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Reducing inter-individual variability in amikacin clearance in preterm neonates

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The bactericidal efficacy of amikacin mainly relates to intermittent, discontinuous peak concentrations due to the post-antibiotic effect, while renal side effects and oto-toxicity relate to the average plasma concentration, based on saturation of renal and cochlear cell binding sites.

This combination of efficacy and safety has resulted in the concept of administration of relative larger doses with extended dosing intervals between consecutive administrations. However, the important inter-individual variability in amikacin pharmacokinetics (PK) due to renal maturation makes it difficult to achieve a safe and effective dosing regimen in the individual premature neonate, most prominent in extremely preterm neonates and at birth. We report on the consecutive steps we took over a period of 7 years to reduce inter-individual variability in order to achieve a safe and effective dosing regimen in preterm neonates at birth.

Individual amikacin pharmacokinetics were calculated in 273 preterm neonates (546 paired observations, <31 weeks postmenstrual age (PMA), on respiratory support). Based on different dosing regimes used during consecutive time intervals, we were able to illustrate the PMA-dependent clearance, the negative effect of co-administration of a non-selective cyclo-oxygenase inhibitor on amikacin clearance and the impact of implementation of these observations on the amikacin trough levels observed. However, still important unexplained inter-individual variability was observed.

The subsequent introduction of a paediatric vial in a more recently treated cohort further reduced the variability in amikacin clearance observed. We have illustrated (i) the influence of perinatal renal function on amikacin clearance and (ii) the impact of a paediatric vial on the further reduction of the observed variability in amikacin clearance to dosing regimens.

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Introduction

Clinical pharmacology involves the study of drug-specific effects based on pharmacokinetics (i.e. absorption, distribution, metabolism and elimination) and pharmacodynamics (i.e. dose/effect relationship). Developmental pharmacology focuses on the maturational aspects of these phenomena during perinatal life and later stages of infancy. Important alterations in renal and hepatic function occur in perinatal life reflected by maturational trends in drug metabolism and elimination in preterm and term infants[1-3].

Renal clearance of drugs in preterm and term neonates is in general lower than that in infants and children and increases with postnatal and postmenstrual age (PMA). Neonatal renal clearance is dependant on the glomerular filtration rate (GFR). GFR in early neonatal life itself depends on the vasodilatory effects of prostaglandins on the afferent arterioli. Although non-selective cyclo-oxygenase (COX) inhibitors are effective in the treatment of specific clinical syndromes in neonates, efficacy should be balanced against renal side effects[2-6].

Amikacin is an aminoglycoside almost exclusively eliminated by glomerular filtration in neonates. Amikacin clearance reflects GFR and is a validated tool to study GFR maturation. A strong correlation between gentamicin and creatinine clearance has been demonstrated in preterm infants[7] and critically ill adults[8]. Inter-indivual variability in amikacin clearance reflects in part the inter-individual variability in maturation of the GFR[7,8].

The bactericidal efficacy of amikacin, like any other aminoglycoside, mainly relates to intermittent, discontinuous peak concentrations due to the post-antibiotic effect, while renal side effects and ototoxicity relate to the average plasma concentration, based on saturation of renal and cochlear cell binding sites.

The combination of efficacy and safety of aminoglycosides has resulted in the concept of administration of relatively large doses with extended dosing intervals between consecutive administrations. It is assumed that an initial amikacin target concentration range of 15–30 mg/l and trough concentration of less than 5 mg/l, corresponding to an average steady state concentration of about 10 mg/l are adequate targets in a 'once daily' approach[9-14].

However, the important inter-individual variability in pharmacokinetics (PK) makes it difficult to achieve a safe and effective dosing regimen in the individual preterm neonate, particularly in extremely preterm neonates and at birth[15]. We summarise the consecutive steps we have taken between 1999 and 2006 to reduce this inter-individual variability in order to achieve a safe and effective dosing regimen.

Methods

Patients

An in house database was searched for all neonates admitted between January 1999 and January 2006 in the first day of life with a PMA below 31 weeks, a postnatal age of less than 3 days and requiring respiratory support. Neonates were included in this retrospective study if data on two (peak and trough) plasma samples of amikacin were available. Maternal and neonatal characteristics (PMA at birth, birth weight, Apgar score at 1 and 10 minutes, antenatal betamethasone, antenatal indomethacin, chorio-amnionitis) were extracted from this database. Amikacin (Amukin®, Bristol Myers Squibb Belgium) was given as an intravenous infusion over 20 minutes by syringe driver (SIMS Graseby®, Watford, United Kingdom). Administration was initiated shortly after admission. Blood samples for therapeutic drug monitoring were collected by arterial line or venepuncture just before (i.e. "trough") and one hour after initiation of administration (i.e. "peak") of the second dose of amikacin.

Consecutive time intervals

During this 7 year time interval, consecutive adaptations in either dosing regimes or the co-administration of a non-selective COX inhibitor were implemented and this enabled us to evaluate the impact of these modifications on the development of a safe and effective dosing regimen.

From 1999 to 2002, amikacin (20 mg/kg/36 h in neonates with a PMA below 30 weeks, 20 mg/kg/24 h in neonates with a PMA of 30 weeks or above) was part of the empirical treatment for suspected early onset bacterial infection. A more PMA-adapted dosing chart was implemented in 2002 based on the proposal published by Langhendries et al.[9] (PMA <28 wks: 20 mg/kg/42 h, PMA 28–30 wks: 20 mg/kg/36 h) with an additional 6 h increase in the time interval when a non-selective COX inhibitor was co-administrated[5,15].

There were also changes in the use of non-selective COX inhibitors for prophylactic use in early neonatal life during the time interval evaluated. Before 1999 the Gasthuisberg NICU contributed to the Multicenter Ibuprofen Prophylaxis study (MIPS) trial, acetylsalicylic acid (4 × 20 mg/kg/day of acetylsalicylic acid-lysine, i.e. 4 × 11 mg/kg/day of acetylsalicylic acid for 2 days) was routinely administered in premature neonates who developed respiratory distress syndrome necessitating respiratory support and surfactant administration[6,9].

During inclusion in the MIPS trial (2000-2001) premature neonates with a PMA <31 weeks at birth were randomised in a double-blind manner to receive either ibuprofen-lysine or placebo (normal saline) in the first 3 days of life. The first dose (10 mg/kg, 1 ml/kg) of ibuprofen-lysine was administered as an intravenous infusion of 15 minutes in the first 6 h of life. The two consecutive doses (5 mg/kg, 0.5 ml/kg) were administered 24 and 48 h later. Exclusion criteria for the MIPS trial were perinatal asphyxia (Apgar score at 5 minutes <5), plasma creatinine >1.3 mg/dl, clinical bleeding tendency or thrombocytopenia (platelet count <60 × 10^9/l), life-threatening septicaemia or documented intra-ventricular haemorrhage before inclusion. After completion of the MIPS trial, we temporarily (2002–2003) continued to administer ibuprofen in premature neonates who required respiratory support and surfactant administration until data analysis of the MIPS trial resolved use of prophylactic ibuprofen[6]. Subsequently, in September 2004, in an effort to further reduce unexplained inter-individual variability in amikacin clearance, we investigated the use of a "paediatric" vial (50 mg/ml) instead of the "adult" vial (250 mg/ml).

Based on these consecutive time intervals, we had the unique opportunity to evaluate the impact of: (1) gestational age; (2) co-administration of a non-selective COX inhibitor, betamethasone or dopamine; (3) the dosing regimen and (4) the introduction of a paediatric formulation; on inter-individual variability in amikacin clearance and the number of observations in the target zone (trough <5 mg/l, peak >20 mg/l).

Assay

Amikacin plasma concentration measurements were performed using fluorescence polarisation immunoassay (TDx – Abbott) in the hours following sample collection and were reported in mg/l. Drug recovery from extraction was 100% (SD 2.6%) over the tested concentration range of 3 to 35 mg/l. Precision was assessed at 5, 15 and 30 mg/l: these yielded a within run coefficient of variation (CV) of 1.37–2.09%, between day CV of 0–1.74% and a total CV of 2.6–3.2%. The minimal quantifiable concentration was 0.8 mg/l defined by a CV of less than 20% (Abbott information). CV was typically <5% based on internal quality assessment covering the concentration range up to 50 mg/l.

Pharmacokinetic analysis

Pharmacokinetics were calculated assuming a one-compartment model with instantaneous input and first order output[5,16]. For each patient a logarithmic trend line was calculated based on C_{min} and $C_{max'40}$ (Figure 1). C_{min} and C_{max40} were actual plasma concentration measurements determined by immunoassay. $C_{max'40}$ was calculated using the following formula: $C_{max'40}$=C_{max40}–C_{min}. The slope of the curve [slope= (log C_{min} – log $C_{max'40}$) / (time

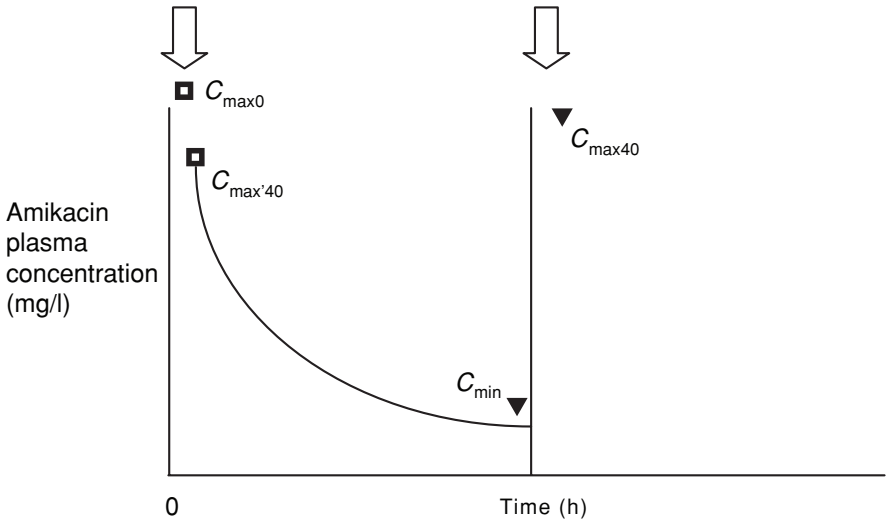

Figure 1 Clearance was calculated based on C_{min} and C_{max40} (▼). Blood samples were drawn before and 40 min after completion of the second administration of amikacin. $C_{max'40}$ (■) was calculated based on C_{max40}–C_{min}. Extrapolated data: (■).

interval)] was used to calculate the time constant K (slope × 2.303). Distribution volume (l/kg, V_d) was calculated based on V_d = dose administered (mg/kg)/C_{max0}. C_{max0} was calculated based on C_{max40} and K. Clearance was calculated based on $Cl_t = K \times V_d$ and reported in ml/kg/min.

Statistics

Results are reported as mean and standard deviation, median and range or incidence. Mann–Whitney U and Chi-square test were used to compare observations between consecutive cohorts and to study the impact of betamethasone, non-selective COX inhibitors or dopamine on amikacin clearance. Spearman's rank correlation was used to study the impact of gestational age on amikacin clearance.

Ethics

No additional ethical approval was sought for the collection and the retrospective analysis of amikacin and clinical data used in this present report.

Results

There were 546 paired observations in 273 preterm neonates (<31 weeks PMA, on respiratory support) available to calculate individual amikacin pharmacokinetics. Mean birth weight was 1078 (SD 334) g and median PMA was 28 (range 24–30) weeks. Amikacin PK observations during consecutive time intervals are reported in Table 1. There were no significant differences in these clinical characteristics between the three consecutive cohorts (Table 1).

In the first time interval (1999–2002), only a very limited number of observations were in the target zone (24%). Following implementation of a more sophisticated PMA-based dosing regimen in 2002, with an additional increase of the time interval between consecutive administration when a non-selective COX inhibitor was co-administered, there was an increase (P<0.01) in the number of observations (58 %) in the target zone with a decrease in mean and SD of the trough amikacin level.

After the introduction of a paediatric vial in September 2004, there was a further increase in the number of observations in the target zone (P<0.05) with a further decrease in the standard deviation of the peak and trough amikacin plasma levels. Although the spread in gestational age of included preterm neonates was limited to 24-30 weeks, a weak but statistically significant correlation was still observed between PMA (r = 0.16, 95 % CI 0.03 – 0.27, P = 0.01) and amikacin clearance. A clinically more relevant and statistically more significant, negative effect of co-administration of a non-selective COX inhibitor (P<0.001) was documented (Figures 2 and 3). No additional impact of either dopamine co-administration or prenatal betamethasone administration was documented.

Discussion

Based on consecutive reports of inter-individual amikacin clearance in a large (n = 273) cohort of extremely preterm (<31 weeks PMA) neonates at birth, we were able to confirm earlier observations on the impact of either PMA, acetylsalicylic acid or ibuprofen on amikacin clearance (Figures 2 and 3). Finally, the introduction of a paediatric vial was associated with further reduction of the inter-individual variability of amikacin clearance with an increase in the number of plasma concentrations in the target zone (Table 1). Nevertheless, there is still uncertainty on the most safe and effective dosing regimen of any aminoglycoside in neonates. Dosing of any antibiotic is based on a balance of maximal efficacy, minimal toxicity, while still avoiding the induction of bacterial resistance.

Table 1 Clinical characteristics and amikacin plasma concentration measurements in the three cohorts of neonates studied. Results in target zone are defined by amikacin peak level >20 mg/l and trough level ≤5 mg/l

	1999–2002	2002–04	2004–06
Number of neonates	129	75	69
Neonatal survival	96%	93%	98%
PMA (weeks) median (range)	28 (24–30)	28 (24–30)	28 (24–30)
Birth weight (g)*	1047 ± 346	1130 ± 332	1080 ± 314
Prenatal indomethacin	10%	3%	4%
Prenatal betamethasone	79%	76%	82%
Aspirin/ibuprofen co-administration	89%	52%	23%
Dopamine co-administration	54%	39%	41%
Plasma concentrations			
Peak amikacin (mg/l)*	45.7 ± 17.8	38.3 ± 13.1	40.9 ± 9.1
Trough amikacin (mg/l)*	8.2 ± 4.4	4.8 ± 2.6	4.3 ± 1.8
Peak result in target zone	95%	95%	98%
Trough result in target zone	24%	63%	73%
Both results in target zone	24%	58%	72%

*Mean ± SD.

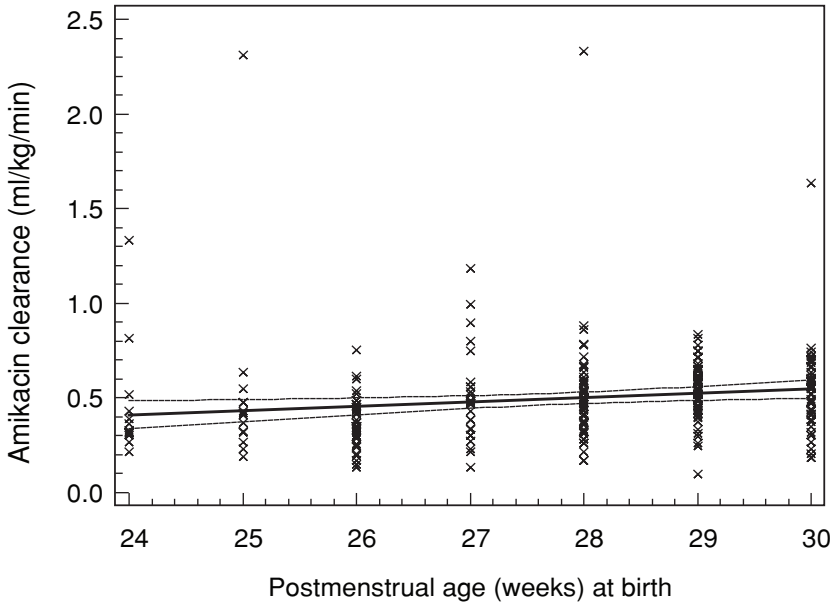

Figure 2 Correlation of amikacin clearance with PMA.

Robust pharmacodynamic indicators like survival during sepsis are not available in this specific population. Therefore, dosing has to be based on surrogate markers to determine the relationships between dosing regimens, susceptibility of micro-organisms, and efficacy. The three surrogate markers or pharmacodynamic indices used are area under the plasma concentration (AUC) versus time curve to minimum inhibitory concentration (MIC) ratio (AUC/MIC), peak concentration to MIC ratio (C_{max}/MIC), and the period during which the concentration of a given antibiotic remains above the MIC (T>MIC). By using this approach, the concentration-effect relationships for antibacterial agents against different micro-organisms can be adequately described and when combined with pharmacokinetic knowledge can be used to further rationalise dosing of a given antibiotic.

In general, antibacterial agents can be divided in two groups (beta-lactams and others). The efficacy of all beta-lactam agents (penicillins, penicillinase-resistant penicillins, the extended-spectrum penicillin derivatives, cephalosporins, carbapenems, and the monobactams) depends on the time during which the free, non-protein-bound concentration remains above the MIC of the micro-organisms while efficacy of virtually all other antibacterial agents is related to the

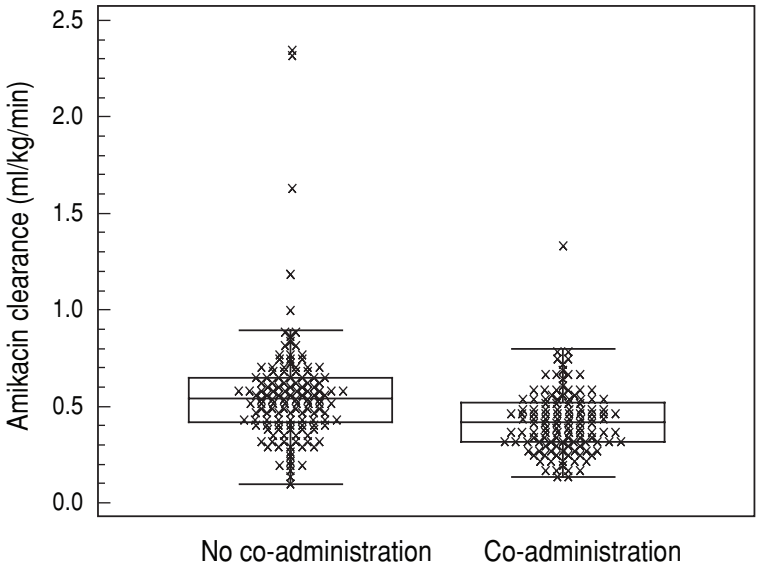

Figure 3 Individual amikacin clearance (ml/kg/min) estimates and box whisker plots in preterm neonates (n = 131) in whom a non–selective COX inhibitor was co–administered were compared to observations in preterm neonates (n = 142) in whom a non–selective COX inhibitor was not co–administered (P <0.001).

AUC/MIC ratio and the C_{max}/MIC ratio. This has important consequences for the design of dosing regimens of either beta-lactam agents or aminoglycosides, like amikacin.

For beta-lactam agents, frequency of dosing is an important factor in determining outcome. Maintaining the concentration above the MIC during the whole dosing interval has become the standard of care. This is in contrast to the aminoglycosides and fluoroquinolones where the total daily dose reflected by the AUC or peak concentration is the most important determinant of efficacy. These antibiotics should be given 'once daily'. Transient higher but less frequent maximum plasma concentrations may allow for a better C_{max}/MIC ratio, increasing bactericidal efficacy and decreasing risk of bacterial resistance. Due to a saturable process in binding of aminoglycosides to the renal proximal tubule brush border membranes, pulse administration probably also diminishes the risk of nephrotoxicity. Although speculative, the nephrotoxicity of amikacin may be lower in neonates due to reduced renal tubular uptake capacity.

Target concentrations for amikacin have not been prospectively defined but clinical convention aims for a trough value <5 mg/l and a peak value >20 mg/l[9-14]. Following implementation of a more complex PMA-based normogram for dose calculation of amikacin in premature neonates, a decrease in the mean trough concentration of amikacin and a increase in the number of observations in the target zone were documented (Table 1), reflecting the impact of maturation of GFR on amikacin clearance[5,7,8]. In addition, the negative effect of any non-selective COX inhibitor on amikacin clearance was reconfirmed (Figure 3). These observations in human neonates are in line with earlier animal experimental observations[4,5].

Based on the population PK study in 205 preterm neonates, weight and PMA were the major contributors to clearance variability[15]. Co-administration of a non-selective COX inhibitor also contributed to the variability observed[15]. Neither prenatal drug exposure (maternal betamethasone, indomethacin) nor early neonatal characteristics (Apgar score, dopamine administration) contributed to the variability in amikacin clearance observed, leaving 35% of amikacin clearance variability still unexplained[15-18].

We hypothesised that this unexplained inter-individual variability may in part be caused by unintended variability in dosing accuracy, inherent to any manipulation of drugs. This has been previously documented in adults with unintended variability in acetylcysteine concentration in infusions[19]. Systematic errors associated with intravenous administration of catecholamines or antibiotics in different populations have also been reported[20-23].

We anticipated that this type of systematic error was more pronounced in neonates and that formulations adapted for use in neonates would result in a more accurate administration of the intended dose since intravenous drugs marketed for use in adults are often too concentrated. The administration of either low volumes or the need for sequential dilutions may cause additional systematic errors. The PMA-dependent dose of amikacin used is 15.5–20 mg/kg. Based on the mean birth weight of 1078 g and the median age of 28 weeks PMA in the present study, this means that 21.5 mg of amikacin, equivalent to 0.085 ml of the adult vial or 0.43 ml of the paediatric vial, should be administered.

In the present cohort, we were able to illustrate that the introduction of a paediatric vial resulted in similar mean peak and trough amikacin concentrations compared to the use of the adult vial but with a smaller standard deviation compared to the second time interval resulting in a significant increase (72 versus 58 %) in the number of paired observations in the target zone (Table 1).

This report illustrates the impact of paediatric vials on the magnitude of random and systematic medication errors in neonates and confirms our earlier report on the reduction of the observed variability of the distribution volume and clearance in a population PK approach in a limited number of these preterm neonates[24].

There still remains some inter-individual variability in amikacin clearance. We recommend predicting initial doses based on weight and PMA with subsequent dose individualisation based on Bayesian estimates of PK parameters from concentrations measured immediately before and 60 minutes after the second dose[15,25]. It remains to be determined if predictability of amikacin clearance becomes more reliable after the first days or week of life since creatinine clearance then becomes a reliable indicator of GFR.

In summary, inter-individual variability of amikacin clearance in extremely preterm neonates at birth can in part be explained by PMA, birth weight and the co-administration of a non-selective COX inhibitor. Co-administration of dopamine or prenatal betamethasone administration has no additional impact on this inter-individual variability. This is an illustration of the relevance of perinatal renal maturation on amikacin clearance. Finally, it was illustrated

that the introduction of a paediatric vial further contributed to reduce the inter-individual variability to a safe range.

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