Population pharmacokinetics of gentamycin in hospitalized ICU patients

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Objectives

To develop a Pop0PK model of gentamycin in ICU patients with either obesity, sepsis or acute respiratory distress syndrome, while some undergoing hemofiltration. Gentamycin is a well studied hydrophilic antibiotic, thus in these special conditions the pharmacokinetic profile of the drug may be altered, therefore a different dosing regimen could be required

Methods

PK data of gentamycin were obtained from 82 hospitalized ICU patients. Dosing regimen was 7 mg/kg as a 1 hour IV infusion. Samples were collected before the administration, at the end of infusion and 8-16 hours after the administration. Fluorometry with TDX analyzer was used for the quantification of gentamycin concentrations. Using the software NONMEM (ver 7.3) with FOCEI method, first a basic model was determined by trying out different compartmental structural models, error models, inter-individual and inter-occasion variability structures. Then statistically significant covariates were screened, including age, weight, and creatinine clearance. Diagnostic plots and Likelihood Ratio Test of OFV decline of at least 3.84 units for 0.05 level significance were used for covariate selection. The final PK model was validated using nonparametric bootstrapping and visual predictive check (VPC).

Patients	Number/ Average	Range
All the patients	82	-
Average age	61	16-87
Average weight	84	50-220
Creatinine clearance	68	10-464.42
Septic	34	-
Obese	24	-
Under continuous veno venous hemodiafiltration (CVVHDF)	42	-
Septic, obese and cvvhdf	5	-
None of the above (“cool”)	19	-

Table 1. General information about patients, and groups that were studied.

Results

The final model was a one compartment model with combined residual error, parameterized as clearance (CL) and volume of distribution (V).

Interindividual variability was included on CL and V. Covariance between CL and V was tested, but did not improve results. IOV (interoccasion variability) was examined in the model but eventually rejected due to high ETA-shrinkage and EPS-shrinkage.

The final model was

$$CL = \theta1 \times (WT/84)^{\theta3} \times (CrCl/68)^{\theta5} \text{ L/h}$$

$$V = \theta2 \times (WT/84)^{\theta4} \text{ L.}$$

Parameter values are shown in Table 1.

In bibliography it has been reported that aminoglycosides, therefore gentamicin, follow three compartment model (especially in decreased kidney function). Nevertheless, when administered as one hour infusion, the fastest phase is not observable due to fast equilibration between compartments, consequently one or two compartment models are candidates for best describing the data. Also, the two compartment model performed worse than the one-compartment in all diagnostic test including bootstrap.

Through covariate screening, weight and creatinine clearance had the biggest impact in OFV reduction. Other covariates like age and IBW caused reduction but not significant in order to include them in the model. Comparison between the groups of patients showed that responsible for the interaction of weight with V are the obese patients as no reduction of OFV was observed in the “normal weight” patients. Also, one could say that patients undergoing hemofiltration showed reduced interindividual variability on clearance compared to others. Furthermore according to results in table 3, septic patients seem to have bigger volume of distribution than the rest of the patients. It is worth mentioning that in bibliography the Vd for gentamicin is 0.25 L/kg , in contrast, in this research it appears to be 0.61 L/kg.

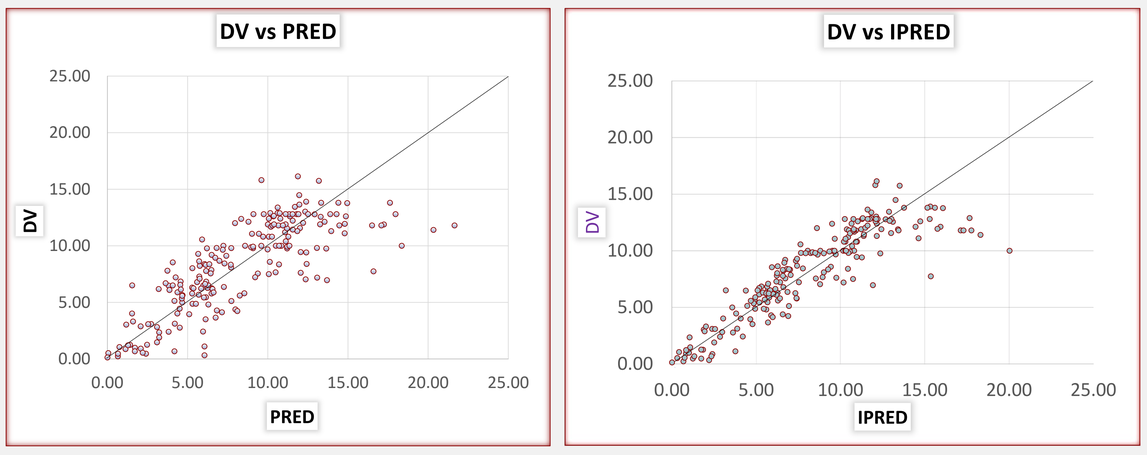
For the validation of the final model bootstrap ran successfully in 1000 out of 1000 bootstraps, with results presented at the table 2.

Tables and Figures

Table 2. Summary of estimates and bootstrap results for final PK model

Parameter(units)	Parameter estimate (RSE %)	Bootstrap average (95% CI) [CV]
Base model parameters		
θ_1 (L/h)	3.56 (5.4)	3.57 (3.17-3.97) [5.7]
θ_2 (L)	51.9 (2.6)	51.9 (49.4-54.9) [2.8]
θ_3	1.05 (30.9)	1.19 (0.61-2.17) [36.4]
θ_4	0.54 (19.1)	0.54 (0.32-0.91) [26.6]
θ_5	0.545 (18.5)	0.554 (0.31-0.80) [22.4]
Interindividual variability		
ω_{CL} (CV%)	29.8 (17.7)	0.272 (0.098-0.39) [26.7]
ω_V (CV%)	18.1 (31.5)	0.141 (0.03-0.26) [62.3]
Residual variability		
σ_1 (CV)	21.5 (14.1)	0.215 (0.15-0.28) [16.2]
σ_2 (CV)	1.0 (24.7)	0.93 (0.31-1.46) [32.5]

Figure 1. Goodness of fit plots for final PK model



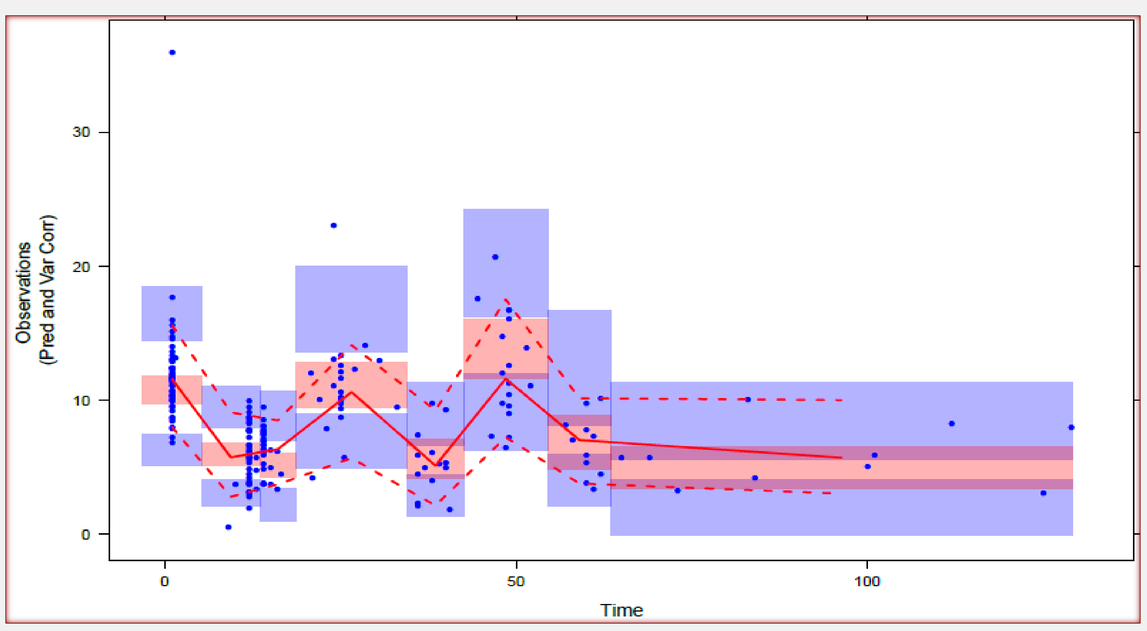


Figure 2 : The 5%, 50 and 95% percentiles of the observations (red lines) fall within the 95% confidence intervals of the corresponding prediction intervals of the model (shaded areas).

Parameters	Obese	Not obese	Septic	Not septic	Cvvhdf	Not cvvhdf	Cool
θ_1	3.94	3.67	3.37	3.74	2.78	3.63	3.70
θ_2	54.3	50.1	55.6	48.0	52.4	49.4	45.0
θ_3	0.534	2.19	1.04	1.31	0.354	1.43	1.47
θ_4	0.511	0.19	0.486	0.386	0.650	0.319	0.01
θ_5	0.378	0.577	0.584	0.526	0.01	0.505	0.388
ω_1	0.0316	0.211	0.361	0.225	0.304	0.317	0.270
ω_2	0.153	0.166	0.00316	0.192	0.00316	0.194	0.250
σ_1	0.115	0.268	0.235	0.210	0.212	0.240	0.251
σ_2	1.93	0.551	1.10	0.758	0.386	0.742	0.602

Table 3 : Model parameters for each group of patients.

Conclusions

A population pharmacokinetic model for gentamycin in ICU patients was developed which includes the effect of cretinine clearance and weight and can be used to determine dosing regimens in these patients by calculating AUC/MIC target attainment probability through Monte Carlo simulations and considering appropriate AUC/MIC targets from literature.