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Background

In the neonatal intensive care unit infection is one of the biggest causes of morbidity and mortality. Gentamicin is a very commonly used antimicrobial for treating newborns and it exhibits concentration-dependent killing, i.e. higher serum concentrations are more efficacious. Due to its narrow therapeutic index gentamicin requires therapeutic drug monitoring (TDM) particularly to avoid acute renal failure due to high exposure. However, there is currently no consensus on how best to perform gentamicin TDM in neonates, although most centres aim for a trough level of <2 mg/L before giving the next dose. Gentamicin is cleared renally yet previous PK studies have not found a relationship between serum creatinine concentration (SECR) and clearance (CL). These studies have not accounted for the changes in expected SECR in early life.

Objectives

The aim of this study is to improve gentamicin TDM in neonates by firstly building a population pharmacokinetic model and then using it to create a Bayesian computer tool, which will predict trough levels from levels taken at earlier and more convenient times. Here we describe Stage 1: model development.

Methods

Concentration-time data from two published studies [1, 2] were used. The data included 174 neonates that had 1163 serum levels taken. Their gestational age ranged from 23.3 to 42.1 weeks, and postnatal age (PNA) from 0 to 65 days. Pharmacokinetic (PK) parameters were established using NONMEM VII with first order conditional estimation with interaction.

Model development

We evaluated one-, two-, and three-compartment structural models. Additive, proportional, and a combination of both models, were tested to describe residual variability, and log-normal distributions were assumed for the inter-individual variability (BSV).

Once a structural model was chosen, fixed allometric weight scaling was added to all parameters and a fixed sigmoid function relating post menstrual age (PMA) with weight (WT) and glomerular filtration was added to CL [3]. The further covariates of PNA (with a logistic function) and SECR (corrected for age) on CL were then tested.

SECR is complicated in newborns, as they have low renal function (and thus high SECR) and also their SECR reflects residual maternal SECR for some time after birth. However, by reviewing the literature [4, 5] we were able to get typical SECR for specific PMA (this was done by linear regression). Then we used an organ function (OF) to standardize measured SECR for age and estimated it as a covariate according to the following:

$$PNAF = \frac{PNA}{P_{50} + PNA}, \quad MF = \frac{PMA^{Hill}}{T_{50}^{Hill} + PMA^{Hill}}, \quad OF = \left(\frac{SECR}{typical\ SECR} \right)^{\theta}$$

where PNAF is function explaining the change in clearance with PNA, MF is the maturation function taken from [3] with fixed values, OF is the organ function; P₅₀ and T₅₀ the PNA and PMA, respectively, when maturation (of e.g. clearance) reaches half-time, and Hill is the sigmoidicity coefficient.

The inter-occasion variability (IOV) was also tested for each parameter. When all covariates and IOV were added, a re-checking of the structural model was undertaken.

Conclusions

- A population pharmacokinetic model for gentamicin in neonates has been developed.
- The best fit to the data was provided by a three-compartment model.
- Serum creatinine proved to be a significant covariate, indicating that it is necessary to correct serum creatinine for age in neonatal studies.
- Neonates with gentamicin concentration above 2 mg/L (Figure 2) at 24 hours post dose will benefit from a TDM program which predicts when it is safe to give the next dose.
- We are actively seeking more high quality neonatal gentamicin datasets to pool – please do get in touch if you can contribute data: eva.germovsek.11@ucl.ac.uk

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Results

Prior to adding the covariates and IOV a two-compartment model described the data best and was thus chosen as a structural model. Adding the covariates PNA and age-corrected SECR both significantly improved model fit (OFV drop of 168.4 and 35.6 units, respectively). Once the covariates, IOV and fixed allometric/renal function parameters were added into the model, we re-examined the structural model, and then a three-compartment model was found to provide a better fit to the data than the two-compartment model. Re-checking the covariates with the three-compartment model showed them still to be significant.

The following equations therefore characterize the final model:

$$CL = \theta_{CL} \cdot \left(\frac{WT}{70} \right)^{0.632} \cdot \left(\frac{PMA^{3.33}}{55.4^{3.33} + PMA^{3.33}} \right) \cdot \left(\frac{PNA}{P_{50} + PNA} \right) \cdot \left(\frac{SECR}{TCRE} \right)^{\theta} \cdot e^{(\eta_{CL} + IOV)}$$
$$V = \theta_V \cdot \left(\frac{WT}{70} \right) \cdot e^{\eta_V}, \quad Q = \theta_Q \cdot \left(\frac{WT}{70} \right)^{0.75} \cdot e^{\eta_Q}$$

where V is volume of distribution, Q is intercompartmental CL, and TCRE is typical SECR.

Final estimates for PK parameters are presented in Table 1. The proportional part of residual error was 15.5%, and the additive part 0.01 mg/L.

Table 1: Results from NONMEM – final parameter estimates

	mean	RSE [%]	BSV [%CV]	IOV[%]	η-shrinkage [%]
Clearance [L/h/70kg]	6.85	4.28	25.7	15.6	13.5
Volume of distribution [L/70kg]	27.5	2.25	9.64		54.4
Intercompartmental clearance 1 [L/h/70kg]	0.29	14.86	0 FIX		-
Peripheral volume of distribution 1 [L/70kg]	157.1	23.49	14.5		92.9
Intercompartmental clearance 2 [L/h/70kg]	2.24	10.58	11.7		85.8
Peripheral volume of distribution 2 [L/70kg]	21.4	5.98	14.7		75.2
Power exponent on OF	-0.17	31.88			
P ₅₀ [days]	2.06	14.13			

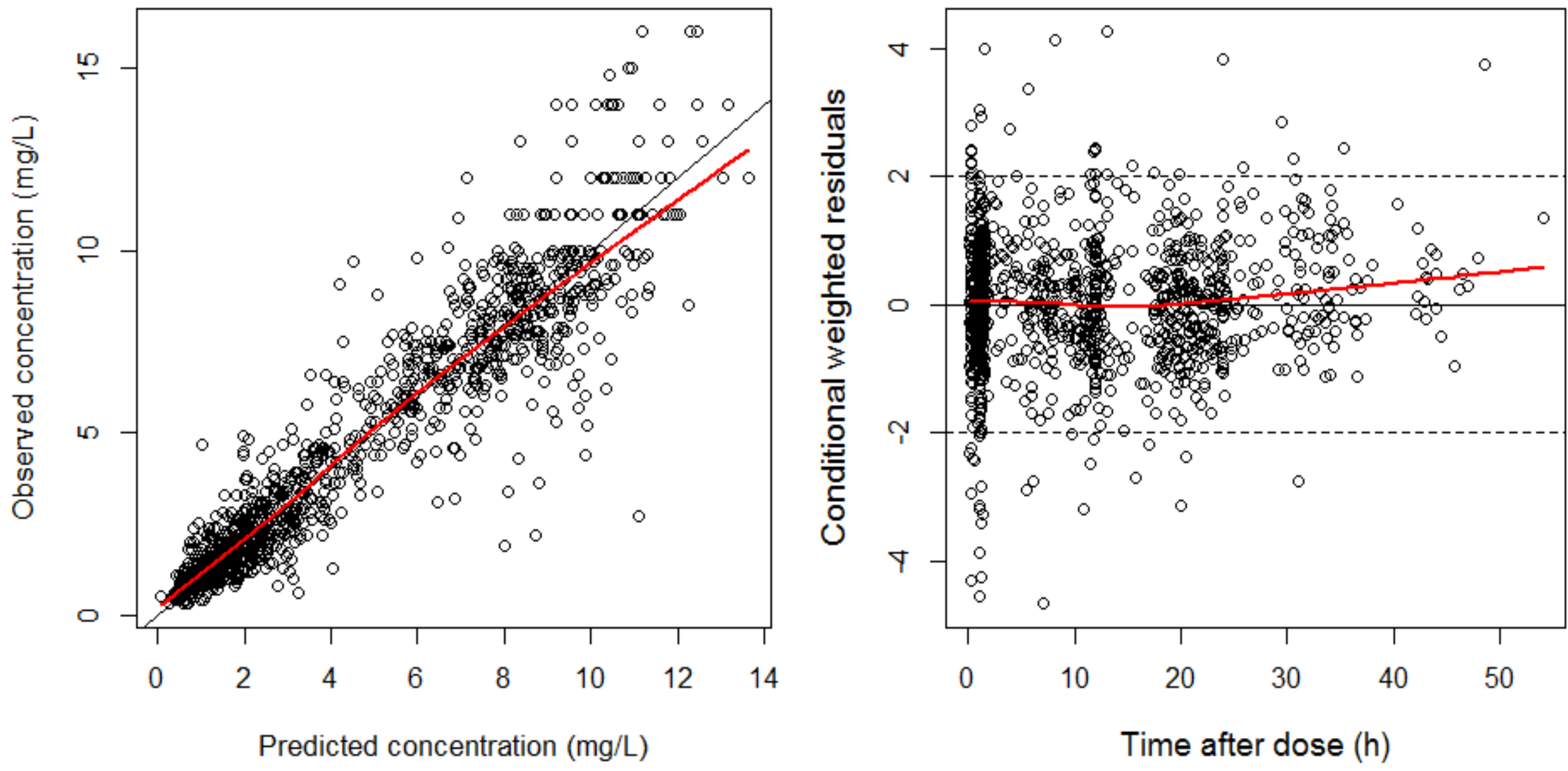


Figure 1: Observed versus population predicted concentration (left) from the final model and conditional weighted residuals versus time after dose (right). Red line is a lowest line and black line is the line of unity (left), and a line showing 0 residuals (right).

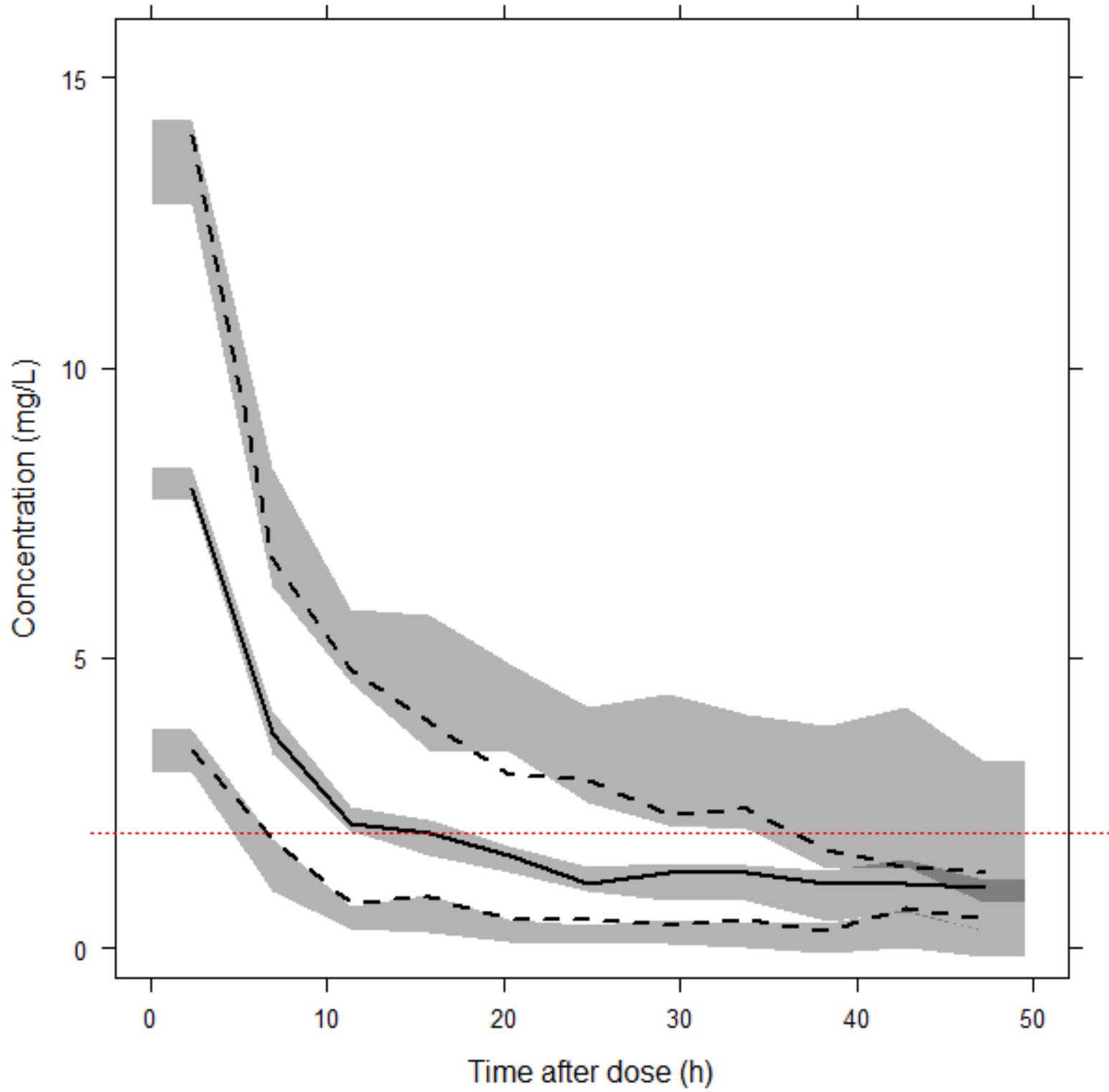


Figure 2: Visual predictive check (from 1,000 simulated datasets) of gentamicin concentration versus time after dose; shaded grey area is the nonparametric 95% confidence interval of the predicted median and 5th and 95th percentile; black solid line is the median of the observed data; black dashed lines are the 5th and 95th percentiles of the observed data; red dotted line is gentamicin concentration=2 mg/L

References

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