studies are necessary to confirm our findings.

Importantly, the pharmacodynamics index correlated with vancomycin effect depends on both drug exposure (AUC) and the susceptibility of the microorganism quantified by the MIC. We did not take into account the latter in this study. We used 400 mg·h/L as the vancomycin target AUC, assuming an MIC of 1. If the actual MIC is <1, lower vancomycin exposure, and hence lower Cmin, would be sufficient to achieve the target AUC/MIC ratio. By contrast, if the MIC is ≥1, it has been shown that it is almost impossible to achieve the target AUC/MIC ratio in most patients using usual vancomycin dose in patients with normal renal function, and therefore the use of vancomycin should be discouraged in such patients.[8] Therefore, trying to achieve an $AUC_{24} \geq 400$ mg·h/L is kind of the worst-case scenario in vancomycin dosing.

Finally, this study was performed in the setting of a "trough-only" monitoring approach for vancomycin therapy, without subsequent PK interpretation. Instead of using a surrogate marker of the AUC, it is preferable to directly estimate the AUC. PK methods and user-friendly software tools are available for doing so, based on minimal sampling, as reviewed by Pai et al.[9] Based on our local experience, we may recommend the use of dosing software using Bayesian estimation for AUC determination, such as BestDose. Reliable estimates of AUC can be obtained based on only 2 or even 1 measured concentration, which can be collected at any time and before the SS is reached.[19] This flexibility is an advantage in routine clinical practice. The drug dosage can then be adjusted precisely if necessary. TDM assisted with Bayesian dose adjustment is considered as a state-of-the-art approach for dose individualization of vancomycin and other antiinfective drugs.[25,26]

CONCLUSION

To conclude, in this study undertaken in elderly patients treated with intermittent IV vancomycin, Cmin was a poor quantitative predictor of AUC_{24}, but achieving Cmin ≥ 15 mg/L was associated with a high rate of $AUC_{24} \geq 400$ mg·h/L. However, a significant proportion of patients achieved $AUC_{24} \geq 400$ mg·h/L with lower trough concentrations. Vancomycin trough concentrations above 10.8 mg/L were found to be optimal for achieving the AUC target of 400 mg·h/L, and this target may be safer in terms of nephrotoxicity.

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