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PHARMACOKINETICS AND DISPOSITION

Clinical pharmacokinetics of aminoglycosides in the neonate: a review

Gian Maria Pacifici

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Abstract
Background Sepsis is common in neonates and is a major cause of morbidity and mortality. Sixty percent of preterm neonates receive at least one antibiotic, and 43% of the antibiotics administered to these neonates are aminoglycosides. The clearance (Cl), serum half-life ($t_{1/2}$), and volume of distribution (Vd) of aminoglycosides change during the neonatal life, and the pharmacokinetics of aminoglycosides need to be studied in neonates in order to optimise therapy with these drugs.
Objective The aim of this work is to review the published data on the pharmacokinetics of aminoglycosides in order to provide a critical analysis of the literature that can be a useful tool in the hands of physicians.
Methods The bibliographic search was performed electronically using PubMed, as the search engine, through July 11th, 2008. Firstly, a Medline search was performed with the keywords "pharmacokinetics of aminoglycosides in neonates" with the limit of "human". Other Medline searches were performed with the keywords "pharmacokinetics of … in neonates" followed by the name of the aminoglycosides: amikacin, gentamicin, netilmicin and tobramycin. In addition, the book *Neofax: A Manual of Drugs Used in Neonatal Care* by Young and Mangum (Thomson Healthcare, 2007) was consulted.
Results The aminoglycosides are mainly eliminated by the kidney, and their elimination rates are reduced at birth. As a consequence Cl is reduced and $t_{1/2}$ is prolonged in the neonate as compared to more mature infants. The high body-water content of the neonate results in a large Vd of aminoglycosides as these drugs are fairly water soluble. Postnatal development is an important factor in the maturation of the neonate, and as postnatal age proceeds, Cl of aminoglycosides increases.
Conclusion The maturation of the kidney governs the pharmacokinetics of aminoglycosides in the infant. Cl and $t_{1/2}$ are influenced by development, and this must be taken into consideration when planning a dosage regimen with aminoglycosides in the neonate. Aminoglycosides are fairly water soluble, and the larger water content of neonates yields a larger Vd in these patients.

Keywords Aminoglycosides · Gentamicin · Netilmicin · Tobramycin · Amikacin · Neonate · Pharmacokinetics · Peak concentration · Trough concentration

G. M. Pacifici (✉)
Department of Neurosciences, Section of Pharmacology,
University of Pisa Medical School,
Via Roma 55,
I-56126 Pisa, Italy
e-mail: pacifici@biomed.unipi.it

Introduction

Aminoglycosides are used for the treatment of neonates with suspected or proven Gram-negative bacterial infection, which is potentially life-threatening in neonates. Aminoglycosides are administered in association with a penicillin such as ampicillin or amoxicillin [1]. Penicillins increase bacterial permeability to aminoglycosides [2]. An evaluation of the use of antibiotics revealed that 60% of neonates receive at least one antibiotic during the first week of life, of which aminoglycosides represent 43% [3].

The high morbidity and mortality of bacterial infections in neonates require that the antibiotic therapy should be started as soon as the infection is suspected [4]. The remarkable interindividual variability in the pharmacokinetics of aminoglycosides requires that their optimum dosing be defined.

The aminoglycosides have a low therapeutic index [5] and thus knowledge about their pharmacokinetics is essential. The main pharmacokinetic parameters are clearance (Cl), serum half-life ($t_{1/2}$), volume of distribution (Vd), and the area under the concentration time curve (AUC). The pharmacokinetics of aminoglycosides are different in neonates than in adults [6], and it is thus necessary to study the pharmacokinetics of these drugs in neonates. In neonates there is a marked interindividual variability in aminoglycoside pharmacokinetic parameters (see the "Discussion" section), and it is necessary to identify the main causes of variability.

Over the past few decades, it has become common to apply pharmacokinetic principles when designing drug regimens. This applies also to neonatology where biological functions rapidly change during development. The main pharmacokinetic parameters, $t_{1/2}$, Cl and Vd, have been collected and organised into this article for gentamicin, netilmicin, tobramycin and amikacin. Therapy with aminoglycosides also requires knowing their peak and trough concentrations, and these two parameters have been collected.

The aminoglycosides have similar uses, and under particular circumstances, have similar minimum inhibitory concentrations (MIC). *Escherichia coli* is often found in neonatal infections and MIC_{90} are 0.25 μg/ml (netilmicin), 0.5 μg/ml (gentamicin and tobramycin) and 1 μg/ml (amikacin) [5].

This work aimed to review the kinetic parameters of gentamicin, netilmicin, tobramycin and amikacin in the neonate in order to provide a tool that may be useful in the hands of physicians.

Bibliographic search

The bibliographic search was performed electronically using PubMed as the search engine, through July 11th, 2008. Firstly, a Medline search was performed with the keywords "pharmacokinetics of aminoglycosides in neonates" with the limit of "human". Other Medline searches were performed with the keywords "Pharmacokinetics of … in neonates" followed by the names of the aminoglycosides: amikacin, gentamicin, netilmicin and tobramycin. In addition, the book *Neofax: A Manual of Drugs Used in Neonatal Care* by Young and Mangum [7] was consulted. The bibliographic search gave rise to 60 original articles, 2 review articles and 3 book chapters. The publication years of this matter ranged from 1962 to 2007.

Results

The demographic data of the neonates and the pharmacokinetic parameters are collected in four tables. The information about gentamicin is summarised in Table 1. Table 2 shows the data relative to netilmicin. Table 3 summarises the information relative to tobramycin, and Table 4 shows the pharmacokinetic parameters of amikacin.

Cl is expressed in different units by different authors. This makes the comparison between studies difficult. To overcome this difficulty we have converted Cl into milliliters per minute per kilogram which is the unit adopted by Thummel et al. [6], and it makes the comparison with the adult values easy. Standard deviation (SD) cannot be converted and therefore Cl is shown without SD.

Gentamicin

A great part of the information on aminoglycoside pharmacokinetics deals with gentamicin. Aminoglycosides are toxic for the eighth cranial nerve [5, 8] and for the kidney [5, 9]. This requires that the concentration of aminoglycosides be within the appropriate interval. Gentamicin trough concentration >2 μg/ml is associated with toxicity [5, 10], and peak concentration <5 μg/ml is associated with lesser efficacy [5, 11] as gentamicin, as well as the other aminoglycosides, exhibits a concentration-dependent bactericidal effect [5]. Formerly, gentamicin was administered at a dose of 2.5 mg/kg every 12 h [12]. Later, it appeared that once-daily gentamicin dosing of 4-5 mg/kg yields higher peak and lower trough gentamicin concentration than twice-daily dosing [13–16] (for review see Rao et al. [17] and Miron [18]). Recently, administering 5 mg/kg gentamicin and extending the dosing interval to 36-48 h has been recommended [19–22]. Extending the dosing interval to 48 h while increasing the gentamicin dose to 5 mg/kg causes an increase in peak concentration and a decrease in trough concentration as compared with a dose of 2.5 mg/kg every 12 h [20, 22, 23].

The extended-interval method of aminoglycosides has been used in 75% of U.S. hospitals since 2002 [24, 25]. Young and Mangum [7] suggest a gentamicin dose of 5 mg/kg every 48 h during the first week of life, when the gestational age is ≤29 weeks, a dose of 4.5 mg/kg every 36 h, during the first week of life, when the gestational age is 30 to 34 weeks and a daily dose of 4 mg/kg when the gestational age is ≥35 weeks. Using these dosing rates, gentamicin peak and trough concentrations should be <12 and <2 μg/ml respectively. Lanao et al. [21] administered 10 mg/kg gentamicin every 36-48 h, and this dosage appeared to be appropriate to obtain the peak concentration of 15-20 μg/ml and the trough concentration <0.5 μg/ml.

Some authors suggested using a loading dose of 4-5 mg/kg to shorten the time between the first dose of gentamicin and the time when gentamicin therapeutic serum concentration is reached [26–29]. The introduction of once-daily

Table 1 Pharmacokinetics of gentamicin in the neonate

Comments	Gestational age (weeks))	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	AUC (μg·h/ml)	Cl (ml min^{-1} kg^{-1})	Vd (l/kg)	$t_{1/2}$ (h)	Peak conc. (μg/ml)	Trough conc. (μg/ml)	Reference
Once daily	26[a]	<10	810[a]	32	2.5	A 78.2[a]	A 0.53[a]	0.50[a]	A 10.2[a]	B 5.9[a]	B 1.3[a]	[57]
Once daily	31[a]	<10	1,560[a]	49	3.0	82.0[a]	B 0.62[a]	0.49[a]	B 8.9[a]	B 6.8[a]	B 1.2[a]	
Once daily	38[a]	<10	3,140[a]	58	4.0	B 85.6[a]	C 0.78[a]	0.46[a]	C 7.0[a]	C 8.9[a]	C 0.8[a]	
Once daily	36±5	na	2,550±1,120	195	2.5±0.2	na	0.76	0.45±0.11	7.2±2.6	5.0±1.1	1.7±0.6	[58]
Once daily	28-33[b]	na	na	11	na	na	1.00[a]	0.60[a]	6.5[a]	na	na	[51]
Once daily	35-38[b]	na	na	31	na	na	1.22[a]	0.54[a]	4.9[a]	na	na	
Once daily	>38	na	na	55	na	na	1.15[a]	0.54[a]	5.2[a]	na	na	
2.5 mg every 18 h	26-32[b]	1	690-1,420[b]	12	2.5 every 18 h	55.1±1.7*	0.93 ml/min[c]	na	12.0±0.9	6.3±0.3	1.6±0.1	[12]
Once daily	26-30[b]	1	720-1,450[b]	6	3.0	75.5±6.7*	0.83 ml/min[c]	na	14.6±1.3	7.2±0.7	1.5±0.1	
Once daily	32±3	6±2	1,800±800	29	3.0	na	0.85	0.69±0.17	9.3[c]	5.4±0.9	na	[59]
Once daily	33±4	15±4	1,950±920	5	3.0	na	1.72	0.75±0.11	5.1[c]	na	na	
P	na	na	na	-	-	-	<0.05	ns	<0.05	-	-	
Twice daily	34±2	na	1,739±527	9	2.5×2	na	na	na	na	3.8±0.8	2.8±0.7	[13]
Once daily	34±1	na	1,940±510	9	4	na	na	na	na	5.9±1.1	1.9±0.6	
P	ns	-	ns	-	-	-	-	-	-	<0.0001	0.019	
Twice daily	36±3	na	2,525±730	32	2.5×2	na	na	na	na	6.4±1.6	2.2±1.0	[14]
Once daily	35±3	na	2,407±757	33	5	na	na	na	na	9.5±1.7	1.4±0.7	
P	ns	-	ns	-	-	-	-	-	-	<0.001	0.002	
Twice daily	37-41	na	3,387±526	21	2.5×2	na	na	na	5.86±1.7	6.4±1.5	1.9±0.5	[15]
Once daily	37-41	na	3,302±674	20	4	na	na	na	5.46±1.4	8.2±1.7	0.9±0.4	
P	-	-	ns	-	-	-	-	-	ns	0.001	0.0001	
Twice daily	37±3	0.6±1.1	2,795±714	28	2.5×2	na	na	na	na	6.7±1.1	2.0±1.1	[16]
Once daily	38±2	0.5±1.0	2,831±613	27	4	na	na	na	na	7.9±1.6	1.0±0.5	
P	ns	ns	ns	-	-	-	-	-	-	<0.05	<0.05	
Once daily	29±2.1	2.3±1.1	1,099±237	28	2.5	na	na	0.76±0.5	11.1±4.1	6.0±2.2	1.25±0.4	[19]
Extended interval	28±3.3	2.3±1.1	1,040±277	30	5 every 48 h	na	na	0.76±0.2	10.7±2.7	8.19±1.3	1.72±0.6	
P	ns	ns	ns	-	-	-	-	ns	ns	<0.0001	0.00013	
Once daily	28±2	na	1,161±230	10	2.5	na	0.35	0.34±0.21	na	2-9[b]	0.3-2.1 [b]	[22]
Extended interval	29±2	na	1,024±200	10	5 every 48 h	na	0.20	0.21±0.08	na	5-12[b]	0.4-1[b]	
P	ns	-	ns		-	-	0.008	ns	-	-	-	
Once daily	27±2	≤30	755±202	13	2.5	na	na	0.61±0.15	10.0±3.2	5.8±2.2	1.2±0.7	[20]
Extended interval	27±2	≤30	867±182	39	5 every 48 h	na	na	0.66±0.13	10.3±3.2	8.0±1.7	0.7±0.5	
P	ns	-	<0.05	-	-	-	-	-	ns	<0.01	ns	

na Not available, *IM* intramuscularly, *ns* not significant

Figures are mean±SD unless otherwise stated

[a] Median

[b] Range, mean is not available

[c] Mean, SD is not available

Statistical analysis relative to the data by Di Cenzo et al. [57]. Only significant differences are reported: AUC: A vs C $P<0.05$. Cl: A vs B $P<0.05$; A vs C $P<0.05$; B vs C $P<0.05$. $t_{1/2}$: A vs B $P<0.01$; A vs C $P<0.001$; B vs C $P<0.001$. Peak concentration: A vs B $P<0.005$; A vs C $P<0.001$; B vs C $P<0.001$. Trough concentration: A vs C $P<0.001$; B vs C $P<0.001$

Table 2 Pharmacokinetics of netilmicin in the neonate

Comments	Gestational age (weeks)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	AUC (μg·h/ml)	Cl (ml min^{-1} kg^{-1})	Vd (l/kg)	$t_{1/2}$ (h)	Peak conc. (μg/ml)	Trough conc. (μg/ml)	Reference
Once daily	<31	3[a]	1,105[a]	42	4	na	na	na	na	na	1.3[a]	[31]
	31-36	1[a]	1,861[a]	47	4	na	na	na	na	na	1.1[a]	
	>37	1[a]	3,220[a]	34	4	na	na	na	na	na	0.9[a]	
Once daily	<34	na	na	5	4.5	110±22.6	1.5 ml/min	0.46±0.07	7.6±0.9	6.7±1.3	1.2±0.4	[30]
	34-36	na	na	4	4.5	108±13.7	1.33 ml/min	0.51±0.10	8.5±1.1	8.6±0.26	1.4±0.4	
	>36	na	na	7	4.5	76.9±17.4	3.16 ml/min	0.51±0.07	6.1±1.4	7.2±1.09	0.9±0.2	
Once daily	40±1	1±0.3	3,700±300	7	6	200±124	0.64	0.41±0.05	4.6±1.3	6.6±1.7	1.9±1.4	[32]
	35±0.5	1±2	2,400±400	6	6	227±38	0.45	0.46±0.08	6.7±2.6	6.2±0.5	2.8±0.8	
	29±3	1±3	1,400±400	8	6	237±63	0.45	0.52±0.09	6.6±2.9	5.0±0.7	2.7±0.6	
Extended interval	28±2	0-7[b]	1,044±375	35	6 every 36 h	na	na	na	17.8±0.6	10.4±2.0	4.8±1.1	[33]
Twice daily	30±1	9±10	1,335±345	12	2.5×2	na	0.84	0.60±0.20	8.6±2.1	9.0±2.3	2.8±0.6	[34]
Twice daily	35±5	1-15[b]	2,267±822	64	2.5×2 (IM)	na	1.06	0.34±0.26	9.6±5.0	7.7±1.6	2.6±0.8	[35]
Once daily	na	<7	≤2,000	16	3 (IM)	33.4[a]	na	0.61[a]	4.7[a]	5.6±0.46[c]	2.7±0.13[c]	[36]
Once daily	na	≤7	≤2,000	8	3 (IM)	29.6[a]	na	0.60[a]	4.1[a]	5.3±0.71[c]	2.3±0.32[c]	
Once daily	na	<7	>2,000	9	3 (IM)	31.2[a]	na	0.47[a]	3.4[a]	6.5±0.64[c]	2.4±0.41[c]	
Once daily	na	<7	>2,000	23	4 (IM)	41.1[a]	na	0.62[a]	4.4[a]	7.2±0.39[c]	3.5±0.29[c]	
Once daily	na	≤7	>2,000	4	4 (IM)	42.9[a]	na	0.51[a]	3.8[a]	8.1±0.85[c]	3.0±0.55[c]	
Loading dose	26±2	na	876±170	35	[e]	na	na	na	na	7.56±1.76	1.61±062	[37]
Loading dose	23±0.3	0	602±33	5	[f]	141±6.5	0.59	0.58±0.12	18.2±3.3	8.1±1.7	2.1±0.3	[38]
	25±1	0	686±226	7	[f]	122±21	0.72	0.70±0.25	17.0±3.4[1]	7.0±1.9	1.8±0.4	
	30±2	0	1,400±286	8	[f]	142±31	0.62	0.88±0.10	17.5±4.8	7.9±1.6	2.0±0.4	
Population pharmacokinetics	38±3	10±7	3,050±760	124	2.44 [d]	na	1.37	0.43±0.16	4.7±2.7	na	na	[60]

na Not available, *IM* intramuscularly

Figures are the mean±SD unless otherwise stated

[a] Mean, SD is not available

[b] Range, the mean is unknown

[c] Mean±standard error

[d] Median

[e] Loading dose of 5 mg/kg followed by a maintenance dose of 3.5 mg/kg

[f] Loading dose of netilmicin of 5 mg/kg followed by maintenance dose of 5 mg/kg (body weight 2,000-2,500 g), 4 mg/kg (body weight 1,500-2,000 g), 3 mg/kg (body weight 1,000-1,500 g), 1.5 mg/kg (body weight 1,000-1,500 g) and 1 mg/kg (body weight <1,000 g)

Table 3 Pharmacokinetics of tobramycin in the neonate

Comments	Gestational age (weeks)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	Cl (ml min^{-1} kg^{-1})	Vd (l/kg)	$t_{1/2}$ (h)	Peak conc. (μg/ml)	Trough conc. (μg/ml)	Reference
Once daily	28±2	3.4[a]	805±105	8	[b]	0.69±0.10	0.59±0.10	9.9±1.5	7.6±1.5	1.7±0.4	[45]
Once daily	29-31	3-4[c]	1,000-1,300[c]	6	[d]	0.72-1.19[c]	0.74-0.94[c]	8.3-12.8[c]	4.6-8.4[c]	1.2-2.0[c]	[42]
Once daily	na	3±2	3,470±380	8	5 (IM)	4.9±2.5 ml/min	0.49±2.50	4.4±1.9	2.7±0.7	na	[61]

na Not available, *IM* intramuscularly
Figures are the mean±SD unless otherwise stated
[a] Mean, SD is not available
[b] 2.5 mg/kg every 18 h or 3 mg/kg every 24 h
[c] Range, mean is unknown
[d] 2.5 mg/kg every 12 or 18 h

dosing and the extended interval between dose regimens, which require 4-5 mg/kg of gentamicin, makes the use of the loading dose unnecessary.

Table 1 summarises the kinetic parameters of gentamicin and shows that $t_{1/2}$ ranged from 4.9 to 14.6 h, Cl ranged from 0.53 to 1.72 ml min^{-1} kg^{-1} and Vd ranged from 0.45 to 0.75 l/kg.

This variability observed for gentamicin, as well as the other aminoglycosides, requires that therapy with these drugs be individualised, especially for critical patients such as premature infants.

Netilmicin

Once-daily dosing of netilmicin was reported by Gosden et al. [30] and Brooks et al. [31]. These authors administered 4-4.5 mg/kg netilmicin and obtained peak and trough concentrations within the expected values. Ettingler et al. [32] administered 6 mg/kg netilmicin, and the trough concentrations were >2 μg/ml in one-third of the cohort. Consistent results were obtained by Klingenberg et al. [33], who administered 6 mg/kg netilmicin every 24 or 36 h. In this study, the trough concentration exceeded 2 μg/ml in 43% of the patients, and these authors suggest a dosing interval of 48 h for gestational age <29 weeks, 36 h for gestational age of 29-36 weeks and 24 h for full-term infants. Interestingly, in full-term infants and in infants with postnatal age >7 days, the percentages of neonates with a trough concentration >2 μg/ml were 15 and 6% respectively suggesting that gestational age and postnatal development influence the trough concentration of netilmicin. Young and Mangum [7] suggest a dosage of netilmicin similar to that of gentamicin given above. With this dosage, the peak concentration of netilmicin should be 5–12 μg/ml and the trough concentration should be <2 μg/ml.

When netilmicin was administered twice-daily at the dose of 2.5 mg/kg every 12 h, the average trough concentration was 2.8 μg/ml [34], and similar results were obtained by Granati et al. [35]. This suggests that the once-daily dose of 4 mg/kg [31] or 4.5 mg/kg [30] is safer than the twice-daily dose.

Siegel et al. [36] administered 3 or 4 mg/kg netilmicin once daily to premature and full-term neonates and obtained average trough concentrations ranging from 2.3 to 3.5 μg/ml. It must be noted that the trough concentrations were measured 6 h after dosing.

The loading dose of netilmicin was introduced by Berger et al. [37] and Rengelshausen et al. [38]. For dosing details see Table 2. The literature on aminoglycosides reveals that the loading-dose regimen is overcome by once daily and extended-interval dosing regimes.

Table 2 shows that $t_{1/2}$ ranged from 3.4 to 18.2 h, Cl ranged from 0.45 to 1.37 ml min^{-1} kg^{-1} and Vd ranged from 0.34 to 0.88 l/kg.

Tobramycin

Little is known about tobramycin pharmacokinetics in the neonate. In an early study, de Hoog et al. [39] modified both the tobramycin dose and the interval between doses according to the neonate age. The tobramycin dosing schedule was 3.5 mg/kg every 24 h (≤28 weeks), then 2.5 mg/kg every 18 h (28-36 weeks) and 2.5 mg/kg every 18 h (≥36 weeks). Using this schedule, the percentage of trough concentrations >2 μg/ml ranged from 19 to 49%. In a successive study, de Hoog et al. [40] administered 4 mg/kg tobramycin to all patients and the interval between doses was 48 h (<32 weeks), 36 h (32-36 weeks) and 24 h (≥37 weeks). Using these dosages, the majority of infants had tobramycin peak concentrations from 5 to 10 μg/ml and trough concentrations from 0.5 to 1 μg/ml. The elimination rate constant (Ke) was 0.064±0.034 and 0.098±0.046 h^{-1} at gestational ages <32 and ≥37 weeks respectively; and Vd was 0.70±0.17 and 0.54±11 l/kg at the gestational ages of <32 and ≥37 weeks respectively [40]. The difference in Cl reflects the reduced clearance of tobramycin in preterm

Table 4 Pharmacokinetics of amikacin in the neonate

Comments	Gestational age (weeks)	Postnatal age (days)	Body weight (g)	No. of cases	Daily dose (mg/kg)	AUC (μg·h/ml)	Cl (ml min^{-1} kg^{-1})	Vd (l/kg)	$t_{1/2}$ (h)	Peak conc. (μg/ml)	Trough conc. (μg/ml)	Reference
Once daily	36±7	11±7	2,445±749	22	7.5 (IM)	na	1.42	0.66±0.19	6.0±2.0	18.6±6.9[a]	na	[62]
Once daily	32±4	<2 weeks	1,740±810	19	5 (IM)	na	0.96	0.72±0.49	9.0±5.0*	na	na	[52]
Once daily	40±1	<2 weeks	3,190±820	13	5 (IM)	na	1.24	0.56±0.26	5.5±1.8*	na	na	
Once daily	34±3	na	1,980±920	29	7.2	na	0.86±0.29	0.49±0.18	6.8±2.9	na	na	[49]
Twice daily	30±3	na	1,380±470	28	[b]	na	0.84±0.28	0.57±0.11	8.4±2.5	23.9±4.2	8.3±3.0	[63]
Population pharmacokinetics	38±6	450±158	7,380±840	155	[c]	na	2.05	0.34±0.32	2.8±2.0	6.8-35.7[e]	<0.8-17.1[e]	[47]
Population pharmacokinetics	38±4	10±7	2,900±900	30	7.5-10	na	1.71	0.64±0.22	3.7	na	na	[64]
Ibuprofen	27±2	1	982±380	34	[d]	na	0.36[a]	0.63[a]	16.4[a]	47.7[e]	9.9[e]	[65]
Placebo	28±2	1	1,060±390	39	[d]	-	0.60[e]	0.59[e]	12.4[e]	40.9[e]	6.2[e]	
P^f	ns	-	ns	-	-	-	<0.005	ns	<0.02	ns	<0.01	

na Not available, *IM* intramuscularly, *ns* not significant
*P=0.009
Figures are the mean±SD unless otherwise stated
[a] Median
[b] 7.5 mg/kg every 12 h until age was 7 days, and 7.5 mg/kg every 8 h >7 days of age
[c] The loading dose was 11.7±1.3 and the maintenance dose was 9.8±1.4 mg/kg. In the first drug dosing regimen, neonates received a loading dose of 10 mg/kg amikacin followed by a maintenance dose of 7.5 mg/kg every 12 h. The infants and children received 7.5 mg/kg amikacin every 12 h. In the second drug dosing regimen, we considered an infusion of 15 mg/kg amikacin every 12 h for neonates, infants and children
[d] 20 mg/kg every 36 h when gestational age was <30 weeks and 20 mg/kg every 24 h when gestational age was ≥30 weeks
[e] Range, the mean is unknown

neonates [41–43]. The difference in Vd is primarily attributable to a higher percentage of body water in premature infants resulting in a higher Vd as tobramycin is fairly water soluble [41–43].

Young and Mangum [7] suggest a dose of tobramycin similar to that of gentamicin given above. Ke and Vd of tobramycin were measured in 470 neonates by nonlinear mixed effects model (NONMEM) and by nonparametric expectation maximization (NPEM2) [44]. Population estimates and variation coefficients (CV%) for optimal models were Ke 0.071 h^{-1} (27%) and Vd 0.59 l/kg (9%) (NONMEM) and Ke 0.079 h^{-1} (42%), Vd 0.65 (48%) (NPEM2). NONMEM showed less bias (P<0.05) than NPEM2. These data are in agreement with those by Nahata et al. [42, 45] (see Table 3).

Table 3 summarises the kinetic parameters of tobramycin and shows that $t_{1/2}$ ranged from 4.4 to 9.9 h, Cl ranged from 0.69 to 1.19 ml min^{-1} kg^{-1} and Vd ranged from 0.49 to 0.94 l/kg.

Amikacin

The literature on the pharmacokinetics of amikacin in the neonate is sparse and scanty. A study on the extended interval between doses is lacking. Langhendries et al. [46] suggest administrating amikacin to neonates once daily. These authors compared peak and trough concentrations of amikacin after once-daily and twice-daily dosing. The peak concentration was 23.1±3.3 μg/ml (once daily, 15 mg/kg) and 13.6±3.2 μg/ml (twice-daily, 7.5 mg/kg every 12 h) (P <0.001). Conversely, the trough concentration was not different with two dosages. Young and Mangum [7] suggest an amikacin dose of 18 mg/kg every 48 h during the first week of life when the gestational age was ≤29 weeks; a dose of 18 mg/kg every 36 h during the first week of life when the gestational age was 30–34 weeks; and a daily dose of 15 mg/kg when the gestational age was ≥35 weeks.

Tréluyer et al. [47] studied the population pharmacokinetics of amikacin in neonates, infants and children, and the kinetics parameters are an average of all cases. There was a remarkable interindividual variability. Cl ranged from 0.16 to 4.16 ml min^{-1} kg^{-1}, and $t_{1/2}$ ranged from 0.59 to 21.8 h. The plot of Cl versus postnatal age shows that Cl increased up to 20 months of age and then reached a plateau up to at least 80 months. Vd showed an opposite trend; the highest values were found in neonates and then Vd decayed up to 80 months of age. A remarkable interindividual variability in Cl was also observed in extremely premature neonates [48].

Assael et al. [49] studied the effect of intrauterine maturation on the pharmacokinetics of amikacin in 29 neonates whose gestational age and body weight ranged

between 28 and 42 weeks and 0.9 and 4.5 kg respectively. The patients received a daily dose of 7.2 mg/kg amikacin. The trough concentration inversely correlated with the gestational age (R=-0.56) and neonates with gestational age <34 weeks showed significantly higher accumulation of amikacin. The pharmacokinetic parameters of amikacin are shown in Table 4.

Table 4 shows that $t_{1/2}$ ranged from 3.0 to 16.4 h, Cl ranged from 0.36 to 1.71 ml min^{-1} kg^{-1} and Vd ranged from 0.34 to 0.72 l/kg.

Discussion

There is a remarkable variation in the pharmacokinetic parameters of gentamicin [21, 50], netilmicin [30–32, 38], tobramycin [39, 40] and amikacin [51, 52]. Such a variation is due to renal maturation [50] as aminoglycosides are fairly water soluble and are eliminated with the urine. There is a correlation (R=99) between gentamicin Cl and creatinine Cl [53], and gentamicin $t_{1/2}$ correlates (R=0.78) with plasma creatinine concentration [54]. The variability in $t_{1/2}$ and Cl of gentamicin could be due to variability in the glomerular filtration rate [54]. Another source of variability is the gestational age [52]. Other factors generating variability are malnutrition, disease, developmental stage or genetics. These factors can coexist, and it is difficult to divide them between different factors. Monitoring aminoglycoside serum concentration is necessary, especially in critical patients such as the premature infant.

The dose of aminoglycosides and the interval between doses have been changed in neonates during recent years. Increasing the gentamicin dose to 4-5 mg/kg and administering it once daily has been suggested [14–16]. This dose yields peak and trough concentrations which are 5–12 and <2 μg/ml respectively. Additionally, increasing the gentamicin dose to 5 mg/kg and extending the interval between doses to 24-48 h depending on the gestational age has been suggested [19-22]. The extended interval between doses yields peak values of gentamicin between 5 and 12 μg/ml and trough concentrations <2 μg/ml respectively, which are the expected values. Another advantage of the extended interval is to reduce the number of administrations with consequent reduction in the cost of monitoring. Pharmacokinetic parameters such as Vd and Cl are not modified in the extended time interval. The extended interval is also reported for netilmicin [33] and tobramycin [40].

The pharmacokinetic rationale for increasing the gentamicin dose and extending the interval between doses is related to the pharmacokinetics of gentamicin. This drug has a long $t_{1/2}$ and a large Vd, especially in premature infants [21]. The same applies to the other aminoglycosides. The peak concentration is determined by the dose and Vd. When the gentamicin Vd is large, as in premature infants, a dose of 5 mg/kg is correct [7]. At sepsis, Vd of gentamicin increases. The trough concentration is determined by the interval between doses and by $t_{1/2}$. The trough concentration is modified by disease and malnutrition. The once-daily regimen and the extended interval between dose regimens yield trough concentrations <2 μg/ml.

The MIC_{90} of *Escherichia coli* and *Klebsiella pneumoniae*, which are often found in cases of newborn infection, is 0.5 μg/ml for gentamicin [5]; and assuming a peak-to-MIC_{90} ratio above 10, a peak gentamicin serum concentration of 5-12 μg/ml is appropriate to eradicate the infection.

Netilmicin Cl measured in infants with gestational age >36 weeks is double that measured in neonates with gestational age <34 weeks [30], indicating that the dose of netilmicin must be modified according to the developmental stage. The MIC_{90} of *Escherichia coli* and *Klebsiella pneumoniae* is 0.25 μg/ml for netilmicin [5]; and assuming a peak-to-MIC_{90} ratio above 10, a peak netilmicin serum concentration of 2.5 μg/ml is desirable. However it is opportune to have a netilmicin serum concentration of 5-12 μg/ml. The trough concentration obtained with 6 μg/ml every 36 h [33] is lower than that obtained after 2.5 mg/kg twice daily [34] and with 2 mg/kg thrice daily [55]. This suggests that the extended-interval dosing regimen is safer than fractioning the dose of netilmicin during the day. Using the therapeutic schedule given by Young and Mangum [7], peak concentration should range from 5 to 12 μg/ml.

Tobramycin MIC_{90} values for *Escherichia coli* and for *Klebsiella pneumoniae* are 0.5 and 1 μg/ml respectively [5]; and assuming a peak-to-MIC_{90} ratio above 10, a peak tobramycin serum concentration higher than 10 μg/ml should be desirable [40]. What has been stated for gentamicin holds true for tobramycin as well: $t_{1/2}$ is greater in the premature than full-term neonate and the opposite is true for Cl [39].

The peak concentration of amikacin is 26 μg/ml in the adult [6] and is five-fold higher than that of gentamicin [5]. The therapeutic schedule of amikacin differs in different studies. According to the schedule by Young and Mangum [7], peak concentration should be >40 μg/ml and trough concentration should be <6 μg/ml. Amikacin MIC_{90} value for *Escherichia coli* and *Klebsiella pneumoniae* is 1 μg/ml [5], and assuming a peak-to-MIC_{90} ratio above 10, a peak tobramycin serum concentration higher than 10 μg/ml should be appropriate.

The scenario of the aminoglycoside pharmacokinetics in the neonate is complex. Aminoglycosides are mainly eliminated by the kidney and the glomerular filtration rate is lower in the premature than full-term neonate [53], and creatinine Cl correlates with gentamicin Cl [54]. The kinetic parameters of individual aminoglycosides differ

among neonates, and the gestational age is an important factor determining variability [51]. Monitoring aminoglycoside serum concentration is important in neonates [56] and in particular in critical patients such as premature infants.

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