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

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Background: With the increasing incidence of MRSA worldwide, there is also an increased 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 of2000 mg in the morbidly obese population. Those results were then compared with the VAN PK/PD for an 80 kg patient.

Material/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 140 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 $\int AUC_{0\text{-}12h}$/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 $fAUC_{0\text{-}12h}$/MIC of 100 or greater based on interstitial fluid levels.

Conclusions: 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.