Simulation and Development of a Netilmicin Extended Dosing Regimen for Extremely Premature Neonates

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Introduction

Netilmicin is commonly used in the treatment of suspected and proven neonatal sepsis.

Despite extensive use of netilmicin in neonates, there remain unanswered questions regarding the optimal dose and frequency particularly in extremely low birth weight and/or neonates with a gestational age (GA) <30 weeks.

Objectives

To develop an optimal extended dosing regimen for netilmicin in neonates using population derived pharmacokinetic estimates.

Methodology

A retrospective chart review included 97 neonates aged from two days up to an age of 28 days, corrected for GA at birth, admitted to the neonatal unit at Dunedin Hospital between 1 February 1999 to 27 July 2003 who were treated with netilmicin for suspected sepsis.

Patients received a loading dose of 4mg/kg netilmicin by intravenous (IV) infusion over 30min. Loading doses =5mg in total, were followed with a 1mL saline flush. Maintenance doses as outlined in Table 1, were given by IV bolus over 3–5 min. The dosing interval was determined by gestational age (GA) and postnatal age (PNA).

Table 1 Dosing regimen for netilmicin (Netromycin®)

GA (weeks)	*PNA (days)*	*Current weight (kg)*	*Maintenance dose (mg/kg)*	*Interval (h)*
< 30	0 - 7	< 1.0	2.5	24
	0 - 7	1.0 - 1.5	2.5	18
	> 7		2.5	18
30 – 35	0 - 7		2.5	18
	> 7		2.5	12
= 36	0 - 7		2.5	12
	> 7		2.5	8

Netilmicin (peak and trough) concentrations were determined at the third dose after initiation of treatment or after a change in dose or dosing interval. Trough samples were taken immediately prior to the next dose and were considered to indicate a lesser risk of toxicity if they were less than 2mg/L. Peak concentrations were taken 60min after commencement of the IV bolus. A total of 361 netilmicin therapeutic concentrations were collected, an average of three samples per patient.

Results

Table 2 Demographic summary of the netilmicin study population

	Septic	*Non-septic*	*All*
Characteristics of patients n(%)	47 (48%)	50 (52%)	97
	Median (range)	***Median (range)***	***Median (range)***
Sex (male)	26 (58%)	27 (52%)	53 (55%)
Birth weight (kg)	0.87 (0.53 to 2.86)	0.84 (0.47 to 3)	0.99 (0.47 to 3)
Current weight (kg)	1.18 (0.53 to 3.13)	1.16 (0.47 to 3.59)	1.1 (0.47 to 3.59)
C-reactive protein maximum (mg/L)	66 (1 to 339)	6 (1 to 177)	9.5 (1 to 339)
Postnatal age (days)	22 (2 to 91)	16 (3 to 127)	10 (2 to 127)
Apgar score at 1 min	6 (2 to 10)	7 (0 to 10)	7 (0 to 10)
Apgar score at 5 min	8 (5 to 10)	9 (0 to 10)	9 (0 to 10)
Gestational age (weeks)	27 (23 to 41)	26 (23 to 37)	27 (23 to 41)
Serum creatinine (mmol/L)	62.9 (20 to 147)	60.9 (20 to 129.9)	70 (20 to 147)

All data analyses were performed using NONMEM (version.5). A mixed effects one-compartment, first order elimination model was developed to fit the dataset. The principle factors influencing netilmicin clearance (CL) were PMA (postmenstrual age, the sum of gestational age and postnatal age in weeks) and CWT, and the principal determinant of volume of distribution (V) was CWT. The final covariate model was $CL = 0.192 \bullet (CWT/2)^{1.35} \bullet (PMA/40)^{1.03}$, $V=1.5 \bullet (CWT/2)^{0.3}$.

The pharmacokinetic (PK) model was used to simulate various dosing regimens using a nonparametric dataset that comprised of covariate distribution values for CWT and PMA from 719 individual neonates. PMA ranged from 24.7–44.1 (weeks) and CWT 0.45–4.43 (kg) within the dataset.

MATLAB (student version 7.1) was used to perform simulations for each proposed dosing regimen. Consistent with other neonatal dosing regimens PMA was split into groups based on renal maturation. The model simulated the administration of two doses via IV infusion at duration of 0.5 h. For this simulation, the criteria were achievement of maximum peak plasma concentration (C_{max}) and area under the curve over 24 h (AUC_{24}) on day one and day two, 5–12 mg/L and 50–300 mg/L h respectively.

Simulation was assessed by determining the percentage of success against specific criteria. The primary evaluation of treatment success was based on achieving C_{max} within the stated boundaries. The independent variables used in the simulation included number of patients (n = 1000), dose interval (24–48 h) and dose given (3–8 mg).

Currently recommended dosing regimens indicate a dose of 4 mg/kg in neonates > 34 weeks. The dosing regimen in the present study based on overall achievement of treatment success (C_{max} and AUC_{24} for days 1 and 2), proposed a higher dose (7 mg/kg) for neonates PMA = 34 weeks.

The optimal dosing was 5 mg/kg 36 hourly, 5 mg/kg 24 hourly, 6 mg/kg 24 hourly and 7 mg/kg 24 hourly for neonates =27, 28 to 30, 31 to 33, and =34 weeks PMA respectively (Table 3). The variability in netilmicin PK and the use of higher doses, necessitates the monitoring of trough levels to avoid toxicity.

Table 3 Proposed dosing regimen based on achievement of treatment success

PMA (weeks)	*Dose (mg/kg)*	*Interval (h)*	*AUC_{24} success % day 1*	*AUC_{24} success % day 2*	*C_{max} success % day 1*	*C_{max} success % day 2*
=27	5	36	94	96	98	96
28-30	5	24	95	98	97	97
31-33	6	24	95	95	99	93
≥ 34	7	24	72	73	97	91

Note: (C_{max} and AUC_{24} for days 1 and 2)

Conclusions

Individualisation of netilmicin dosing in neonates requires adjustment of dose by body weight, and dosing interval by postmenstrual age. The optimal population PK model also included current weight as a covariate fixed effect upon CL.

Overall, the simulated netilmicin dosing regimen suggested realistic recommendations. The simulated dosing regimen appears to be very well suited for extremely premature neonates, with GA <30 weeks.