



Population Pharmacokinetics of Vancomycin in Tunisian Patients

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INTRODUCTION

Vancomycin (VCM) is a glycopeptide antibiotic generally used for the treatment of gram-positive infections it's widely prescribed for sepsis

AIM

The purpose of this study is to investigate the population pharmacokinetic of

VCM in a population of Tunisian patients to identify the covariates that influenced pharmacokinetic parameters and for individualized optimal VCM dosage

MATERIAL AND METHODS

PATIENTS AND PROTOCOL

- Population pharmacokinetics of VCM was investigated in 202 patients aged from eight month to 64 years (40 ± 20 years), following sepsis.
- Dose of VCM was varied between 0.04 to 6 g per day with median equal to 1.5 g and was administered by intravenous infusion.
- Patients benefited from two plasma samples:
 - T0 immediately before VCM infusion
 - Tmax: 60 minute following completion of VCM infusion.
- The serum concentrations of VCM were measured by a fluorescence polarization (Axym® Abbott).
- The population data set comprised 473 concentration measurements

PHARMACOKINETIC ANALYSIS

- To assess the VCM pharmacokinetic profile of each patient, individual analysis of the blood concentration data were performed by nonlinear regression using **NONMEM VI software** (NONMEM Project Group, University of California, San Francisco, USA).
- The population means parameters; between-subject variance and residual variance were estimated using the first order conditional estimate (FOCE) interaction method (residual intraindividual variability was modeled as log-normally distributed, by log transforming the concentrations and the using an exponential model to describe residual variability of VCM concentration using the PREDPP subroutine ADVAN 1 of NONMEM VI (level 1.1).
- Convergence criterion was three significant digits and MAXEVAL=9000. Microsoft windows Vista™ was used to compile and execute NONMEM.

- The structural model was established initially, followed by development of the covariate model.
- The following clinical factors were tested for their influence on clearance (CL) and volume of distribution (V): sex; age, weight and creatinine clearance.
- Model comparisons were based on the change in objective function value (OFV).

RESULTS AND DISCUSSION

Figure 1: Scatter plots of population model predicted concentration (PRED) versus observed concentrations (DV)

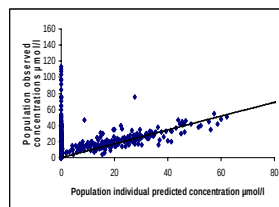
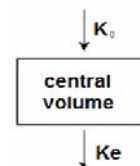


Figure 2: Representation of the selected model with one compartment.



Ke: elimination rate constant from the central compartment.

VC: central volume of distribution.

- A one compartment population pharmacokinetic model described the VCM concentration-time data.
- Several pharmacokinetic models (one, two and three-compartment) have been used to describe VCM pharmacokinetic profile. However, in clinical setting the one and two compartment models are the most used
- A good correlation was obtained between Bayesian-estimated and experimental observation ($R^2 = 0,84$, $p < 0,01$).
- Estimates of mean pharmacokinetic parameters were shown on the table below.

	CL (l/h)	V1 (l)	Ke (h ⁻¹)
MEAN	4.09	55.10	0.058
Inter-individual variability CV%	59.3	320	-

- Covariate selection revealed that total body weight (TBW) affected V, and creatinine clearance influenced VCM clearance
- In the other studies the covariates cited were age, TBW influenced V or creatinine clearance influenced VCM clearance

CONCLUSION

The models could be used to estimate appropriate VCM dosage guidelines, which are not clearly defined for this high-risk population. Their simple structure should allow easy implementation in clinical software and application to dosage individualizes using Bayesian approach.

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