Pharmacokinetic and pharmacodynamic evaluation of vancomycin for the prophylaxis of surgical site infections in morbidly obese patients

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ABSTRACT

Objectives: With the increasing prevalence of MRSA worldwide, there is also an increasing need for vancomycin (VAN) prophylaxis to prevent surgical site infections. Dosing of VAN at 15 mg/kg in the obese population may require larger than usual doses to be administered. The aim of our study was to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of a weight-based 15 mg/kg dose versus a fixed dose approach of 2000 mg in the morbidly obese population. Those results were then compared with the VAN PK/PD for an 80 kg patient.

Methods: Models of VAN established in morbidly obese and a model for an 80 kg patient were used in this analysis. Concentrations of VAN in interstitial fluid were calculated for a body weight of 80 kg, then for 160 kg to 260 kg at 20 kg intervals. Doses of 15 mg/kg based on total weight and the fixed dose of 2000 mg were evaluated for probability of target attainment (PTA) with Monte Carlo Simulation (n=5000) for the following indices: 1.) attaining concentrations over the MIC of 1 mg/L within 90 minutes of the start of infusion; 2.) target attainment for *ƒ*AUC0-12h/MIC of 100 or greater at the MIC of 1 mg/L; and 3.) maintaining concentrations of greater than the MIC of 1 mg/L at 6 and 12 hours after the start of infusion.

Results: Simulations showed the PTA of interstitial fluid concentrations of 1 mg/L or higher within 90 minutes was predicted in 98% of 80 kg patients and an average of 97% for the fixed 2000 mg and for the weight based dosing in the morbidly obese patients.

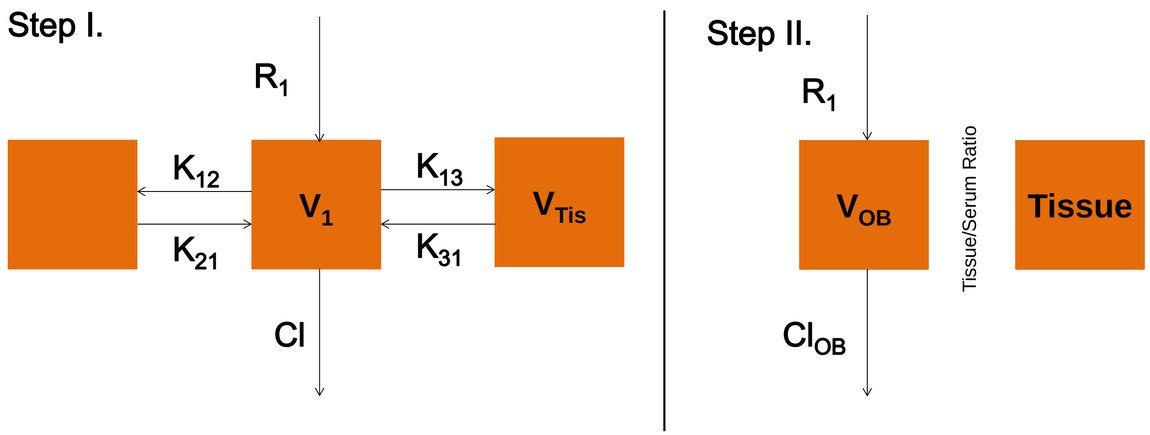
The PTAs are 87.1% and 74.7% for maintenance of interstitial fluid concentrations above the MIC of 1 mg/L for 80 kg patients at 6 and 12 hours. For the morbidly obese, the fixed approach resulted in PTAs over 94% and 88% at 6 and 12 hours, respectively. All weight-based regimens in the obese exceeded the PTA values generated by the fixed regimen at both time points for this target. The weight-based and fixed regimen's PTAs both exceeded the PTAs of the 80 kg patients for the target of *ƒ*AUC0-12h/MIC of 100 or greater based on interstitial fluid levels.

Conclusion: In silico simulations for both the 15 mg/kg weight-based regimen and 2000 mg fixed VAN dosing approach resulted in adequate tissue penetration and drug exposure for the prophylaxis of surgical site infections in morbidly obese patients when compared to non-obese patients. Capping the dose at 2000 mg appears reasonable based on the results, which may allow for the standardization of the dosing of VAN in this particular setting and population of patients.

INTRODUCTION AND METHODS

- VAN is widely used for the prevention of surgical-site infections
- Current guideline recommendation for dosing of VAN for surgical site infections is a weight-based 15 mg/kg dose
- No limitation in dose has been established for the obese population.
- The objective of our study was to compare the PKPD target attainment of a 15 mg/kg weight-based approach with a fixed 2000 mg regimen between 80 kg and obese patients.
- The R® software application and deSolve package was used to build the structural model for the pharmacokinetic analysis of VAN.[1]
- Step I. VAN serum and tissue concentration time profiles were simulated for patients using the published population pharmacokinetic model from diabetic patients of mild to moderate limb infections.[2] The results of these simulations were used to calculate tissue/serum penetration ratios.
- Step II. VAN serum concentration time profiles were simulated for an 80 kg (reference) and morbidly obese patients for weight based and fixed dosing regimens, which were later multiplied by the tissue/serum penetration ratios from Step I. at 15 minute intervals to estimate interstitial fluid levels in the morbidly obese.[3,4]
- PTAs in tissue for achieving > 100 $AUC_{0\text{-}12}$/MIC ratios, attaining concentrations over the MIC of 1 mg/L within 90 minutes of the start of infusion, and maintaining concentrations of greater than the MIC of 1 mg/L at 6 and 12 hours after the start of infusion were calculated with Monte Carlo Simulation.

METHODS



R1 represents the intravenous infusion rate of VAN, *Cl* is the clearance, *V1* is the volume of the central compartment ,*VTis is* he volume of the tissue compartments, *K1-2* and *K1-3* are the inter-compartmental transfer rate constants, *ClOB* is the clearance of vancomycin for the morbidly obese patients, *VOB* is the volume of the central compartment for the morbidly obese patients, *Tissue* is the tissue compartment for the obese patients

Figure 1. Structural mathematical model applied in this analysis

RESULTS

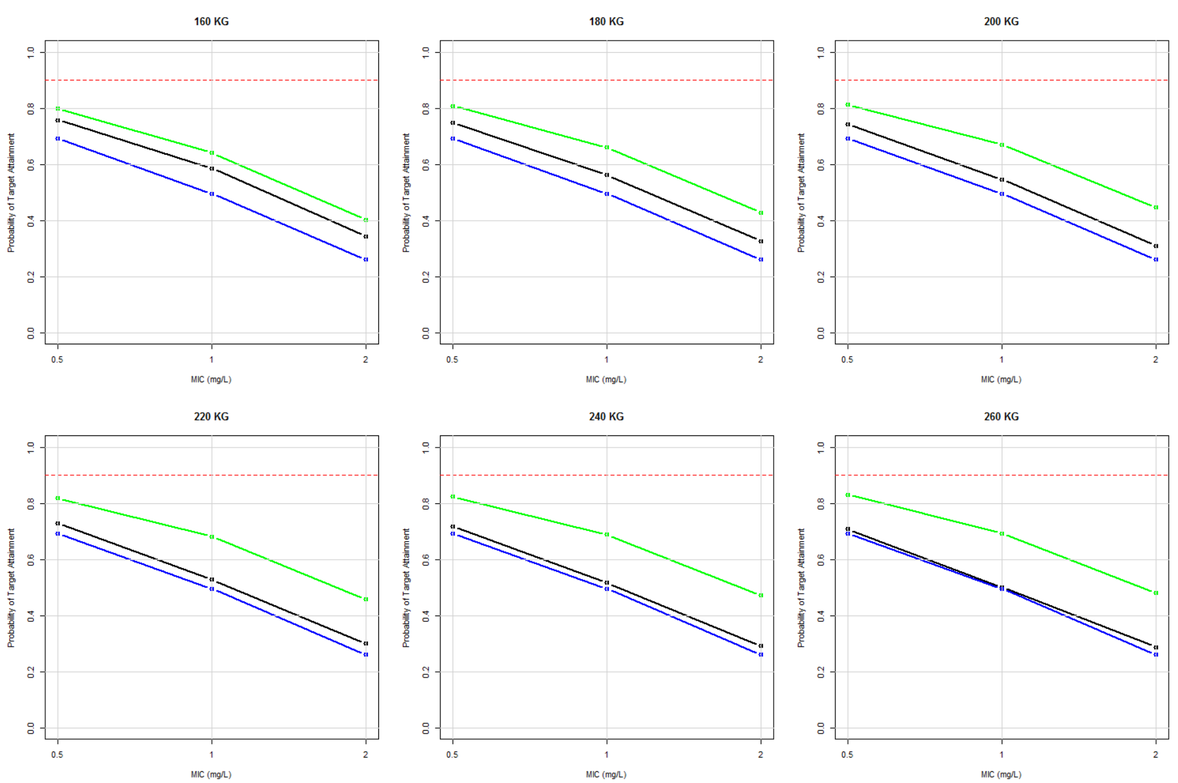


Figure 2 . PTAs in tissue for the $ƒAUC_{0\text{-}12}$/MIC ratio of >100 for the fixed dose of 2000 mg (black), weight based dose of 15 mg/kg (green), and 15 mg/kg for 80 kg weight reference (blue)

RESULTS

Figure 3. PTAs of attaining tissue concentrations greater then 1 mg/L in 90 minutes

Figure 4. PTAs of maintaining tissue concentrations greater then1mg/L at 6 hours after infusion

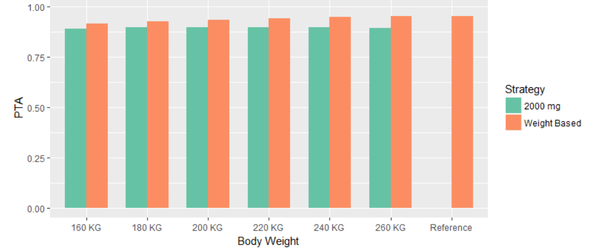


Figure 5. PTAs of maintaining tissue concentrations greater then1mg/L at 12 hours after infusion

CONCLUSION

Based on interstitial fluid levels, a fixed-dose approach of 2000 mg in the obese population ranging from 160-260 kg exceeded the PTAs of the 80 kg patients at both 6 and 12 hours. Based on the results of these models, limiting the dose of VAN in the obese population to 2000 mg for surgical prophylaxis appears reasonable.

A fixed-dose approach of 2000 mg for the obese population for surgical prophylaxis with VAN may be desirable for institutions. This standardization will allow for decreased labor and resources for compounding and preparation; minimize unnecessary drug exposure; and avoid the delay of a procedure due to VAN's limitations in infusion rate.

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