Vancomycin serum concentrations do not adequately predict tissue exposure in diabetic patients with mild to moderate limb infections

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Objectives: Vancomycin is a common treatment for complicated skin and skin structure infections (cSSSIs) caused by MRSA. This analysis aimed to understand the variability of vancomycin tissue exposure at the site of infection.

Methods: Vancomycin serum and interstitial tissue fluid concentration data for nine patients with cSSSI and normal renal function were derived from an in vivo microdialysis study. Using Pmetrics, the non-parametric population modelling package for R, we co-modelled serum and tissue concentration data. A 5000-patient Monte Carlo simulation was conducted for 1 g of vancomycin every 12 h and every 8 h to calculate the penetration distribution (AUCtissue/AUCserum) and probability of target attainment (PTA) at an fAUC/MIC target of ≥200 in tissue fluid.

Results: A three-compartment model fitted the data best. The mean (SD) and median penetration ratios into tissue of the simulated population were 1.91 (4.56) and 0.85, respectively, which were consistent with observed values in the original patients. PTAs for 1 g of vancomycin every 12 h and every 8 h in tissue fluid were 39.6% and 56.6% at an MIC of 1 mg/L. Serum trough concentrations ($R^2 = 0.06$) and serum AUC exposure ($R^2 = 0.002$) were poor predictors of vancomycin AUC tissue exposure.

Conclusions: Standard dosages of vancomycin provide a low likelihood of obtaining target pharmacodynamic exposure in the tissue of a lower limb infection. This low likelihood is due to wide variability in vancomycin penetration in the interstitial tissue fluid, which could not be predicted by serum concentrations.

Keywords: skin infections, population pharmacokinetics, penetration, Staphylococcus aureus

Introduction

Given the common threat of MRSA as a cause of complicated skin and skin structure infections (cSSSIs), vancomycin has become one of the most widely used antimicrobials to empirically treat this infection. Unlike linezolid and tigecycline, which have similar or greater drug exposure in the interstitial space of infected soft tissue compared with that in serum, there is some evidence that vancomycin penetrates poorly to the site of infection. Understanding the pharmacokinetics of vancomycin in infected tissue may help to understand if appropriate pharmacodynamic targets are readily achievable at the site of infection and if therapeutic monitoring in serum is predictive of tissue exposure. Our group has reported the mean tissue exposure of vancomycin in nine diabetic patients with lower-extremity wound infections utilizing in vivo microdialysis. Using non-compartmental pharmacokinetic methods, we observed a mean (standard deviation) penetration ratio equal to 0.8 (0.2), which was based on the ratio of the area under the curve (AUC) in tissue to the free AUC (fAUC) in serum. The current analysis aimed to fit these data to a population model and then simulate tissue exposure for common vancomycin dosing regimens, thereby addressing questions of penetration variability and probability of achieving requisite exposures at the site of infection.

Methods

Patients and setting

Serum and tissue concentrations for vancomycin were acquired from patients participating in an open-label pharmacokinetic study at Hartford Hospital, Hartford, CT, USA, as previously described. This study was reviewed and approved by the Hartford Hospital Institutional Review Board. All patients provided written informed consent to participate.
Population pharmacokinetics

Vancomycin serum and tissue fluid concentrations were co-modelled using the Non-parametric Adaptive Grid program with Adaptive Gamma in the Pmetrics package for R (version 1.2.9). Two- and three-compartment models with zero-order input and first-order elimination were explored. A total of 91 serum and tissue fluid concentrations from nine patients were used to construct the model. Weighting was done using a multiplicative random error term attributed to the drug assay and additional process noise. Pmetrics weights each observation by the reciprocal of this total interday assay variance, calculated as (∑y×SD), where SDserum = (0.037 + 0.0245×C1) and SDtissue = (0.00682 + 0.0309×C2). C1 and C2 are the vancomycin concentrations in serum and tissue fluid, respectively, and γ represents residual process noise. The best-fit model was determined by the rule of parsimony and the lowest Akaike’s information criterion (AIC) score. Predictive performance of the final model was based on the mean weighted predicted−observed error (bias) and bias−adjusted, mean weighted squared predicted−observed error (imprecision).

Monte Carlo simulations

A 5000-patient Monte Carlo simulation was conducted using the Pmetrics simulator to simulate steady-state serum and tissue concentrations every 15 min after the fifth dose of 1 g of vancomycin every 12 h or the seventh dose of 1 g of vancomycin every 8 h. The AUC in serum (AUCserum) and tissue fluid (AUCtissue) for the dosing interval was calculated by the trapezoidal rule for all 5000 simulated patients. We assumed that vancomycin concentrations in tissue were already representative of free, unbound, active drug. Serum concentrations were corrected assuming a fraction unbound of 0.5 in order to estimate the free AUCserum (fAUCserum).9

Pharmacodynamic analyses

The penetration ratio was calculated for each simulated patient as the AUCtissue/fAUCserum for the dosing interval. The mean, standard deviation (SD), median and 10th and 90th percentiles are reported. The probability of target attainment (PTA) was calculated to determine the likelihood of each drug regimen achieving threshold exposures in serum and tissue. For vancomycin, the total drug serum AUC/MIC ratio is predictive of positive clinical response across a range of infections. The most common total drug AUC0–24/MIC threshold reported is 400;10 therefore, after correcting this threshold for the fraction unbound, an fAUC0–24/MIC of ≥200 was targeted in this pharmacodynamic analysis for both serum and tissue fluid. The PTA was queried for MICs from 0.25 to 4 mg/L. In line with the common clinical practice of measuring vancomycin trough concentrations, the PTA in tissue was also estimated for those achieving a trough between 15 and 20 mg/L. Linear regression was employed to determine a relationship between simulated vancomycin trough concentrations and AUC0–24 in tissue fluid, as well as serum AUC0–24 versus tissue fluid AUC0–24.

Results

Patient characteristics

The mean (SD) age, total body weight, ideal body weight, BMI, creatinine clearance (CLCR) and mg/kg dose of vancomycin for the nine patients were 54 (19) years, 105.6 (31.5) kg, 70.7 (11.1) kg, 34.1 (9.5) kg/m², 101 (33) mL/min and 12.8 (3.9) mg/kg, respectively.

Population pharmacokinetics

A three-compartment base model fitted the data best. The value for γ was 3.98, suggesting that reasonable residual or environmental process noise was present. The observed versus population-predicted concentrations in serum were reasonable with R², bias and imprecision values of 0.52, 3.85 and 84.2, respectively. The MAP Bayesian observed versus predicted concentration plot in serum was excellent with R², bias and imprecision values of 0.975, −0.101 and 1.09, respectively. In the intestinal tissue fluid, these values were 0.319/0.302, 10.2/0.886 and 0.04/1.16, respectively, for population-predicted and MAP Bayesian-predicted versus observed concentrations. The final mean (SD) parameters were: CL = 5.98 (3.00) L/h, Vc = 22.86 (19.36) L, Vtissue = 46.71 (27.82) L, k12 = 2.15 (1.89) h⁻¹, k21 = 2.29 (2.05) h⁻¹, k13 = 1.11 (0.64) h⁻¹ and k31 = 1.19 (1.27) h⁻¹, where CL is clearance, Vc is the volume of the central compartment, Vtissue is the volume of the sampled tissue fluid compartment, k12 and k21 are transfer rate constants between central and peripheral compartments, and k13 and k31 are transfer rate constants between central and sampled tissue fluid compartments. Based on the individual patient pharmacokinetic parameter estimates, the mean (SD) and median penetration ratios for the nine patients were 1.03 (0.33) and 1.00, respectively.

Monte Carlo simulations

The mean (SD) and median penetration ratios for 5000 simulated patients were 1.91 (4.56) and 0.85, respectively. The 10th and 90th percentiles for penetration were 0.25 and 3.75, respectively. Table 1 provides results for PTA in serum and tissue. In simulated patients obtaining a serum trough of 15–20 mg/L, the PTA in tissue for 1 g every 12 h was 97.9%, 90.8%, 59.9%, 22.2% and 6.3% at MICs of 0.25, 0.5, 1, 2 and 4 mg/L, respectively. The PTA in tissue for a 1 g every 8 h regimen was 99.9%, 89.9%, 67.3%, 33.0% and 10.1% at these MICs, respectively. Figure 1(a) displays the simulated vancomycin serum trough concentration for 1 g every 12 h versus the tissue fluid AUC0–24. Figure 1(b) displays the results from simulated serum AUC0–24 versus tissue fluid AUC0–24.

Discussion

Using the population pharmacokinetic parameter estimates from nine patients with lower limb infections, we simulated the probability of achieving pharmacodynamic AUC/MIC exposure≥200 in serum and tissue fluid for dosing regimens of vancomycin of 1 g every 12 h and every 8 h. Table 1. Probability of achieving pharmacodynamic AUC/MIC exposure≥200 in serum and tissue fluid for dosing regimens of vancomycin of 1 g every 12 h and every 8 h

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>1 g every 12 h</th>
<th>1 g every 8 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA (%)</td>
<td>fAUCserum/MIC</td>
<td>fAUCtissue/MIC</td>
</tr>
<tr>
<td>0.25</td>
<td>99.7</td>
<td>87.0</td>
</tr>
<tr>
<td>0.5</td>
<td>89.9</td>
<td>67.3</td>
</tr>
<tr>
<td>1</td>
<td>31.5</td>
<td>39.6</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>16.9</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>5.8</td>
</tr>
</tbody>
</table>

aFor serum, an fAUC/MIC ratio was the targeted threshold; therefore, simulated total drug concentrations were corrected for a fraction unbound of 0.5 prior to analysis. For tissue fluid, it was assumed that simulated tissue fluid concentrations were unbound, so no further correction prior to calculation of the AUC was conducted.
vancomycin AUC exposure in serum and interstitial tissue fluid, as well as the penetration ratio into tissue fluid. The simulated mean (SD) and median penetration of vancomycin into the interstitial tissue fluid of the nine patients was 1.03 (0.33) and 1.00, with a range of 0.56–1.68. Not surprisingly, the Monte Carlo simulation displayed a wider range of penetration, given that outliers can be included in the final 5000-patient subset. As a result, the mean (SD) and median penetration ratios were 1.91 (4.56) and 0.85, respectively, and the 10th and 90th percentiles for penetration were 0.25 and 3.75, respectively. These estimates suggest that nearly half of patients receiving vancomycin for cSSSI may have exposure in the interstitial tissue fluid that is lower than observed in serum.

Although penetration into interstitial tissue fluid was observed to vary widely, it is the actual pharmacodynamic exposure at the site of infection that is important for antibiotic efficacy.11 Vancomycin efficacy against Staphylococcus aureus is predicted by a serum total drug AUC/MIC ratio of at least 400 in most studies.10 However, the target exposure in tissue has not been established. We assumed that the exposure needed in tissue fluid would be similar to serum for this analysis and that vancomycin concentrations in tissue fluid collected via microdialysis were unbound. As demonstrated in Table 1, the likelihood of achieving an fAUC/MIC ≥200 in tissue fluid declines as the MIC increases, but not as rapidly as the decline in serum. At an MIC of 1 mg/L, the PTA in tissue fluid was 39.6% and 56.6% for a 1 g every 12 h regimen and a 1 g every 8 h regimen, respectively. PTAs declined to 16.9% and 29.4%, respectively, at an MIC of 2 mg/L. For simulated patients achieving a serum trough concentration of 15–20 mg/L, PTAs improved only modestly. These low PTA results are notable, as most contemporary studies report the vancomycin MIC90 against S. aureus as 1 mg/L.12–14

We also estimated the value of serum trough concentrations or serum AUC exposure in predicting AUC in interstitial tissue fluid. As demonstrated in Figure 1(a and b), vancomycin exposure in serum was not predictive of obtainable exposures in tissue fluid. These data collectively suggest a low and variable probability of standard vancomycin dosing regimens achieving this pharmacodynamic exposure against most S. aureus that cannot be improved by therapeutic drug monitoring alone. It is possible that the pharmacodynamic exposure required to kill S. aureus in skin infections is less than the target applied here, particularly when the local immune response and supportive wound care (e.g. surgery, drainage, dressing changes) are also considered. Additional studies to define the pharmacodynamic exposure in tissue fluid required for clinical efficacy for the treatment of cSSSI are still needed.

In summary, these data suggest that standard dosages of vancomycin provide a low likelihood of obtaining target pharmacodynamic exposure in the tissue of a lower limb infection; furthermore, therapeutic drug monitoring based on serum concentrations are unlikely to predict tissue fluid concentrations.

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Transparency declarations
None to declare.

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