

# Central nervous system pharmacodynamics of intraventricular doses of Vancomycin in neurosurgical patients with external ventricular drains

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## ABSTRACT

**Background:** Vancomycin (VAN) is a glycopeptide antibiotic with a sustained susceptibility profile against gram-positive organisms commonly identified in hospital-acquired central nervous system (CNS) infections. The aim of our study was to describe the Cumulative Fraction of Response (CFR) achieved by concomitant intravenous and intraventricular (IVC) VAN dosing regimens against a population of *Staphylococcus aureus* (SA) isolates in US and European medical centers.

**Methods:** A CNS population pharmacokinetic model in post-neurosurgical patients with external ventricular drains and a recent SA VAN MIC distribution were used in this analysis. A target attainment for selected pharmacodynamic indices in the CNS was established using data from patients with predicted VAN serum trough concentrations of 15 to 20 mg/L. Probability of Target Attainment (PTA) and CFRs in the CNS for achieving 5, 10, 15 and 20 times the trough over MIC ratios were calculated with Monte Carlo Simulations for IVC VAN doses of 5 mg to 20 mg daily at 1 mg intervals.

**Results:** Optimal PTAs were predicted to be achieved up to an MIC of 0.5 mg/L for all IVC doses and for the target trough/MIC > 5. At an MIC of 1 mg/L and for the same target, the PTAs were over 90% for doses greater than 10 mg. Doses 11 mg and higher are also expected to achieve optimal target attainment at the MIC of 0.5 mg/L and the target of trough/MIC > 10. All IVC doses and at all other targets evaluated showed suboptimal PTAs. When evaluated against the population of SA MICs, doses greater than 10 mg showed CFRs of 90% or higher at the target trough/MIC > 5. All CFRs are expected to be below the values of 80%, 60%, and 40% for the targets of trough/MIC > 10, trough/MIC > 15 and trough/MIC > 20, respectively.

**Conclusion:** Commonly used IVC doses of VAN achieve a permissive pharmacodynamic index of trough/MIC > 5 and provide reasonable coverage in neurosurgical patients with external ventricular drains up to an MIC of 0.5 mg/L for the treatment of SA CNS infections. However, the results are less impressive for more conservative targets, which demonstrates the need to utilize the more aggressive dosing regimens. When selecting an empiric dose of VAN via the IVC route, CFR estimates suggest using a dose of at least 20 mg to maximize the chance of optimal target attainment.

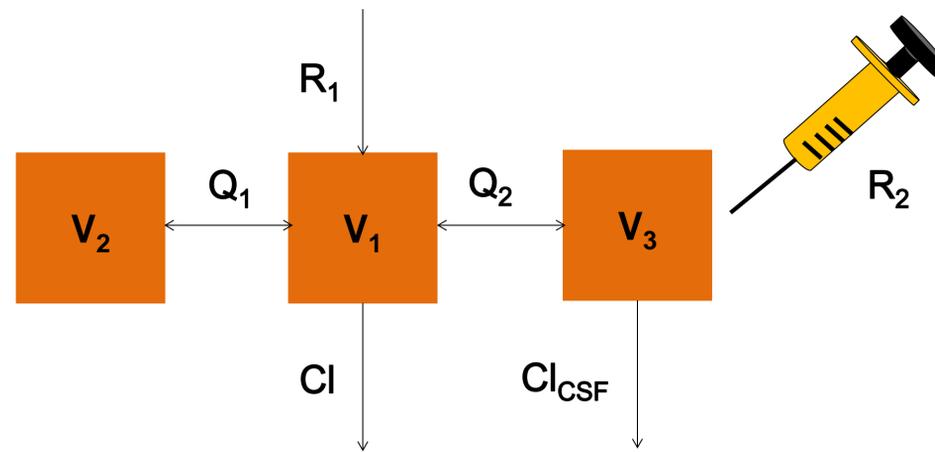
## INTRODUCTION AND OBJECTIVES

- The use of IVC VAN has become increasingly common due to the use of intracranial devices, toxicities of systemic vancomycin, and nosocomial pathogens such as SA
- Dose ranges for IVC VAN have been evaluated in the literature, but vary widely and PTAs and CFRs are not well-established
- Monitoring of CNS levels have reported in several studies, but levels were variable with no clear relationships between concentration data, MIC, efficacy, or toxicity
- The objective of this study was to use a CNS population pharmacokinetic model in post-neurosurgical patients and a recent SA VAN MIC distribution to establish PTAs and CFRs of IVC doses of VAN.

## METHODS

- The R<sup>®</sup> software application and deSolve package was used to build the structural model for the pharmacokinetic analysis, where an input event was added to the base model representing periodic administration of IVC VAN.<sup>1</sup>
- VAN serum and CSF concentration time profiles were simulated for patients using the published population pharmacokinetic model from neurosurgical patients with external ventricular drains.<sup>2</sup>
- The subset of patients with predicted trough concentrations of 15 to 20 mg/L were selected for further analysis
- PTAs and CFRs in the CNS for achieving 5, 10, 15 and 20 times the trough over MIC ratios were calculated with Monte Carlo Simulation for intraventricular VAN doses of 5 mg to 20 mg daily at 1 mg intervals

## METHODS



$R_1$  represents the intravenous infusion rate of VAN,  $Cl$  is the clearance,  $V_1$  is the volume of the central compartment,  $V_2$  is the volume of the peripheral compartments,  $V_3$  is the volume of the central nervous system compartments,  $Q_1$ - $Q_2$  are the inter-compartmental clearances,  $Cl_{CSF}$  is the clearance of vancomycin from the CSF compartment through the ventricular drain,  $R_2$  is the infusion rate of the intra-ventricular VAN

Figure 1. Structural mathematical model applied in this analysis

## RESULTS

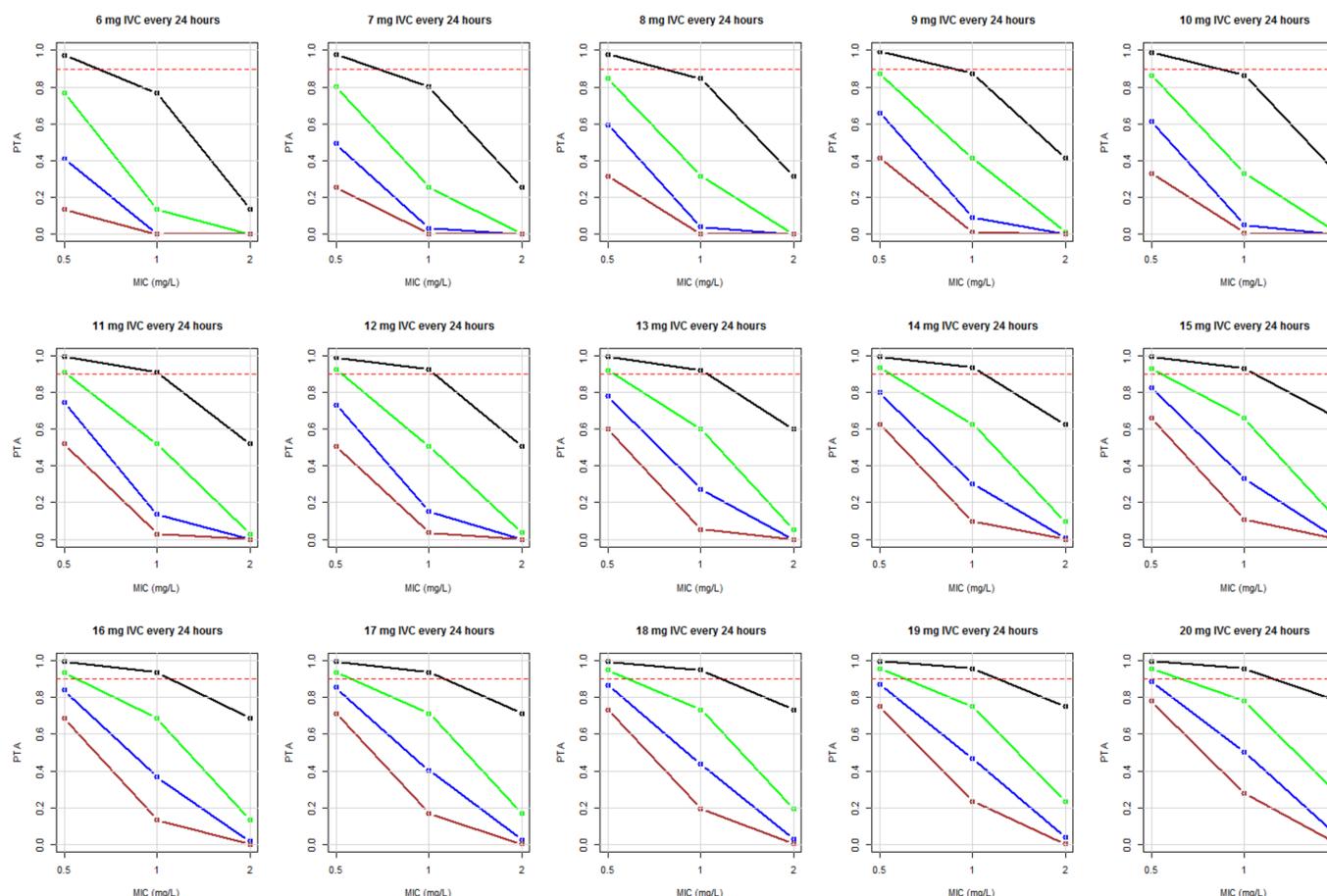


Figure 2. PTAs for the pharmacodynamic index of TROUGH/MIC ratio of 5 (black), 10 (green), 15 (blue), and 20 (brown) in the CSF

## RESULTS

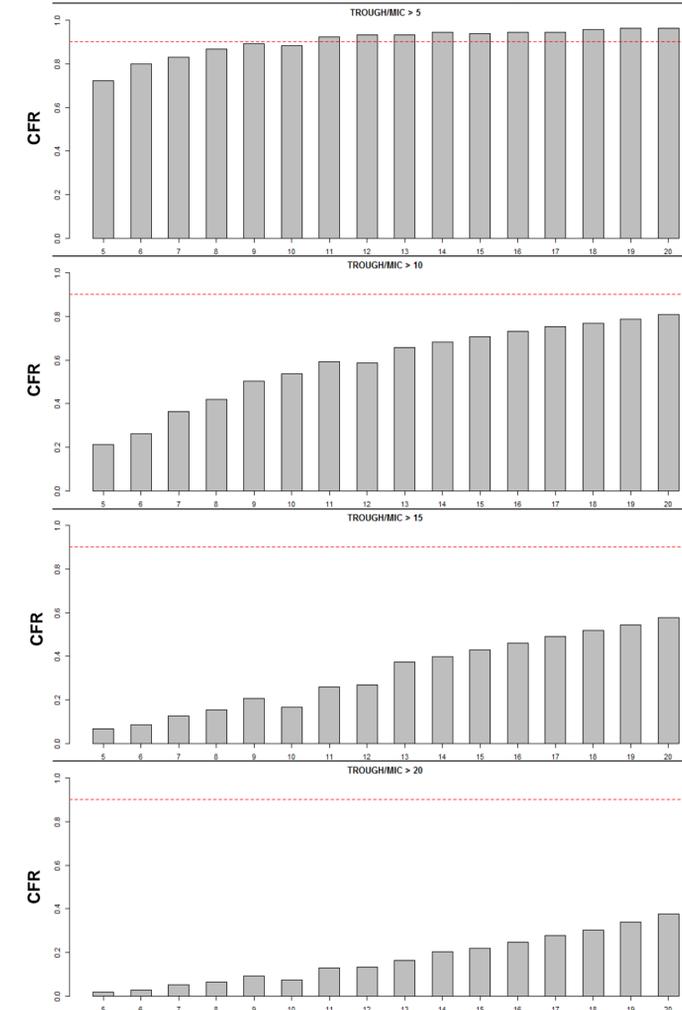


Figure 3. CFRs of daily IVC VAN regimens at the specified target

## CONCLUSION

PTAs for commonly used IVC doses of VAN achieved a permissive pharmacodynamic index of trough/MIC > 5 and provided reasonable coverage in neurosurgical patients up to an MIC of 0.5 mg/L for the treatment of SA CNS infections. However, the results are less impressive for more conservative targets, which demonstrates the need to utilize the more aggressive dosing regimens. When selecting an empiric dose of VAN via the IVC route, CFR estimates suggest using a dose of at least 20 mg to maximize the chance of optimal target attainment. More studies are required to establish higher dosing ranges above 20 mg.

## REFERENCES

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