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Administration of betamethasone before birth has no effect on amikacin pharmacokinetics in preterm infants at birth

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Introduction: **We have recently described significant inter-individual variation in amikacin clearance in preterm neonates, which is only partly explained by co-administration of ibuprofen. We therefore evaluated the potential impact of various perinatal characteristics (ibuprofen, betamethasone, gestational age, weight, Apgar score, neonatal survival) on amikacin clearance at birth with specific emphasis on the potential association of prenatal administration of betamethasone and amikacin clearance at birth in preterm infants.**

Methods: **Clinical characteristics and amikacin pharmacokinetics were retrospectively collected in a cohort of 159 preterm infants (< 31 weeks gestational age (GA), day 1, on respiratory support). Pharmacokinetics were calculated assuming a one-compartment model with instantaneous input and first order output in every individual neonate and were based on amikacin blood samples collected just before (trough) and after (peak) the second administration of amikacin. Results are reported as median and range. Spearman's rank correlation was used to analyse the effect of GA and birth weight on amikacin clearance. Mann Whitney *U* test was used to analyse the effects of ibuprofen and betamethasone on amikacin clearance.**

Results: **There was considerable inter-individual variation in amikacin clearance (median 0.47, range 0.03–2.6 ml/kg/min). Amikacin clearance in infants treated with ibuprofen at birth (median 0.41, range 0.11–1.48 ml/kg/min) was significantly lower compared to infants not treated with ibuprofen (median 0.55, range 0.03-2.6 ml/kg/min), (Mann-Whitney *U* test *P*=0.017). Maternal betamethasone administration had no significant effect on amikacin clearance in the first day of life (median 0.50, range 0.09–2.6 ml/kg/min versus 0.55, 0.25–1.72 mg/kg/min, *P*=0.18).**

Conclusions: **There is considerable inter-individual variation in amikacin clearance in preterm infants. Ibuprofen significantly reduces amikacin clearance, whereas betamethasone has no effect.**

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Keywords: ibuprofen – betamethasone – pharmacokinetics – amikacin – preterm infants

Introduction

Clearance of aminoglycosides in preterm neonates strongly depends on glomerular perfusion and filtration since renal tubular function is still very limited at birth. It therefore is likely that factors that affect the glomerular filtration rate in early neonatal life will also have an impact on aminoglycoside clearance.

The administration of non-selective cyclo-oxygenase (COX) inhibitors is well known to be associated with a reduction of the glomerular filtration rate due to reduced glomerular perfusion while prenatal administration of betamethasone is reported to be associated with an enhanced renal clearance in neonatal life from day 3 and beyond[1–6].

We recently documented that administration of ibuprofen was associated with a significant and clinically relevant reduction in amikacin clearance but still observed important unexplained variability in amikacin clearance in a cohort of preterm infants (n = 74, range 24–30 weeks (w) gestational age (GA), day 1) included in a multicentre trial on the effects of prophylactic administration of ibuprofen (MIPS)[7,8].

To evaluate whether administration of betamethasone before birth or any other neonatal variable has an impact on amikacin clearance of preterm infants at birth, data on amikacin clearance were calculated in a larger cohort of preterm infants (< 31 w GA, day 1) on respiratory support.

Methods

Population

All infants (GA < 31 w) who entered the Leuven cohort (2000–2001) of the MIPS trial who were on respiratory support in the first day of life were included in the present report if amikacin concentrations were available to calculate pharmacokinetics. Exclusion criteria for the MIPS trial were perinatal asphyxia (Apgar score at 5 minutes < 5), serum creatinine > 1.3 mg/dL, observed clinical bleeding tendency or thrombocytopenia (< 60, 000/ mm^3), life-threatening septicaemia or documented intraventricular haemorrhage before inclusion. The MIPS trial was approved by the local ethical committee of the University Hospital, Gasthuisberg, Leuven and infants were included after informed consent of the parents[8].

Shortly after finalisation of the MIPS trial, it was decided to prescribe ibuprofen in ventilated newborns in a prophylactic approach to induce closure of an asymptomatic patent ductus arteriosus when surfactant was administered.

All preterm infants (< 31 w GA) on respiratory support in the first day of life admitted in an additional time interval (2002–1/6/2004) after finalisation of the MIPS study were retrospectively included if amikacin plasma concentrations were available to calculate pharmacokinetics.

Perinatal characteristics (gestational age, birth weight, Apgar score at one and ten minutes, prenatal betamethasone, prenatal indomethacin, neonatal survival, ibuprofen administration) were collected prospectively during the MIPS trial and retrospectively in the second part of the study. Gestational age was calculated using the expected date of delivery based on an ultrasound performed before 20 w gestation, or if not available, was based on neonatal clinical findings. Maternal administration of betamethasone (first dose, 12 mg administered intramuscular before delivery) was recorded.

Amikacin administration

During the MIPS study, combined administration of amikacin (20 mg/kg/36 h in infants with a GA < 30 w and 20 mg/kg/24 h in infants with a GA ≥ 30 w) and ampicillin (2 × 50 mg/kg/day) was the standard empiric treatment for suspected early-onset bacterial infection. During the second part of the study, a more elaborate dosing chart was implemented in the unit based on the GA at birth (< 28 w: 20 mg/kg/42 h; 28–30 w: 20 mg/kg/36 h; 31–33 w: 18.5 mg/kg/30 h; 34–37 w: 17 mg/kg/24 h; > 37 w: 15.5 mg/kg/24 h) with a dosing interval increase of 6 h if ibuprofen was co-administered or if neonates had suffered asphyxia or hypoxia[7,9]. Amikacin infusion was given over 20 minutes by syringe driver (Sims Graseby, Watford, UK).

Analysis and pharmacokinetics

Blood samples for amikacin therapeutic drug monitoring were routinely drawn by arterial line or by venepuncture before and 40 minutes after completing the administration of the second dose of amikacin. Amikacin plasma concentrations were determined using fluorescence polarisation immunoassay (TDx, Abbott)[7]. 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. A within run variability of 1.37–2.09%, a between day variability of 0–1.74% and a total variability of 2.6–3.2% were observed. The minimal quantifiable concentration was 0.8 mg/l (defined by a CV of less than 20%).

Pharmacokinetics were calculated assuming a one-compartment model with instantaneous input and first order output in every individual neonate. For

every single patient a logarithmic trend line was calculated based on C_{min} and $C_{max'40}$. $C_{max'40}$ was calculated from the equation $C_{max'40}=C_{max40}-C_{min}$. The slope of the curve [slope= (log C_{min} – log $C_{max'40}$) / (time interval)] was used to calculate the time constant K (slope x 2.303). The distribution volume (l/kg, V_d) was calculated based on V_d = dose administered (mg/kg)/C_{max0}. Therefore, C_{max0} was calculated based on $C_{max'40}$ and K. Clearance was calculated based on $Cl_t = K \times V_d$ [7].

Statistics

Clinical characteristics and pharmacokinetic variables were reported as median and range or by the absolute number. Spearman's rank correlation was used to study the correlation of gestational age and birth weight on amikacin clearance. Mann-Whitney U test was used to assess the impact of dichotomous variables (ibuprofen, betamethasone) on amikacin clearance. A P value < 0.05 was considered statistically significant.

Results

There were 318 paired amikacin plasma concentrations recorded from 159 infants (day 1, GA <31 w) on respiratory support. Clinical characteristics and pharmacokinetics of amikacin in all infants are reported in Table 1. Seventy four preterm infants (46%) were co-treated with ibuprofen. Prenatal administration of betamethasone was documented in 124/159 (78%) of these infants.

Table 1 Clinical characteristics and amikacin pharmacokinetics in 159 preterm infants. Data are reported as median and range or absolute numbers.

Clinical characteristics	
Gestational age (weeks)	28 (24 – 30)
Birth weight (g)	1050 (450 – 1980)
Apgar score 1 min	7 (1-9)
Apgar score 10 min	9 (6-10)
Betamethasone administration	124
Ibuprofen administration	74
Neonatal survival (day 28)	152/157
Amikacin pharmacokinetics	
Amikacin peak level (mg/l)	37.2 (15.5 – 100)
Amikacin trough level (mg/l)	4.4 (0.8 – 19.9)
Clearance (ml/kg/min)	0.47 (0.03 – 2.6)
Volume of distribution (l/kg)	0.57 (0.17 – 2.31)
Terminal elimination half life (h)	13.4 (6.7 – 92.1)

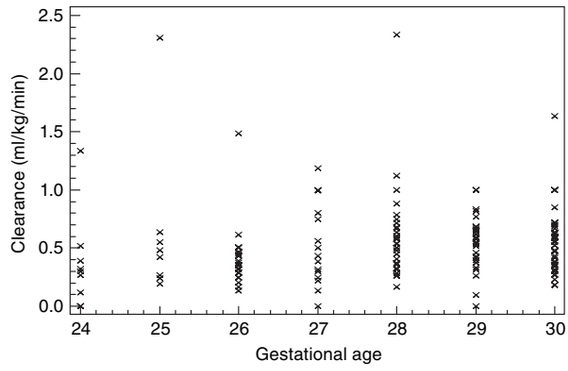

Figure 1 Correlation of amikacin clearance (ml/kg/min) with gestational age.

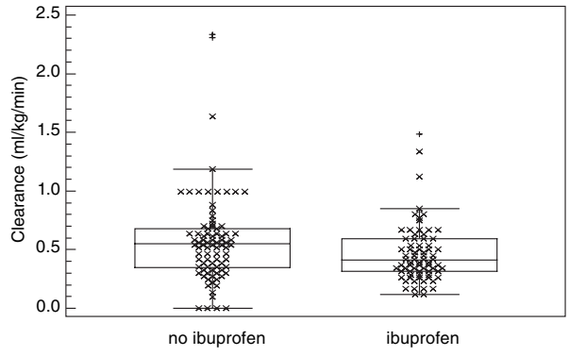

Figure 2 Amikacin clearance (ml/kg/min) in infants co-treated with ibuprofen (n=74) or not co-treated with ibuprofen (n=85).

Median amikacin clearance was 0.47 ml/kg/min (range 0.03–2.6 ml/kg/min). There was no significant correlation of amikacin clearance with birth weight (P=0.07) or birth weight$^{0.75}$ (P=0.15) but a significant correlation of gestational age (r=0.26, P=0.008) with amikacin clearance was observed (Figure 1). Median amikacin clearance was significantly lower (0.41 versus 0.55 ml/kg/min, P=0.017) in infants co-treated with ibuprofen (Table 2, Figure 2).

The clinical characteristics of preterm neonates who received antenatal betamethasone was not significantly different to those who did not. There were no differences in median estimates of clearance or volume of distribution between these two groups of infants (Table 3). The same

Table 2 Amikacin pharmacokinetics in relation to administration of ibuprofen. Pharmacokinetics in preterm infants co-treated with ibuprofen were compared to preterm infants not co-treated with ibuprofen. Data are reported by median and range (Mann-Whitney U)

	Ibuprofen ***n* = 74**	**No ibuprofen** ***n* = 85**	***P*-value**
GA (weeks)	28 (24–30)	28 (24–30)	NS
Birth weight (g)	1005 (480–1910)	1070 (450 – 1980)	NS
Amikacin clearance (ml/kg/min)	0.41 (0.11–1.48)	0.55 (0.03 – 2.6)	P=0.017
Amikacin volume of distribution (l/kg)	0.55 (0.22 – 2.31)	0.6 (0.17 – 1.91)	NS

Table 3 Amikacin pharmacokinetics in relation to administration of betamethasone. Data are reported by median and range (Mann-Whitney *U*).

	Betamethasone n = 124	**No betamethasone n= 35**	**P-value**
GA (weeks)	28 (24–30)	27 (24–30)	NS
Birth weight (g)	1057 (450 – 1910)	1010 (480 – 1980)	NS
Amikacin clearance (ml/kg/min)	0.5 (0.09–2.6)	0.39 (0.03–1.33)	NS
Amikacin volume of distribution (l/kg)	0.57 (0.17–2.31)	0.55 (0.25–1.72)	NS

results were documented when the population was subdivided in infants co-treated (Figure 3) or not co-treated with ibuprofen (Figure 4).

Discussion

Important variability in amikacin clearance (median 0.47, range 0.03–2.6 ml/kg/min) at birth was observed in a large cohort of preterm infants. Amikacin clearance was related to gestational age and ibuprofen administration but betamethasone had no influence.

Amikacin pharmacokinetic estimates are similar to other populations of preterm infants described in the literature [1,10]. The significant positive correlation of amikacin clearance on gestational age reflects the progressive GA-dependent increase in glomerular filtration rate since Koren *et al.* documented a strong correlation of aminoglycoside clearance on creatinine clearance in human neonates[11].

It is not surprising that co-administration of ibuprofen had a significant negative effect on amikacin clearance. The reduction in amikacin clearance probably reflects a clinically relevant reduction of glomerular filtration rate in early neonatal life when ibuprofen or any other non-selective cyclo-oxygenase inhibitor is administered[2-4].

There are, however, some methodological issues to be considered. Based on the retrospective design of the present study, pharmacokinetics were calculated based on trough concentration before and peak concentration of amikacin after the second administration. In addition, we assumed instantaneous input although intravenous administration took 20 minutes. These factors may contribute to the unexplained variability in amikacin clearance. Additionally, perinatal conditions such as renal dysfunction, perinatal asphyxia, sepsis or circulatory failure may also have an impact on amikacin clearance in early neonatal life but have not been considered in this study.

Transitory higher but less frequent maximum serum concentration allows an optimal C_{max}/Minimal Inhibitory Concentration (MIC) ratio, increasing bactericidal efficacy and decreasing risk of bacterial resistance. Due to a saturable process in binding of aminoglycosides on the renal proximal brush border membranes, pulse administration probably diminishes the risk of toxicity provided that the trough concentration is low[1,9,10,12]. Based on the results described here, prolongation of the dosing interval is necessary when ibuprofen is co-administered whereas no changes to the dosing regimen are required in the event of prenatal betamethasone administration.

In human preterm neonates treated before birth with betamethasone, a significant increase in glomerular filtration rate on postnatal day 3 and day 10 has been demonstrated, using inulin clearance [4]. The positive effects of prenatal steroids on water and sodium homeostasis in extremely low birth weight infants in the first week of life have also been demonstrated[5]. These positive and significant effects of prenatal steroids on renal function in the first week of life are in contrast

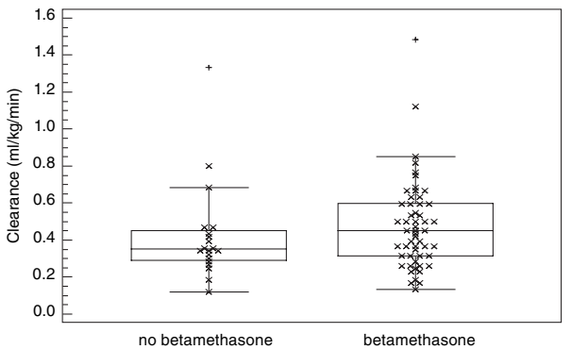

Figure 3 Amikacin clearance in infants co-treated with ibuprofen in whom betamethasone was co-administered (*n*=54) or not (*n*=20) before birth.

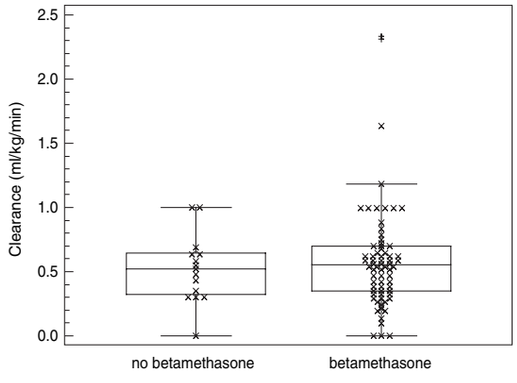

Figure 4 Amikacin clearance (ml/kg/min) in infants not co-treated with ibuprofen in whom betamethasone was co-administered (*n*=70) or not (*n*=15) before birth.

with the work of others who, using gentamicin clearance as marker, were not able to document a positive effect of prenatal glucocorticoids on renal clearance in early neonatal life in preterm infants[13].

The apparent contrast between the lack of impact of prenatal betamethasone on renal clearance in this report compared to earlier studies can be explained by the relevance of the postnatal age at evaluation of renal clearance, either in the very first day of life or at day 3 and 10[4,5,13,14].

It is possible that prenatal administration of betamethasone accelerates postnatal maturation of either the glomerular filtration rate or tubular functions, resulting in accelerated maturation of clearance of aminoglycosides but not yet observed at birth[1,4-6,14]. A population pharmacokinetic approach with the inclusion of neonates of various gestational and postnatal age should be performed to further assess the potential impact of betamethasone on postnatal maturation of aminoglycoside clearance.

In conclusion, variability in clearance of amikacin at birth was confirmed in a large cohort of preterm infants on respiratory support. This variability could only in part be explained by the significant effect of the gestational age and the co-administration of ibuprofen. Prenatal betamethasone does not contribute to this variability in amikacin clearance observed in preterm neonates at birth.

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