

Amikacin in premature babies: A new therapeutic proposal from a PopPK model

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OBJECTIVES:

- To develop a population pharmacokinetic model of amikacin in premature newborns babies.
- Evaluate the therapeutic protocol implemented in the clinical setup .
- Propose a new therapeutic protocol for initial therapy, from the estimated population model.

METHODS:

- Amikacin plasma concentrations (302) collected from 90 premature newborn babies were used to develop a population pharmacokinetic model with Monolix 4.3.3 (Lixoft).
- Model evaluation was performed by pc-VPC and cross validation.
- A 1000-database Monte Carlo simulation was conducted to evaluate both the therapeutic protocol implemented in the clinical setup and new proposed therapeutic protocol, with Mlxm 1.20 (Inria).
- Therapeutic protocols were assessed by plasma concentrations 30min after the end of infusion ($C_{\max}$) and at the end of the interval of administration ($C_{\min}$).

RESULTS:

Table 1 – Final Model Parameters Estimates

Parameter	Estimate	r.s.e. %
V	32.7 L/70kg	6
β_V_weight	1	-
Cl	2.07 L/h/70kg	11
β_Cl_weight	0.75	-
β_Cl_PMA	0.0377	28
β_Cl_CLcr	0.278	36
β_Cl_NP	-0.308	24
BSV V	37.6 %	13
BSV Cl	36.9 %	10
Correlation_V_CL	0.68	15
Residual error		
Additive	0.335 mg/L	35
Proportional	35.4 %	8

Table 2 – Proposed Therapeutic Protocol

WITH PARENTERAL FEEDING									WITHOUT PARENTERAL FEEDING							
Plasma creatinine (mg/dL)	PMA (weeks)								PMA (weeks)							
	< 32		32 - 34		35 - 40		> 40		< 32		32 - 34		35 - 40		> 40	
	Dose	Interval	Dose	Interval	Dose	Interval	Dose	Interval	Dose	Interval	Dose	Interval	Dose	Interval	Dose	Interval
	(mg/kg)	(h)	(mg/kg)	(h)	(mg/kg)	(h)	(mg/kg)	(h)	(mg/kg)	(h)	(mg/kg)	(h)	(mg/kg)	(h)	(mg/kg)	(h)
0.1	13.22	12	13.71	12	14.15	12	13.58	8	13.29	18	12.67	12	13.13	12	13.63	12
0.2	13.00	18	13.37	18	12.73	12	13.24	12	12.87	24	12.57	18	12.92	18	13.31	18
0.3 - 0.5	12.63	24	12.27	18	12.65	18	13.04	18	11.88	24	12.25	24	12.57	24	12.90	24
0.6 - 0.9	11.67	24	12.06	24	12.38	24	12.72	24	12.05	36	12.35	36	11.59	24	11.99	24
1.0 - 1.3	12.14	36	11.86	24	12.20	24	12.55	24	12.18	48	12.20	36	11.67	36	12.04	36
> 1.4	11.62	36	11.96	36	12.23	36	11.47	24	11.73	48	12.02	48	12.25	48	11.90	36

$$Cl\ (L/h) = 2,07 \times \left(\frac{WT}{70}\right)^{0,75} \times \exp(0,0377 \times (PMA - 40) + 0,278 \times (CLcr - 0,534) - 0,308 \times NP)$$
$$V\ (L) = 32,7 \times \frac{WT}{70}$$

Table 3 – Monte Carlo Simulations

Therapeutic protocol	C _{max}			C _{min}		
	> 30 mg/L	20 – 30 mg/L	< 20 mg/L	> 10 mg/L	< 5 mg/L	< 1 mg/L
In clinical use	39%	48%	14%	6%	81%	35%
Proposed	16%	67%	17%	4%	82%	28%

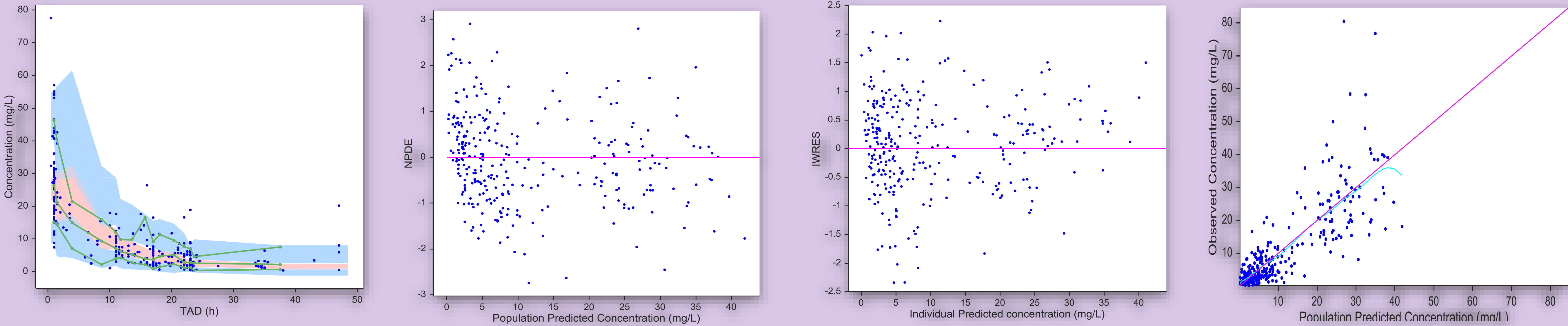


Figure 1 – Model Diagnostics and Evaluation

CONCLUSIONS:

- Allometric scaling accounted for 60% of Volume (V) initial unexplained between subject variability.
- Allometric scaling (WT), creatinine clearance (CLcr), post-menstrual age (PMA) and parenteral nutrition (NP) need, explained 50% of clearance (Cl) initial unexplained between subject variability.
- The therapeutic protocol implemented in the clinical setup can be improved, as showed by the large percentage of supratherapeutic peak plasma concentrations.
- The now proposed therapeutic protocol has the potential to increase both amikacin’s safety and efficacy.

References:

- Lavielle M, Mentré F. Estimation of Population Pharmacokinetic Parameters of Saquinavir in HIV Patients with the MONOLIX Software. J Pharmacokinet Pharmacodyn. 2007 Mar 30;34(2):229–49.
- Murphy J. Aminoglycosides. Clinical Pharmacokinetics: Pocket Reference. 1993. p.1-20