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Impact of a paediatric vial on the magnitude of systematic medication errors in neonates

K Allegaert[1,5], BJ Anderson[2], M Vrancken[1], A Debeer[1], K Desmet[3], K Cosaert[4], D Tibboel[5], H Devlieger[1]

[1]*Neonatal Intensive Care Unit, University Hospital Gasthuisberg, Leuven, Belgium*

[2]*Department of Anaesthesiology, University of Auckland, New Zealand*

[3]*Department of Microbiology, University Hospital Gasthuisberg, Leuven, Belgium*

[4]*Hospital Pharmacy, University Hospital Gasthuisberg, Leuven, Belgium*

[5]*Department of Paediatric Surgery, Erasmus Medical Centre, Sophia's Children Hospital, Rotterdam, the Netherlands*

Corresponding author

K Allegaert, Neonatal Intensive Care Unit, Department of Paediatrics, University Hospital, Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium E-mail: karel.allegaert@uz.kuleuven.ac.be

***Purpose*: A paediatric vial introduces additional costs and potential confusion when an adult vial already exists. The impact of a paediatric vial (amikacin 50 mg/ml) on pharmacokinetic parameter variability was compared to the variability associated with an adult vial (250 mg/ml).**

***Methods:* A population PK approach (NONMEM) was used to investigate clearance (CL) and volume of distribution (V) changes as markers of dose accuracy and variability from time-concentration profiles in 254 preterm neonates given intravenous amikacin. The paediatric vial was used in 56 and the adult vial in 198 neonates. Neonates had a mean gestational age (GA) of 28 weeks (range 24–30) and a mean weight of 1100 g (SD 33). Separate scale factors were applied to V and CL and their variability for neonates given a dose from the 50 mg/ml vial. Differences in V and CL parameter estimates and their variability before and after introduction of the 50 mg/ml vial reflect differences in dose administered and bioavailability.**

***Results:* There were more amikacin plasma concentrations in the target zone with the paediatric than the adult vial (72% and 58% respectively). The final model demonstrated an apparent 8% reduction in the estimate of V and a 29% reduction of its variability after introduction of the paediatric vial. Clearance was the same in neonates given adult or paediatric vials, but clearance variability was reduced by 53%.**

***Conclusions:* The introduction of a paediatric vial was associated with a reduction in observed variability of V and CL, reflecting improved dosing precision. The 8% reduction in the estimate of V suggests that there may be differences in bioavailability between both types of vials when used in neonates due to dosing imprecision.**

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Introduction

Unintended variability in dose administration is inherent to any manipulation of drugs[1]. This has been illustrated by Ferner et al. who documented unintended variability in acetylcysteine concentration in infusions[2]. Only 66/184 infusions bags had a concentration within the 10% range of the intended dose. Systematic errors associated with intravenous administration of catecholamines or antibiotics in different populations have also been reported[3,4].

We anticipate that this type of systematic error will be more pronounced in neonates and that formulations adapted for the use in neonates are likely to result in a more accurate administration of the intended dose. Intravenous drugs marketed for use in adults are often too concentrated and the administration of either low volumes or the need for sequential dilutions may cause additional systematic errors[5]. However, a paediatric vial introduces additional costs and potential confusion when an adult vial already exists. There are few data concerning the impact of such a paediatric vial on dose precision.

We recently reported on the variability in amikacin clearance in 205 preterm neonates. Weight explained 48%, gestational age 15% and the use of a non-selective cyclo-oxygenase inhibitor 2% of clearance variability. Neither betamethasone administration nor the need to administer dopamine in early neonatal life had an independent effect, leaving 35% of variability unexplained[6-9].

A 'paediatric' vial (50 mg/ml, Amukin ready to use 100 mg®, Bristol-Myers Squibb, Belgium) instead of the 'adult' vial (250 mg/ml, Amukin ready to use 500 mg®, Bristol-Myers Squibb, Belgium) was introduced in the unit in September 2004. In the present paper, we evaluated whether the introduction of this paediatric vial improved dose precision.

Methods

Patients

Perinatal data of infants admitted in the unit since 1 January 1996 are available in a prospectively collected database. This database was retrospectively searched for all admissions between January 1999 and September 2005 [gestational age (GA) < 31 weeks (w), postnatal age < 3 days, on respiratory support, peak and trough serum samples of amikacin available]. Maternal and neonatal characteristics (GA, birth weight, Apgar score, antenatal betamethasone, antenatal indomethacin, chorio-amnionitis, ibuprofen co-administration) were extracted. There were paired observations in 254 premature neonates available for study. These neonates had a mean GA of 28 w (SD 1.7) and a mean birth weight of 1100 g (SD 337).

Amikacin: administration, sampling and assay

From 1999 to 2002, amikacin (20 mg/kg/36 h in neonates with a GA below 30 w and 20 mg/kg/24 h in neonates with a GA of 30 w or above at birth) was part of the empiric treatment for suspected early onset bacterial infection. A more GA adapted dosing chart was implemented in 2002 based on Langhendries et al. (GA < 28 w: 20 mg/kg/42 h, GA 28–30 w: 20 mg/kg/36 h)[10]. A paediatric vial (50 mg/ml) instead of the 'adult' vial (250 mg/ml) was introduced in the unit in September 2004 in an effort to reduce unexplained inter-individual variability observed in a cohort of 205 preterm neonates (1999–2004).

Amikacin (Amukin®, Bristol Myers Squibb Belgium) was administered as an intravenous infusion over 20 min by syringe driver (SIMS Graseby®, Watford, UK). Blood samples for therapeutic drug monitoring were collected just before (trough) and 1 h after initiation of administration (peak) of the second administration. Amikacin serum concentration measurements were analysed using fluorescence polarisation immunoassay (TDx – Abbott) in the hours following sample collection. There were no other important changes in the analytical techniques, equipment or medical staff during the time interval evaluated.

Pharmacokinetic analysis

A one compartment, first order elimination model was used. We wished to evaluate the dose given and its variability when the amikacin 50 mg/ml vial was used compared to the 250 mg/ml vial. This was achieved indirectly using the surrogate marker, volume of distribution (V). V is a proportional term relating dose to peak concentration for a one compartment, first order elimination model. The relationship between dose, volume and concentration is only true for a peak concentration measured immediately after an IV bolus injection with instantaneous distribution. At all other times, V relates the serum concentration to the amount of drug in the body, not the dose. In the present case the peak concentration was measured 1 h after initiation of administration by short infusion (20 min). Consequently, clearance (CL) will affect the measured peak concentration, albeit to a limited extent. Differences in the V and CL variability

before and after introduction of the 50 mg/ml vial therefore reflect differences in dose variability. Differences in V estimates before and after introduction of the 50 mg/ml vial therefore reflect, to some extent, differences in relative bioavailability.

Population parameter estimations

Population parameter estimates were obtained using a non-linear mixed effects approach (NONMEM). The model was the same as that described in the paper investigating the influence of age, size and NSAID use on amikacin clearance in neonates[6]. Inter-individual variability in model parameters was modelled by exponentiating random effects (equivalent to assuming a log-normal distribution). Residual unexplained variability was modelled using an additive random effect (equivalent to assuming a normal distribution). Parameter values were standardised for a body weight of 70 kg using an allometric model [$P_i = P_{std} \times (W_i / W_{std})^{PWR}$] where P_i is the parameter in the ith individual, W_i is the weight in the ith individual and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. This standardisation has a strong theoretical and empirical basis and allows comparison of neonatal parameter estimates with those reported for adults. The PWR exponent was 0.75 for CL and 1 for V.

The population mean parameters, inter-subject variance and residual variance were estimated using the first order conditional estimate method using ADVAN 1 TRANS 2 of NONMEM V. Convergence criterion was 3 significant digits. Model improvements were judged by NONMEM's objective function and by visual examination of plots of observed versus predicted concentrations. Models were nested and an improvement in objective function was referred to Chi-squared distribution to assess significance e.g. an objective function change (OBJ) of 3.84 is significant at α=0.05. Separate scale factors were applied to Vol (Fvol) and its variability (FvarV) for neonates given a dose from the 50 mg/ml vial:

$V = Fvol \times (Vstd \times (Wt/70)) \times EXP\ (FvarV \times PPVV)\ l$

where *Vstd* is the population estimate for V, standardised to a 70 kg person using allometric models; *Fvol* and *FvarV* are scaling factors applied to those individuals given a dose from the 50 mg/ml vial. PPV is the population parameter variability for volume of distribution.

Separate scale factors were also applied to CL (Fcl) and its variability (FvarCL) for neonates given a dose from the 50 mg/ml vial:

Table 1 Clinical characteristics and amikacin plasma concentrations in relation to target concentrations

Clinical	Adult vial	Paediatric vial
Number of neonates	75	56
Neonatal survival (day 28)	70 (93%)	55 (98%)
GA (w) median (range)	28 (24–30)	28 (24–30)
Birth weight (g)*	1130 ± 332	1080 ± 314
Prenatal indomethacin	2 (3%)	2 (4%)
Prenatal betametasone	56 (75%)	46 (82%)
Ibuprofen co-administration	40 (53%)	13 (23%)
Plasma concentrations		
Peak amikacin (mg/l)*	38.3 ± (13.1)	40.9 ± 9.1
Trough amikacin (mg/l)*	4.8 ± (2.6)	4.3 ± 1.8
Peak result in target zone	70 (93%)	55 (98%)
Trough result in target zone	47 (63%)	41 (73%)
Both results in target zone	44 (58%)	40 (72%)

* Mean ± SD

$CL = Fcl \times (CLstd \times (Wt/70)^{0.75}) \times FNSAID \times EXP(SLPCL \times (GA-24) \times EXP(FvarCL \times PPVCL)\ l/h$

where CLstd is the population estimate for CL, standardised to a 70 kg person using allometric models; *Fcl and FvarCL* are scaling factors applied to those individuals given a dose from the 50 mg/ml vial. Clearance was unchanged (Fcl=1) in those children given the paediatric vial and this parameter was fixed at 1. *FNSAID* is a scaling factor for those premature neonates given a NSAID. *SLPCL* is the factor relating GA to developmental changes in CL.

Results

Data from 508 drug assay samples in 254 subjects (1999–2005) were available. Clinical characteristics and drug assay samples since implementation (n = 75, 2002–2004) of the more GA-adapted scheme and in a more recently treated cohort (n = 56, 2004–2005) in whom this more GA-adapted scheme was combined with the paediatric vial are presented in Table 1.

Results in the target zone, defined by amikacin peak level > 20 mg/l and trough level ≤ 5 mg/l were observed in 58% with the adult vial and in

Table 2 Amikacin population pharmacokinetic parameter estimates (PPV is the population parameter variability expressed as the square root of its variance, SE is the standard error of the structural parameter estimate)

Parameter	Estimate	% SE	PPV
CLstd (l/h/70kg) at 24 w GA, without NSAID	0.506	6.4	0.347
Vstd (l/70kg)	40.3	3.3	30.453
SLPCL	0.0953	11.5	–
FNSAID	0.817	3.8	–
Residual unidentified variability (mg/l)	1.47	29.3	–

$V = (Vstd \times (Wt/70))\ l$
$CL = (CLstd \times (Wt/70)^{0.75}) \times EXP(SLPCL \times (GA-24) \times FNSAID\ l/h$
where *Vstd* and *CLstd* are the population estimates for V and CL respectively, standardised to a 70 kg person using allometric models; *GA* is the gestational age in weeks; *SLPCL* is the factor relating GA to developmental changes in CL; *FNSAID* is a scaling factor for those premature neonates given a NSAID.

Table 3 Impact of a 50 mg/ml amikacin dose vial on the estimated volume of distribution and parameter variability {PPV is the population parameter variability expressed as the square root of its variance for Volume (PPVV) and clearance (PPVCL)}

	Fvol	FvarV	Fvarcl	PPVV	PPVCL	ΔOBJ
Basic model	–	–	–	0.419	0.599	0
Addition of Fvol	0.901	–	–	0.418	0.312	3.456
Addition of Fvar	–	0.669	–	0.446	0.319	10.448
Addition of Fvol and FvarV	–	0.649	–	0.446	0.318	15.546
Addition of Fvarcl	0.918	0.609	0.47	0.453	0.348	20.947

V = Fvol x *(Vstd* x *(Wt/70))* x *EXP (FvarV* x *PPVV) l*
CL = (CLstd x *(Wt/70)$^{0.75}$)* x *FNSAID* x *EXP(SLPCL* x *(GA-24)* x *EXP(FvarCL* x *PPVCL) l/h*
where *Vstd* and *CLstd* are the population estimate for V and CL, standardised to a 70 kg person using allometric models; *Fvol*, *FvarV* and *FvarCL* are scaling factors applied to those individuals given a dose from the 50 mg/ml vial. CL was unchanged in those children given the paediatric vial.

72% of neonates with the paediatric vial with a simultaneous reduction in standard deviation in peak and trough amikacin levels (Table 1).

Estimates for a slope parameter (SLPCL) relating GA to CL maturation and a scaling factor describing CL reduction with NSAID use (FNSAID) were the same as reported previously[6] (Table 2). The effect of the addition of scaling factors applied to volume (Fvol) and its variability (FvarV) as well as clearance variability (FvarCL) are shown in Table 3. The final model demonstrated an apparent 8% reduction in the estimate of V and this V had a 29% reduction of its variability after introduction of the paediatric vial (CV 45.3% vs 27.6%). CL was unaffected by vial type, but we observed a reduction of CL variability of 53% in those children given the paediatric vial. CL estimates are expressed using the allometric and linear per kilogram model in Table 4.

Discussion

Effective and well tolerated drug therapy in neonates requires a thorough understanding of various developmental aspects such as the maturation of CL with GA and the effect of concomitant therapy. A reduction of population parameter variability through identification of covariates also improves attaining target concentration and drug therapy. We have demonstrated improved dose precision in neonates when a paediatric vial was used in preference to an adult vial. V and CL parameter variability were hereby used as surrogate markers of dose and its variability. Using a population PK approach, a 29% reduction in population parameter variability of V and a 53% of CL variability were observed.

In addition, there was also an apparent 8% reduction in the estimate of V, suggesting that there may be differences in bioavailability between both types of vials when used in neonates due to dosing imprecision. With the current study design, further identification of the source of bioavailability differences (e.g. ampoule strength, dose measure accuracy, dilution requirements) was not possible. There is insufficient evidence in this study to be confident about this specific finding.

Ferner et al. documented that acetylcysteine concentrations in infusions had a concentration within a 10% range (90–110%) of the intended concentration in only 66/184 bags. Inadequate mixing (54%) was the most important contributor to this unanticipated variability with additional effects of calculation errors (28%) and major errors in drawing up the drug (18%)[2,11].

The GA-dependent dose of amikacin used is 15.5 to 20 mg/kg[10]. Based on the mean birth weight of 1100 g and the median age of 28 w GA, this means that 22 mg of amikacin, equivalent to 0.088 ml of the adult vial or 0.44 ml of the paediatric vial, should be administered. We anticipated that the introduction of a paediatric vial would be associated with a more accurate administration of the prescribed dose, reflected by the reduction in parameter variability. Decreased dose variability contributed to a greater proportion of children achieving target concentrations.

This report illustrates the impact of paediatric vials on the magnitude of random and systematic medication errors. Concerted efforts of caregivers, hospital pharmacists, policy markers and industry are therefore needed to get or keep such formulations on the market. In the absence of paediatric formulations, dedicated hospital pharmacists with their specific training to manipulate drugs by sequential dilution and mixing under sterile conditions are likely to be the most appropriate

Table 4 Weight and gestational age-related amikacin clearance estimates using the allometric "3/4 power" model (/70kg) and the linear per kilogram model.

Gestational age (w)	Weight (kg)	CL (l/h/70kg)	CL (l/h/kg)	V (l/kg)
24	0.5	0.506	0.025	0.576
25	0.6	0.557	0.026	0.576
26	0.8	0.612	0.027	0.576
27	0.9	0.673	0.028	0.576
28	1.0	0.741	0.031	0.576
29	1.15	0.815	0.033	0.576
30	1.3	0.896	0.035	0.576

approaches to keep random and systematic medications errors to the minimum.

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