A pharmacokinetic/pharmacodynamic model to determine optimal dosing targets for amikacin in neonatal sepsis

Catherine M.T. Sherwin[1 & 2], Sofia Svahn[3], Antje J. Van Der Linden[4], Natalie J. Medlicott[2], Roland Broadbent[1], David M. Reith[1]

[1]Dept. of Women's and Child Health, Dunedin School of Medicine, Dunedin, New Zealand, [2]School of Pharmacy, University of Otago, Dunedin, New Zealand

[3]University of Uppsala, Uppsala, Sweden, [4]Microbiology, Otago Diagnostic Laboratory, Dunedin Hospital, Dunedin, New Zealand.

Introduction

- Conventional dosage regimens are not well adapted to neonates and produce inconsistent results, particularly in extremely premature infants (1).
- Neonates are ill equipped to deal with Gram-negative infections.
- There is greater variation associated with patients treated for Gram-negative sepsis and the variation is greater in the initial treatment phase.
- Amikacin peaks need to be higher to treat these type of infections (2).
- Maximum amikacin serum concentrations are often too low for an optimal bactericidal effect and minimum concentrations too high to be considered safe (3).

Objectives

- PK/PD model to explore the determinants of treatment failure (TF) in neonates treated with amikacin.
- Evaluation of current dosing regimen and proposal of optimal dosing regimen.

Methodology

A retrospective chart review was performed for all neonates treated with amikacin at Dunedin Hospital from Oct 2003 to Jan 2007. Amikacin was commenced for treatment of suspected late onset neonatal sepsis.

TF was defined when an infant was diagnosised with a repeat infection caused by the same bacteria or a treatment switch to vancomycin due to no apparent clinical improvement.

Amikacin E-tests were performed on the bacteria cultured from septic infants to determined amikacin MIC (Table 1).

Table 1: Amikacin MIC's for bacterial isolates from positive blood cultures.

Bacterial Species	MIC range (mg/L)	Isolates (n=26)
Staphylococcus sp. (not *S. aureus*)	0.75 - 3	10 (38.46%)
Staphylococcus epidermidis	1.5 - 12	10 (38.46%)
Staphylococcus aureus	1.5 - 3	3 (11.54%)
Staphylococcus warneri	2	1 (3.85%)
Escherichia coli	4	1 (3.85%)
Staphylococcus hominis	0.5	1 (3.85%)
Breakpoints:		
Staphylococcus sp. ≤ 16 = sensitive, 32 = intermediate, ≥ 64 resistant		
Gram-negative e.g. *E.coli* : same as for *Staphylococcus* sp.		

The population PK analysis included all study subjects and was performed using NONMEM, version 5. The PD analysis included only the neonates with culture proven sepsis and used the posthoc estimates from the PK model, the MIC data and clinical characteristics in a logistic regression model using Stata®, version 8.

The final PK covariate model used nonparametric covariates to perform simulations for 1000 virtual patients for proposed dosing schedules using MATLAB (version 7.1).

Catherine Sherwin is supported by a Freemasons Paediatric Fellowship

catherine.sherwin@stonebow.otago.ac.nz

Results

The PK model analysed 358 amikacin concentrations from 80 preterm and term neonates. A one-compartment first order elimination model was utilised (Figure 1). The final PK covariate model estimated:
Clearance (CL) = 0.23 ^ 0.0746 (PMA) ^ 0.691 (CWT) and volume of distribution (V) = 0.957 ^0.89(CWT.

The PD model included 35 confirmed septic episodes from 26 infants (Table 2). Fourteen episodes met the TF criteria. Median (range) amikacin peak concentration was 27.7 (17.1 to 36.8) mg/L, MIC was 3 (<0.5 to 12) mg/L and peak/MIC was 10.8 (2.3 to 71).

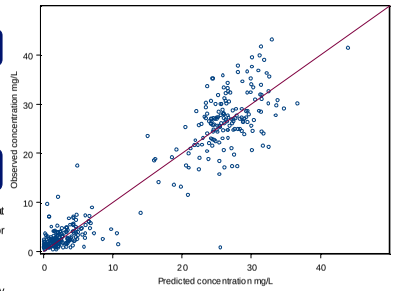

Figure 1: Final covariate model observed vs. predicted conc.

Table 2: Patient characteristics (PD analysis).

Patient characteristics (n = 26)	Mean ± SD (range) or %
Male	61.54 %
Gestational age (weeks)	27.60 ± 2.61 (24.00 – 34.00)
Postnatal age (days)	10.57 ± 10.97 (3.00 – 64.00)
Birth weight (kg)	0.98 ± 0.36 (0.58 – 2.06)
Current weight (CWT) at treatment (kg)	1.07 ± 0.56 (0.63 – 3.51)
C-Reactive Protein (CRP) maximum (mg/L)	58.64 ± 67.95 (1.00 – 239.00)

In the PD model, two infants with peak/MIC <6 had TF, relative risk (RR) 2.86 (1.57–5.19). Three out of four patients with peak/MIC <8 had TF, RR 2.25 (0.95–5.34) (Table 3).

Table 3: Risk Ratio TF Peak_Rat6 vs. TF Peak_Rat8.

TF Peak_Rat6	Exposed	Unexposed	Total
Cases	2	7	9
Non cases	0	13	13
Risk	1	0.35	0.41
		95% CI	
Risk difference	0.65	0.44 – 0.86	
Risk ratio	2.86	1.37 – 5.19	
TF Peak_Rat8	**Exposed**	**Unexposed**	**Total**
Cases	3	6	9
Non cases	1	12	13
Risk	0.75	0.33	0.41
		95% CI	
Risk difference	0.42	-0.06 – 0.89	
Risk ratio	2.25	0.95 – 5.34	

Table 4: Logistic regression model.

Description of logistic regression	Number of observations	Odds Ratio	Std. Error	95% CI
TF MIC	25	1.30	0.28	0.85 - 1.98
TF Peak	31	0.88	0.78	0.74 - 1.04
TF CWT	35	1.35	0.83	0.40 – 4.50
TF Cmax	35	1.01	0.30	0.96 – 1.07
TF AUC	35	1.01	0.004	1.00 – 1.01
TF Sex	35	0.42	0.31	0.10 – 1.80
TF PNA	35	0.97	0.11	0.78 – 1.21
TF Peak_MIC	22	1.02	0.31	0.96 – 1.08
TF Cmax_MIC	24	1.01	0.02	0.98 – 1.05
TF Peak_Rat6*	20	-	-	-
TF Peak_Rat8	22	6	7.55	0.51 – 70.67

Note:
* Peak_Rat6 = 0 (predicts success perfectly)
Peak_Rat6 dropped and 2 obs not used.

There was no influence from area under the curve (AUC), gender, postnatal age (PNA), peak or MIC as independent variables. Hence, other than peak/MIC <8, there were no independent predictors of TF (Table 4).

Evaluation of the dosing regimens (Table 5 & 6) was based on achieving a success in the following criteria:

- AUC success lower limit ≥ 130 mg.h/L/24h
- AUC success upper limit ≤ 590 mg.h/L/24h
- C_{max} success lower limit ≤ 24 mg/L
- C_{max} success upper limit ≥ 35 mg/L

Table 5: Percentage of success rate achieved with simulation of current dosing regimen.

PMA (weeks)	Dose (mg/kg)	Interval (h)	AUC success % Day 1	AUC success % Day 2	Cmax success % Day 1	Cmax success % Day 2
≤ 27	18	48	98	96	11	7
28-30	18	36	96	97	65	57
31-33	16	36	30	31	18	19
≥ 34	15	24	2	3	1	1

PMA – postmenstrual age; Cmax – maximum concentration; AUC – area under the curve.

Table 6: Percentage of success rate achieved with simulation of proposed dosing regimen.

PMA weeks)	Dose (mg/kg)	Interval (h)	AUC success % Day 1	AUC success % Day 2	Cmax success % Day 1	Cmax success % Day 2
≤ 27	12	36	99	99	67	60
28-30	16	32	95	96	68	70
31-33	24	32	91	92	63	64
≥ 34	30	24	35	34	26	28

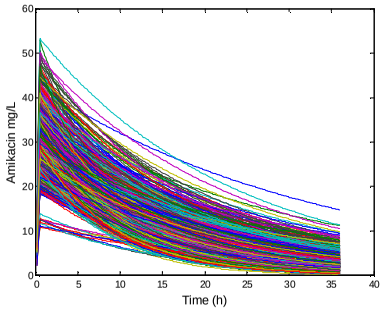

Figure 2: Simulation of amikacin concentrations on Day 1 for dosing infants ≤ 27 weeks PMA using proposed dosing regimen.

Conclusions

- The present study confirms the need for adequate amikacin peak concentrations to reduce the risk of TF.
- A dosing regimen that reliably delivers a peak/MIC ratio greater than 8 is required to treat septic neonates for amikacin to be effective.

Future directions

- Further investigate amikacin toxicity in neonates.
- Implement and trial the new proposed dosing regimen.

References

1. Bleyzac, N., V. Varnier, et al. (2001). "Population pharmacokinetics of amikacin at birth and interindividual variability in renal maturation." European Journal of Clinical Pharmacology **57**(6-7): 499-504.
2. Labaune, J. M., N. Bleyzac, et al. (2001). "Once-a-day individualized amikacin dosing for suspected infection at birth based on population pharmacokinetic models." Biology of the Neonate **80**(2): 142-147.
3. Langhendries, J. P., O. Battisti, et al. (1998). "Adaptation in neonatology of the once-daily concept of aminoglycoside administration: Evaluation of a dosing chart for amikacin in an intensive care unit." Biology Of The Neonate **74**(5): 351-362.

Acknowledgement

Stephen Duffull – School of Pharmacy, University of Otago, Dunedin, NZ