SUPPLEMENTARY FILE

Population pharmacokinetics with Monte Carlo simulations of gentamicin in an adult severely ill sub-Saharan African patient population

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Supplementary Information Methods

Population pharmacokinetic analysis

Structural model

One and two compartment models were tested. Estimated PK parameters were V, CL and, in case of testing of a two-compartment model, peripheral V and intercompartmental clearance. BPV of V and CL was estimated exponentially. [1]

The residual variability, i.e. the difference between measured gentamicin concentrations and the corresponding gentamicin concentrations predicted by the model, was modeled with additive or proportional models or a combination of both. The so-called M3 method was used for the handling of gentamicin concentrations below the LLQ and therefore the Laplacian method with interaction was used throughout the modeling process. [2]

Covariate model

Tested covariates included age, sex, weight, length, BMI, hemoglobin, albumin, creatinine, CL_{CR}, augmented renal clearance (ARC) defined as a $CL_{CR} \geq 130$ mL/min, and gamma-GT, ALAT and ASAT concentrations. All covariates were screened for significance of an association with CL or V by univariate analysis, using a p-value cut-off of 0.05. Furthermore, a reduction in BPV or residual variability, as well as biological plausibility of a covariate-PK parameter association was used as a criterion for covariate selection. All covariates selected during the univariate analysis subsequently entered an intermediate model for a backward elimination procedure (multivariate analysis) with a cut-off for statistical significance of 0.001, which yielded the final model.

Potential improvement of the model by adding a parameter or by introducing a correlation between a covariate and a PK parameter was evaluated using the likelihood ratio test, in which the difference between the minimum objective function value (OFV) generated by NONMEM® for two hierarchical models is determined. Improvement in model fit is defined as an OFV decrease of ≥ 3.8 units while using a chi-squared distribution with one degree of freedom, corresponding to a p-value cut-off of 0.05. For the backward elimination covariate-procedure, an OFV increase of ≥ 10.8 units was used. Model performance was also evaluated by visual inspection of diagnostic 'goodness-of-fit' plots. [3] These were generated using Pirana (version 2.9.0) and Xpose (version 4.3.2) software (Uppsala, Sweden). [4,5]

Model robustness and predictive performance

The robustness of the parameter estimates from the final model resulting from the 2nd step was tested using a bootstrap analysis. In this analysis, the dataset was resampled 1000 times with replacement. Based on 1000 simulations, Visual Predictive Checks (VPC) investigated whether the final model could adequately predict the time course of the observed total gentamicin concentrations, including the observed variability. Bootstrap and VPC analyses were performed using Perl-speaks-NONMEM (PsN) version 3.5.3 software (Uppsala, Sweden). [6]

Results

Population pharmacokinetic analysis

Structural model

The data did not contain sufficient information to reliably fit a two-compartmental model and therefore a one-compartmental model was used. The OFV decrease for a two compartmental model relative to a one compartmental model was small, 6.8 units, and there was no obvious improvement seen in the GOF plots. In addition, the shrinkage in BPV was higher for a two compartmental model relative to a one compartmental model (12% for CL and 34% for V respectively 8% for CL and 29% V). The estimated BPV for CL and V were 91% and 44% respectively. The correlation between these two parameters was estimated to be 35%. Residual variability was modeled with a combined proportional and additional error model and was estimated to be 31% and 0.095 mg/l respectively.

Covariate model

The covariate analysis, based on complete covariate results from all participants, yielded one significant association after univariate analysis, between gentamicin CL and CL_{CR}. This association was modeled as a linear association ($p<0.001$, equation 1):

$$\text{Gentamicin CL}i\ (\text{L/h}) = 5.7 * (1 + 0.0091 * (CL_{CR,\,i} - 74)) \qquad \text{Eq. 1}$$

Where CL*i* is the gentamicin CL of individual *i*, $CL_{CR,i}$ is de creatinine clearance of individual *i*, 5.7 L/h is the population estimate of gentamicin CL for the median patient in the population with a CL_{CR} of 74 mL/min and 0.0091 is a factor determining the association between gentamicin CL and CL_{CR}. Consequently, a patient with a CL_{CR} of 119 ml/min (being the 90th percentile of the population) has a gentamicin CL of 8.0 L/h, while a patient with a CL_{CR} of 31 ml/min (10th percentile) has one of 3.5 L/h. Incorporation of this association in the structural model explained 28% of the BPV in

gentamicin CL. Yet, a substantial part of the BPV in CL, 74%, remained unexplained The association between CL and CL_{CR} is shown in Figure S2. In addition, ARC was tested as a binary covariate on gentamicin CL. This resulted in an OFV drop of 4.4 units ($p<0.05$), but during multivariate analysis the OFV was only 0.4 units ($p>0.05$). It was therefore concluded that ARC did not seem to improve model fit on top of an association between CL_{CR} as estimated by the Cockcroft and Gault formula (CRG) [7] and gentamicin CL. As univariate analysis with CRG on gentamicin CL resulted in an OFV drop of 15 units ($p<0.001$) and in a larger drop of the estimated BPV of CL (28% vs 16% for ARC on gentamicin CL), eGFR as estimated by CRG as such seems to be a more informative covariate for gentamicin CL than ARC.

References

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Table S1. Probability of C_{max}/MIC target attainment

Regimen	MIC 0.5 mg/L	MIC 1.0 mg/L	MIC 2.0 mg/L	MIC 2.5 mg/L
1.5 mg q8h	51.5	7.5	0.1	0.0
4 mg q24h	97.9	71.7	17.9	7.6
5 mg q24h	99.5	83.4	29.8	16.5
6 mg q24h	99.8	92.2	48.7	30.3
7 mg q24h	100	96.5	61.7	41.6

Probability of target attainment, i.e. the percentage of 1000 simulated patients predicted to achieve a C_{max}/MIC ratio ≥ 8 with the use of five different gentamicin dosing regimens, for infections with pathogens with four different MICs. All simulations were done assuming a median creatinine clearance (74 mL/min).

Figure S1. Study profile

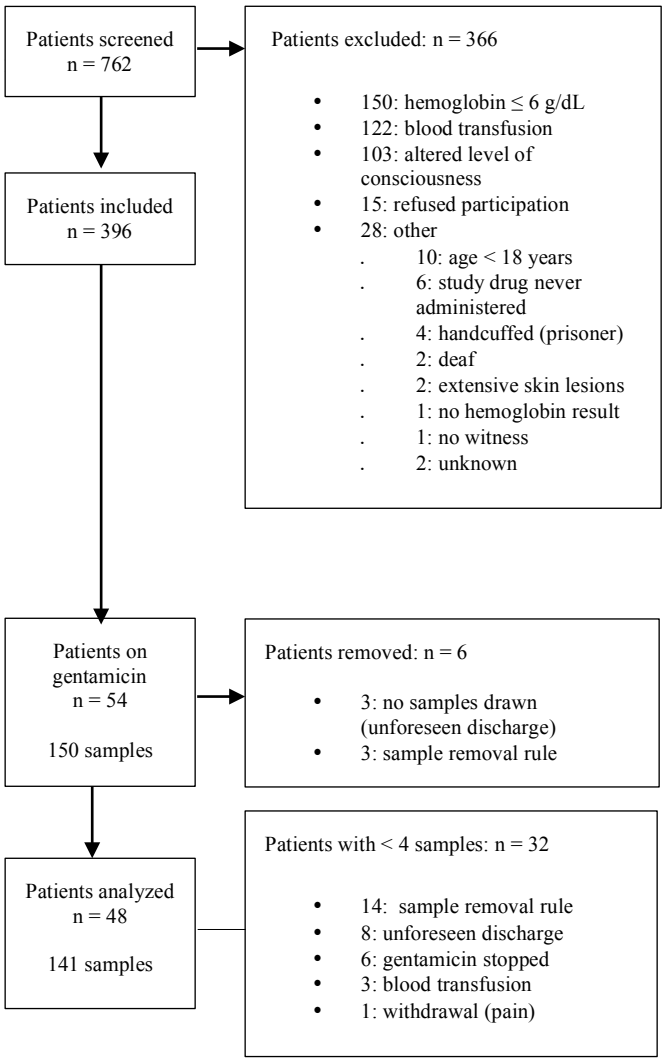
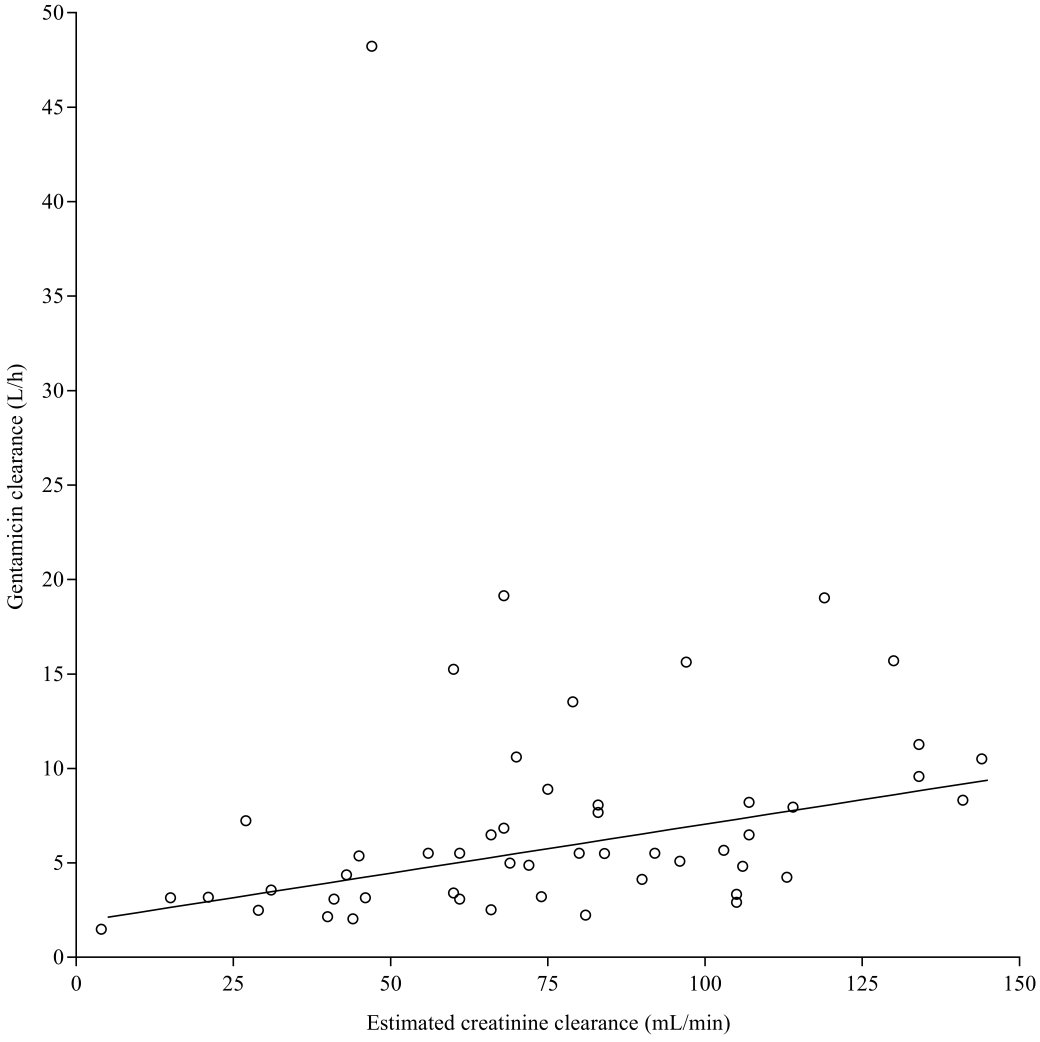


Figure S2. Covariate relationship between creatinine clearance and the clearance of gentamicin.



The dots represent the individual estimates of the gentamicin clearance. The line represents the model predicted association between creatinine clearance and gentamicin clearance. Creatinine clearance was estimated using the Cockcroft and Gault equation. [7]