

# Population pharmacokinetics of Amikacin in newborns

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## Background and Aims

Amikacin is an aminoglycoside widely used for the treatment of severe infections caused by gram-negative bacteria. The pharmacokinetics of aminoglycosides has been shown to be highly variable in neonates and children. Information on drug disposition in target populations allows clinicians to optimize the design of dosage regimens both *a priori* and later in the course of the therapy. Moreover, individualization of dosage requirements is especially necessary in high-risk populations, such as newborns.

The aim of this study was to establish the population pharmacokinetics (PK) of Amikacin in newborns from serum concentration data obtained in routine therapeutic drug monitoring, to explore the influence of patient covariates on drug disposition and to evaluate the performance of this model on the studied population.

## Methods

### Study design

- Newborns with a postnatal age less than 90 days that were admitted in the neonatal unit between July 2000-July 2006 who were treated with amikacin and for which at least two serum concentration of amikacin were available were included in this retrospective study.
- Amikacin was administered as an i.v. infusion over 30 or 60 min.
- Blood samples were collected just before (through) and 1 hour after initiation of administration (peak).
- Demographic and clinical characteristics, laboratory values, dosing histories and amikacin concentrations were collected.
- Amikacin serum concentration measurements were done using fluorescence polarization immunoassay (TDx; Abbott Laboratories).

### Data analysis

- PK analysis was performed using NONMEM (version 7.1), with the first-order conditional estimation method with interaction (FOCE-I) throughout model building.
- A different data set (n=53) was used for external validation.
- Model evaluation was performed using goodness of fit plots, a bootstrap analysis (n=1000), normalized prediction distribution errors (NPDE), and a posterior predictive check (PPC)

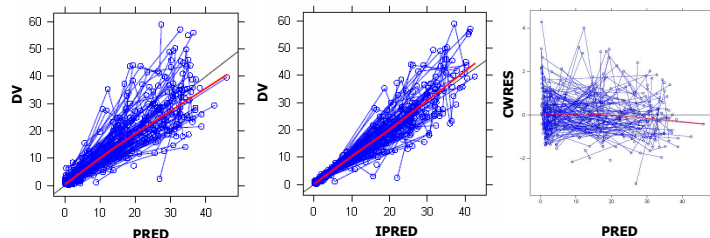


Figure 2. Goodness of fit plots for the final population PK model

DV: Observed amikacin concentrations; PRED: population amikacin predictions; IPRED: individual amikacin predictions; CWRES: Conditional weighted residuals. Black line: identify line; Red Line: Data smooth. Amikacin concentrations given in mg/L and time in hours.

## Conclusions & Perspectives

- A population PK model for Amikacin in newborns patients has been developed.
- Creatinine clearance (CLCR) and body weight (WT) were identified as the best predictors of plasma clearance, and WT of distribution volume of amikacin in neonates.
- Model evaluation indicated that the model could adequately describe the observed data and all the parameters with good precision.
- External validation with an independent dataset indicated adequate predictive performance.
- This model can be implemented in a Bayesian dose optimization software. Additionally, the model can be used to further investigate optimal dosing strategies.

## References

- Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J., NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.
- Botha J.H, Preez M.J, Miller R, Adhikari M. "Determination of population pharmacokinetic parameters for amikacin in neonates using mixed-effect models". *Eur J Clin Pharmacol.* 53(5). 337-341 (1998).

## Results

- 446 amikacin levels were simultaneously analyzed from 148 newborns (**Table 1**).
- The PK of amikacin after iv administration in the population of the newborns was best described by a two-compartment model (**Figure 1**). The results are shown in **Table 2**.
- CLCR was the most predictive covariate for CL, followed by WT
- WT explained part of the IPV in V1

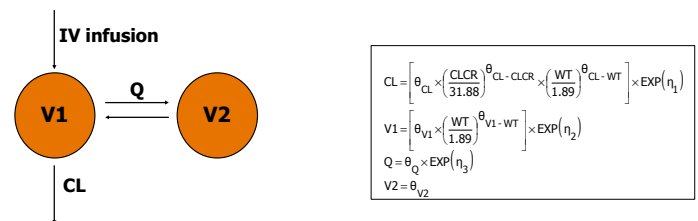


Figure 1. Schematic representation of the PK model

Table 1. Demographic and biochemistry characteristics of patients

| Patient characteristics         | Units  | Mean (SD)      |
|---------------------------------|--------|----------------|
| Gender (male/female)            | n      | 85/63          |
| Gestational age (EG)            | weeks  | 31.48 (5.22)   |
| Post natal age (EPNA)           | days   | 27.11 (17.56)  |
| Post conception age (EPCO)      | days   | 247.49 (38.97) |
| Birth Weight (WTN)              | Kg     | 1.60 (0.95)    |
| Current Weight (WT)             | Kg     | 1.89 (0.99)    |
| Birth Height (HGTN)             | cm     | 39.69 (6.57)   |
| Current Height (HGT)            | cm     | 42.04 (6.64)   |
| Current Head Circumference (PC) | cm     | 29.58 (4.34)   |
| Urea concentration (UREA)       | mg/dl  | 26.26 (20.34)  |
| Creatinine concentration (CREA) | mg/dl  | 0.58 (0.29)    |
| Creatinine clearance (CLCR)     | ml/min | 31.88 (17.75)  |

Table 2. Final Population PK estimates and results from Bootstrap

| Parameter (units)                 | Parameter Estimate (RSE%) | Bootstrap Results Median (95% PI)* |
|-----------------------------------|---------------------------|------------------------------------|
| <b>Pharmacokinetic parameters</b> |                           |                                    |
| theta_CL (L/h)                    | 0.09380 (4.52)            | 0.0934 (0.0855 – 0.1023)           |
| theta_CL~CLCR                     | 0.649 (9.83)              | 0.6438 (0.4985 – 0.7659)           |
| theta_CL~WT                       | 0.752 (12.1)              | 0.7599 (0.5869 – 0.9434)           |
| theta_V1 (L)                      | 0.640 (3.9)               | 0.6389 (0.5888 – 0.6884)           |
| theta_V1~WT                       | 1.090 (4.85)              | 1.0978 (0.9905 – 1.2075)           |
| theta_V2 (L)                      | 0.409 (24.7)              | 0.4127 (0.2512 – 0.6747)           |
| theta_Q (L/h)                     | 0.0391 (30.7)             | 0.0387 (0.0192 – 0.0645)           |
| <b>Interpatient variability</b>   |                           |                                    |
| CL (%)                            | 34.50 (16.39)             | 33.96 (27.22 – 39.50)              |
| V1 (%)                            | 21.07% (25.23)            | 20.81 (15.33 – 26.55)              |
| Q (%)                             | 70.21 (40.37)             | 68.14 (34.09 – 94.95)              |
| <b>Residual variability</b>       |                           |                                    |
| Additive (mg/L)                   | 28.4 (6.94)               | 0.2812 (0.2405 – 0.3199)           |
| Proportional (%)                  | 50.4 (15.7)               | 69.94 (27.44 – 95.52)              |

\* Derived from 1000 successful bootstrap sample runs

- The bootstrap analysis indicated parameters could be estimated with adequate precision (**Table 2**).
- Evaluation of the predictive performance of the model using an external dataset indicated adequate performance (median bias 4.53, inter-quartile range 8.70–11.85 and median precision 11.16, inter-quartile range 5.41-27.86).
- Data was adequately described based on NPDE results (**Figure 3**).

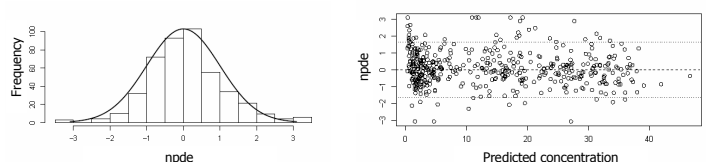


Figure 3. NPDE results using internal dataset