

Utility of Vancomycin Loading: A Pharmacokinetic Analysis in Critically Ill Patients

Investigators:

Roy T. Hendley, M.S., Pharm.D.¹, Jeffrey J. Bruno, Pharm.D., BCPS, BCNSP¹, Timothy Madden, Pharm.D., DABCP, FCCP²; Elizabeth Coyle, Pharm.D., BCPS³, Mike Hernandez, MS⁴; Carla Baker, RN, APN⁵; Ara A. Vaporciyan, M.D., F.A.C.S⁵

¹ Division of Pharmacy, UT M. D. Anderson Cancer Center

² Department of Experimental Therapeutics, UT M. D. Anderson Cancer Center

³ Department of Pharmacy, University of Houston, College of Pharmacy

⁴ Department of Biostatistics, UT M. D. Anderson Cancer Center

⁵ Department of Thoracic Surgery, UT M. D. Anderson Cancer Center

Since the appearance of methicillin resistant *S. aureus* (MRSA) in 1961, MRSA has become widespread in hospitals and corresponds to the most common cause of bacterial nosocomial infection. Patients who receive a delay in appropriate treatment are at higher risk to develop secondary complications such as abscesses, septic shock and death. There is growing evidence of a vancomycin MIC “creep” in various MRSA isolates. For example, a study from UCLA Medical Center showed that there was a shift in vancomycin MICs from ≤ 0.5 to 1mg/L during a 5-year study. Further, a study from University of Texas M. D. Anderson Cancer Center (MDACC) demonstrated from 1985 to 2004 the number of MRSA isolates with an MIC ≥ 1 mg/dL increased significantly by 81%. Recent consensus guidelines recommend vancomycin trough concentrations between 15 and 20 mg/L and a 24 hour area under the curve (AUC₂₄) / minimum inhibitory concentration (MIC) ratio of greater than 400 mcg•h/mL for treatment of MRSA. However, animal and human data have suggested that monitoring vancomycin via an AUC₂₄/MIC correlated best with bacterial kill and clinical outcomes, respectively. Recent published literature has eluded for the need of loading doses with 25-30 mg/kg to attain the target AUC₂₄/MIC; however, only simulated data exists advocating the potential benefit of this suggested loading dose. Further, limited data suggest that higher vancomycin trough values (> 15 mg/L) are associated with higher rates of nephrotoxicity.

The purpose of this pilot observational study will be to demonstrate the utility of an intravenous vancomycin loading dose for attaining target therapeutic troughs and an AUC₂₄/MIC ratio more rapidly and efficiently. The study is designed as an open-label, single-center, prospective, pilot study estimated to complete accrual within 6 months of activation. Ten total patients will receive a loading dose of 30 mg/kg based upon actual body weight. Beyond the first dose, patients will then receive the standard dose of 15 mg/kg according to standard practice. Renal function will determine dosing frequency. A nursing protocol will be utilized to ensure proper vancomycin administration, documentation for pharmacokinetic analysis, and acquisition of serum vancomycin samples. Further, that protocol will describe procedures for proper storage and delivery of samples to the processing laboratory to ensure viability and accuracy of serum sample.

The primary objective will be to evaluate the percent of patients attaining a target trough of 15 to 20 mg/L following the 30 mg/kg vancomycin loading dose. The secondary objectives will include evaluation of: 1) the number of total vancomycin doses needed for attainment of a target trough, 2) the number of patients requiring an increase or decrease in dose following the 4th dose, 3) the calculated AUC₂₄/MIC for each theoretical vancomycin MIC breakpoint (i.e. 0.5, 1, 2 mg/L), 4) the percent of calculated AUC₂₄/MIC > 400 mcg•h/mL for each theoretical vancomycin MIC breakpoint (i.e. 0.5, 1, 2 mg/L), 5) nephrotoxicity as defined by “Injury” utilizing the R.I.F.L.E. criteria, and 6) adverse drug reaction (ADR) rates secondary to study drug.

The working hypothesis of this study is the administration of a vancomycin loading dose of 30 mg/kg will result in attainment of the target serum trough level of 15 to 20 mg/L in 50% of study patients and will not compromise renal function.