J Pharmacol Sci **124**, 138 – 143 (2014)

Journal of Pharmacological Sciences

Full Paper

Pharmacokinetic Variability of Amikacin After Once-Daily and Twice-Daily Dosing Regimen in Full-Term Neonates

Katarina Vučićević[1,*], Zorica Rakonjac[2], Branislava Miljković[1], Borisav Janković[2,3], and Milica Prostran[4]

[1]*Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade-Faculty of Pharmacy, 11000 Belgrade, Serbia*
[2]*Institute for Mother and Child Care of Serbia "Dr. Vukan Čupić", 11000 Belgrade, Serbia*
[3]*Department of Pediatrics, University of Belgrade-School of Medicine, 11000 Belgrade, Serbia*
[4]*Department of Pharmacology, Clinical Pharmacology and Toxicology, University of Belgrade-School of Medicine, 11000 Belgrade, Serbia*

Received July 30, 2013; Accepted November 10, 2013

Abstract. The purpose of the study was to compare peak (C_{peak}) and trough (C_{trough}) amikacin levels after twice-daily (TD) or once-daily dosing (OD) in full-term neonates. Additionally, the study aimed to address amikacin pharmacokinetics and its variability. Data included 31 patients born on term. Amikacin daily dose was 15 or 20 mg/kg depending on the neonate's age. Patients randomly received amikacin every 12 or 24 h. In all patients corresponding C_{peak} and C_{trough} were taken. Volume of distribution (Vd), clearance (CL) and half-life ($t_{1/2}$) were calculated. Mean C_{peak} of 21.79 μg/ml in the TD group was statistically different from C_{peak} of 36.39 μg/ml in the OD group. Average C_{trough} in TD (5.67 μg/ml) was statistically different from the corresponding 3.99 μg/ml in the OD group. Mean amikacin Vd, CL, and $t_{1/2}$ were 0.78 ± 0.38 l/kg, 86.99 ± 48.22 ml/h·kg, and 6.81 ± 2.51 h, respectively. High interindividual pharmacokinetic variability was observed. Further analysis showed that neonatal age contributed to the pharmacokinetic parameters' values. Statistically significant difference in CL and $t_{1/2}$ was observed between patients age ≤ 2 and > 2 days on therapy initiation. As expected, amikacin given OD achieved higher C_{peak} and lower C_{trough} than TD. Based on the results, observed variability in amikacin pharmacokinetics was possibly due to the renal maturation process.

Keywords: amikacin, pharmacokinetics, full-term neonate, dosing regimen

Introduction

Amikacin is commonly used with β-lactam antibiotics for the treatment of presumed or proven sepsis in neonates. Concentration-dependent pharmacokinetics, post-antibiotic effect, and adaptive resistance provide a starting point for once-daily (extended) dosing regimen (OD) where higher doses are given less frequently (1, 2). OD is as effective and safe as multiple-daily (traditional) dosing regimen (3). Nevertheless, when aminoglycozide antibiotics are administered OD, better pharmacokinetic profile with target drug levels is achieved (3, 4). However, there is still uncertainty, and no consensus on the target amikacin concentration range. According to British National Formulary for Children, target amikacin peak levels (C_{peak}) for twice daily (TD) should not be > 30 μg/ml, and trough levels (C_{trough}) should be < 10 μg/ml, while for OD, C_{trough} should be < 5 μg/ml (5).

Amikacin pharmacokinetics depends on physiological characteristics of neonates. Due to hydrophilic properties, amikacin distributes in the extracellular space. As neonates have rather high percentage of extracellular fluid compared to total body weight, volume of distribution (Vd) expressed in liters per body weight is larger in neonates than infants, children, adolescents, and adults (6, 7). Reported Vd values in neonatal patients range from 0.3 to 0.77 l/kg (8 – 13). Amikacin is almost completely eliminated by the kidneys. Hence, glomerular filtration rate (GFR) determines the clearance (CL) of amikacin. Anatomical and functional renal development

*Corresponding author. kacav@pharmacy.bg.ac.rs
Published online in J-STAGE on January 18, 2014
doi: 10.1254/jphs.13126FP

occurs throughout the gestational and neonatal period. Nephrogenesis is completed at 36 weeks of gestation (14). In full-term neonates, renal function further changes due to kidney maturation and the growth process, and these changes can be observed day-to-day (15). Assessing renal function in the first days of life is difficult in clinical practice. Because serum creatinine (Scr) poorly reflects kidney function, GFR estimation is rather inaccurate in neonates (16). Therefore, GFR may be estimated via drugs completely eliminated via the renal route (17 – 19) or in an alternative way (20). Previous studies indicated that amikacin CL was in the range of 31.3 – 91 ml/h·kg, while half-life ($t_{1/2}$) was in the range of 4 – 9.3 h (8, 11 – 13, 21). High interindividual variability in amikacin pharmacokinetics was previously observed, and it was described in detail in pre-term neonates (9, 11, 22). In pre-term neonates, weight and gestational and/or neonatal age significantly contributed to amikacin pharmacokinetic variability (9, 10, 23). However, in full-term patients, there were only few studies on amikacin pharmacokinetics (8, 21).

The purpose of this study was to compare C_{peak} and C_{trough} amikacin after two dosing regimens in full-term neonates and to address amikacin pharmacokinetics and its variability.

Materials and Methods

Data for this prospective study were collected in the period from 1st September 2009 until 31st January 2010, in the Neonatal Intensive Care Unit (NICU), Institute for Mother and Child Health Care of Serbia "Dr. Vukan Čupić", Belgrade, Serbia. The protocol of the study was reviewed and approved by the Ethics Committee of the Institute. Written informed consent was obtained from the patients' parents before the enrollment in the study. The study was performed in accordance with the Declaration of Helsinki and its amendments and in compliance with the Guidelines of Good Clinical Practice. Inclusion criteria for the enrollment in the study were neonates (aged 0 – 28 days) born on term (≥ 37 gestation weeks) with suspected or confirmed sepsis. Exclusion criteria were neonates born before 37 weeks of gestation, renal insufficiency, patients already treated with other antimicrobial drugs, and patients with congenital anomalies requiring surgical intervention. Before the initiation of therapy the diagnosis of sepsis (proven, probable, possible, nosocomial) was made according to the recommendations of the International Sepsis Definitions Conference.

The neonates were randomly allocated into two groups (TD or OD) according to the amikacin dosing regimen. The daily dose of amikacin was 15 mg/kg for patients of neonatal age ≤ 7 days or 20 mg/kg for age > 7 days. In the TD group, the amikacin daily dose was divided into two doses with a dosing interval of 12 h, while the daily dose in the OD group was given every 24 h. Amikacin® (100 mg/2 ml) injection (Galenika a.d., Belgrade, Serbia) was administered as a 1-h intravenous infusion in 5% glucose solution, with concentration not higher than 5 mg/ml. All patients received intravenous β-lactam antibiotic concomitantly, separate from amikacin.

In all patients two blood samples (volume of 0.5 – 1 ml) were obtained immediately after the discontinuation of the infusion and just before the next dose. These samples corresponded to C_{peak} and C_{trough}. In patients treated with the TD dosing regimen, samples were taken after the 5th dose and in patients with the OD dosing, after the 3rd dose from the initiation of the therapy. In patients with existing central line, venous/arterial sampling was performed. Otherwise a venepuncture procedure was performed. An appropriately trained and experienced medical nurse was responsible for taking blood samples.

Relevant demographic characteristics were collected, including the following: gestation age (weeks), body weight (kg) and body length (cm) at the birth, gender, neonatal age (days) and body weight (kg) at the moment of admission to the hospital, and Apgar score at 1 and 5 min. Moreover, data on maternal age, illness during pregnancy, maternal status during labor as well as therapy was collected in order to detect possible risk factors for developing infection. Complete blood test, C-reactive protein, urea, creatinine, electrolytes serum levels, and bilirubin (if indicated) were performed in all neonates on their admission, as well as urinalysis. Moreover, vital functions were monitored: heart and respiratory rate/min, arterial pressure, and oxygen saturation. Levels of Scr were measured on the admission and on the 3rd and 7th day of the therapy. During the first 3 days of hospitalization, β_2-microglobulin was assessed and between the 7th and 10th day if the patient was still on the ward. Additional C-reactive–protein level was determined after 12 – 24 h following the initial measurement. Auditory function was also assessed with the transient evoked otoacoustic emission (TEOAE) method: during the first 3 days and between the 7th and 10th day of the treatment.

The bioanalytical method used for measuring amikacin concentrations was turbidimetric immunoassay (Thermo Scientific, UniCel® DxC Synchron® Systems, Beckman Coulter Inc., USA).

Amikacin concentrations were used for calculating individual pharmacokinetic parameters applying the one-compartment linear model based on the Sawchuk and Zaske method (24). Based on the following equation,

the elimination rate constant (β) was calculated:

$$C_{trough} = C_{peak} \cdot e^{-\beta \cdot (\tau - t_i)}$$

, where τ is the dosing interval, and t_i is the infusion time. Vd was calculated from the following equation:

$$C_{peak} = \frac{R_0 \cdot (1 - e^{-\beta \cdot t_i})}{\beta \cdot Vd \cdot (1 - e^{-\beta \cdot \tau})}$$

, where R_0 is the rate of drug infusion (mg/kg·h), while CL was calculated from estimated values of Vd and β.

Descriptive and statistical analysis was performed using PASW Statistics® (ver.18.0; SPSS Inc., Chicago, IL, USA). Test of normality and equal variances were applied in order to assess if parametric tests may be used. Parameters with normal distribution were presented as the mean value, whereas data with non-normal distribution were given as the median. For comparing the differences in mean/median values between two groups, the unpaired Student's *t*-test or the Mann-Whitney U test was employed. Level of statistical significance was set at $P < 0.05$.

Results

Based on the inclusion/exclusion criteria, 31 neonates were included in the study: 16 patients on TD and 15 patients on OD amikacin dosing regimen. There were no statistical differences in demographic characteristics of patients between groups (Table 1). In 5 patients, sepsis was confirmed by the isolation of *Acinetobacter* spp, *Escherichia coli* (2 patients), *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.

Amikacin levels after the TD and OD dosing regimen are presented on Fig. 1. Mean amikacin C_{peak} in the TD group was statistically different ($P < 0.001$) from the corresponding level in the OD group, as given in Table 2. In 2 (12.5%) patients of the TD group, C_{peak} was below 15 μg/ml and 2 (12.5%) patients reached concentrations above 30 μg/ml. In 2 patients to whom amikacin was administered OD, C_{peak} was below 30 μg/ml. Mean C_{trough} in the TD group was statistically different ($P < 0.001$) from the mean C_{trough} in the OD group (Table 2). In all patients in both groups, C_{trough} values were below 10 μg/ml. However, in the TD group 5 (31.25%) patients had C_{trough} less than 5 μg/ml, whereas in the OD group, in all except 1 patient, C_{trough} values were about or less than 5 μg/ml. No statistical differences in the mean pharmacokinetic parameters' values were observed between groups. According to the results of this study, mean Vd, CL, and $t_{1/2}$ of amikacin in full-term neonates were 0.78 ± 0.38 l/kg, 86.99 ± 48.22 ml/h·kg and 6.81 ± 2.51 h, respectively. High interindividual pharmacokinetic variability was observed. Hence, further analysis revealed that neonatal age contributes to the changes in pharmacokinetic parameters of elimination. Statistically significant difference was observed in CL and $t_{1/2}$ between patients whose neonatal age was ≤ 2 days and those with neonatal age of > 2 days on the day of initiating amikacin therapy, as presented in Table 3. The data on efficacy and safety are not presented, as this study was focused on pharmacokinetic aspects. However,

Table 1. Demographic characteristics of patients

Characteristics	Dosing regimen of amikacin	
	Once-daily (n = 15)	Twice-daily (n = 16)
Number of males (%)	11 (73.33%)	11 (68.75%)
Neonatal age 0 – 7 days (%)	9 (60%)	12 (75%)
Gestational age (weeks)		
37 – 38	4 (26.67%)	11 (68.75%)
39 – 40	10 (66.67%)	4 (25%)
41 – 42	1 (6.67%)	1 (6.25%)
Body weight (kg)	3.44 ± 0.66	3.37 ± 0.52
Proven sepsis (%)	4 (26.67%)	1 (6.25%)

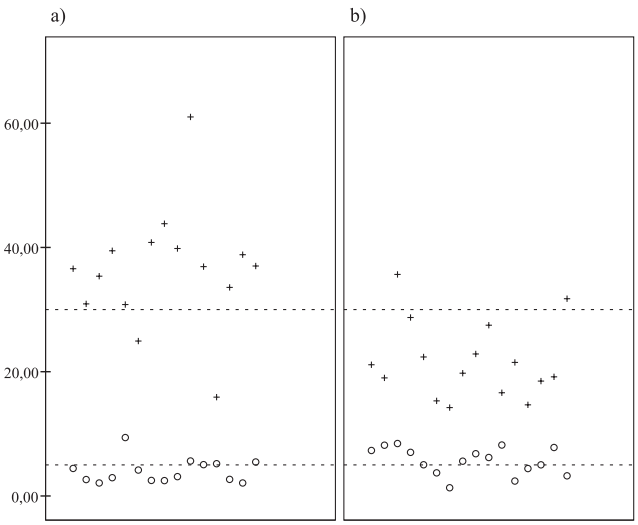

Fig. 1. Trough (circle) and peak (cross) amikacin concentrations after a) Once-daily and b) Twice-daily dosing regimen in neonates.

Table 2. Mean trough and peak amikacin concentrations in neonates on once-daily and twice-daily dosing regimen

Parameter	Dosing regimen of amikacin	
	Once-daily (n = 15)	Twice-daily (n = 16)
Trough concentration (μg/ml)	3.99 ± 1.97	5.67 ± 2.20*
Peak concentration (μg/ml)	36.39 ± 9.75	21.79 ± 6.22**

*$P < 0.05$, **$P < 0.001$.

Table 3. Median values of amikacin pharmacokinetic parameters in neonates

Pharmacokinetic parameters	Neonatal age 1 and 2 days (n = 18)	Neonatal age > 2 days (n = 13)
Volume of distribution, Vd (l/kg)	0.68	0.62
Clearance, CL (ml/hkg)	65.11	79.98*
Half-life, $t_{1/2}$ (h)	6.94	5.64*

*$P < 0.05$.

no difference was observed in the monitored parameters of efficacy and toxicity between groups on different dosing regimens at the beginning and at the end of the therapy. In this study, Scr levels and TEOAE did not show marked change by the end of the amikacin therapy between groups. The results of our study did not show any relationship between amikacin C_{trough} and ototoxicity. All patients were cured by the end of the treatment, and there was no follow up on amikacin ototoxicity upon discharge of the patients from the hospital. Therefore, these data did not allow us to determine correlations of the amikacin concentrations with efficacy and toxicity parameters.

Discussion

The results of the present study confirmed that significantly higher C_{peak} and lower C_{trough} were achieved with OD dosing regimen of amikacin in comparison to TD dosing. Lower C_{peak} levels might be risky for the efficacy, since they may not attain the desired ratio of C_{peak} and minimal inhibitory concentration (MIC) (25). According to the results of our study, this was more probable when amikacin was administered TD, and it might be due to the large values of amikacin Vd. Additionally, as previously described, this might delay the start of the amikacin effect for 1 – 2 days from the initiation of therapy to when the therapeutic steady-state C_{peak} occurs. On the contrary, when amikacin was administered OD, it was expected to reach levels above the usual ones for TD dosing. C_{peak} after extended dosing might be up to 60 μg/ml (26), and they usually relate to enhanced therapeutic outcomes. Measured C_{peak} in patients in this study were consistent with previously reported maximum concentrations in pre-term and term neonates (17.1 – 43.3 μg/ml) (8, 12).

Evidence from in vitro and animal studies indicated that aminoglycoside antibiotics exhibit a post-antibiotic sub-MIC effect that suppressed bacterial growth when a low concentration ($\leq 0.3 \times$ MIC) was added to bacteria previously exposed to a supra-inhibitory concentration (27). Due to prolonged dosing interval in OD compared to TD, a lower C_{trough} was observed in our study (Table 2 and Fig. 1). Since it is not required for the drug to accumulate, target amikacin C_{trough} after OD was lower than that proposed for TD dosing. Therefore, C_{trough} may approximate zero at the end of the extended dosing interval, as it was shown for other aminoglycoside antibiotics (2, 3). Additionally, the developed predictive pharmacokinetic–pharmacodynamic model for gentamicin dosing schedules in neonates supported equivalent efficacy when the dosing interval was 24, 36, or 48 h for the same total dose (28). This result may be extrapolated to amikacin as well, where C_{trough} after OD can be targeted at 1.5 to 3 μg/ml (18, 29). In our study, 53.33% of patients in the OD group had $C_{trough} > 3$ μg/ml. This indicates the need to extend the dosing interval from 24 to 36 h or even to 48 h in order to achieve the defined concentration. The results from our study are in compliance with previously reported data on amikacin C_{trough} in term neonates, which were in the range from 0.5 to 6.6 μg/ml (8). Furthermore, target concentrations for the individual patient will depend on the patient's clinical condition, site of the infection, and particularly on MIC of the suspected/isolated bacterial pathogen (26).

Amikacin pharmacokinetic parameters in our study are comparable to previously published values of Vd, CL, and $t_{1/2}$ (8, 21). No statistical differences in the mean parameters values were observed between groups, as amikacin shows linear pharmacokinetics. However, relatively high coefficients of variation for aforementioned parameters demonstrate significant interindividual pharmacokinetic variability of amikacin in full-term neonates. The findings of other authors confirm that variability in amikacin elimination was caused by gestation age or birth weight which correlates to gestation age. However, in these studies, pre- and full-term neonates were included (10, 18, 30). There were as well conflicting data if postmenstrual (sum of gestational and neonatal) age was a good predictor of aminoglycoside CL (12, 17, 23, 31). Considering the fact that the major changes in blood flow occur during the transition from the intrauterine to the extrauterine environment, it seems rational to observe gestational and neonatal age as independent factors since their influences on amikacin CL are different due to distinct causes (32, 33). For that reason, we must emphasize that our study included neonates $\geq$ 37 weeks, and it would not be expected to

observe variability due to gestation age. However, in our study patients born on 37 – 38 weeks of gestation showed the tendency for lower CL (without significant difference) in comparison to newborns born on 41 – 42 week of gestation, as previously observed (11). Due to the limited number of patients in our study, it was not possible to assess the age influence as continuous covariate. Therefore, the result in the study may seem overemphasized, but we tried to explain the variability observed in the pharmacokinetic parameters. On the other hand, nephrogenesis is completed by 36 weeks of gestation (14), so it may not be expected to detect significant differences in pharmacokinetics between neonates born on 37 and 41 weeks of gestation. Therefore, our results indicate that the change in CL and amikacin $t_{1/2}$ was possibly due to kidney maturation. Findings of this study indicate that amikacin CL was lower in patients in whom therapy was initiated in the first two days of life in contrast to the older full-term neonates (Table 3), and it perhaps reflects the changes in GFR with neonatal age. Data on measured Scr were not presented in this report as no difference in Scr was observed between the initiation of treatment and the end of the treatment. However, it was noticed that Scr levels decreased with neonatal age with the steepest slope in the youngest neonates. Observed changes were physiologically altered, due to maturation of kidneys' function that was extensive in the first days of life (33, 34). Hence, our data show that amikacin $t_{1/2}$ was prolonged immediately after birth in comparison to older neonates. As mentioned, the limitation of this study was that the majority of patients were neonatal age 1 – 2 days, while other age categories (up to 1 month) included only 1 – 2 patients. Consequently, it was not possible to observe the tendency of the changes in CL and $t_{1/2}$ during the neonatal period in the present study, but it has been shown by population pharmacokinetic models (18). However, based on the presented results it may be reasonable to explain the variability in CL with neonatal age and kidney maturation.

Large interindividual pharmacokinetic variability of amikacin in full-term neonates emphasizes the need for further research where factors that contribute to pharmacokinetic variability and hence dosing regimen will be quantitatively determined.

The results of this study highlighted the differences between amikacin C_{peak} and C_{trough} in full-term neonates on twice-daily and once-daily dosing regimen, and our results contribute to defining the optimal therapeutic range of amikacin. Additionally, calculated pharmacokinetic parameters revealed high interindividual variability that may be partially explained by neonatal age.

Acknowledgments

The authors would like to acknowledge the Institute for Mother and Child Health Care of Serbia "Dr. Vukan Čupić", Belgrade, Serbia for providing an excellent environment and facilities to perform this project.

This study was conducted within the project Experimental and Clinical-Pharmacological Investigations of Mechanisms of Drug Action and Interactions in Nervous and Cardiovascular System (No. 175023) funded by Ministry of Science and Technological Development, Belgrade, Republic of Serbia.

Conflicts of Interest

The authors indicated no potential conflicts of interest.

References

1 Craig WA. Once-daily versus multiple-daily dosing of aminoglycosides. J Chemother. 1995;7 Suppl 2:47–52.
2 Lundergan FS, Glasscock GF, Kim EH, Cohen RS. Once-daily gentamicin dosing in newborn infants. Pediatrics. 1999;103: 1228–1234.
3 Rao SC, Srinivasjois R, Hagan R, Ahmed M. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2010:CD005091.
4 Croes S, Koop AH, van Gils SA, Neef C. Efficacy, nephrotoxicity and ototoxicity of aminoglycosides, mathematically modelled for modelling-supported therapeutic drug monitoring. Eur J Pharm Sci. 2012;45:90–100.
5 Paediatric Formulary Committee. British National Formulary (BNF) for Children. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications; 2013–2014.
6 Pacifici GM. Clinical pharmacokinetics of aminoglycosides in the neonate: a review. Eur J Clin Pharmacol. 2009;65:419–427.
7 Touw DJ, Westerman EM, Sprij AJ. Therapeutic drug monitoring of aminoglycosides in neonates. Clin Pharmacokinet. 2009;48: 71–88.
8 Abdel-Hady E, El Hamamsy M, Hedaya M, Awad H. The efficacy and toxicity of two dosing-regimens of amikacin in neonates with sepsis. J Clin Pharm Ther. 2011;36:45–52.
9 Allegaert K, Anderson BJ. Interindividual variability of aminoglycoside pharmacokinetics in preterm neonates at birth. Eur J Clin Pharmacol. 2006;62:1011–1012.
10 Allegaert K, Anderson BJ, Cossey V, Holford NH. Limited predictability of amikacin clearance in extreme premature neonates at birth. Br J Clin Pharmacol. 2006;61:39–48.
11 Schreuder MF, Wilhelm AJ, Bokenkamp A, Timmermans SM, Delemarre-van de Waal HA, van Wijk JA. Impact of gestational age and birth weight on amikacin clearance on day 1 of life. Clin J Am Soc Nephrol. 2009;4:1774–1778.
12 Sherwin CM, Svahn S, Van der Linden A, Broadbent RS, Medlicott NJ, Reith DM. Individualised dosing of amikacin in neonates: a pharmacokinetic/pharmacodynamic analysis. Eur J Clin Pharmacol. 2009;65:705–713.
13 Treluyer JM, Merle Y, Tonnelier S, Rey E, Pons G. Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. Antimicrob Agents Chemother. 2002;46:1381–1387.
14 Quaggin SE, Kreidberg J. Embriology of the kidneys. In: Taal

MA, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM, editors. Brenner and Rector's The Kidney. 9th ed. Philadelphia: Saunders; 2011.
15 Tayman C, Rayyan M, Allegaert K. Neonatal pharmacology: extensive interindividual variability despite limited size. J Pediatr Pharmacol Ther. 2011;16:170–184.
16 Work DF, Schwartz GJ. Estimating and measuring glomerular filtration rate in children. Curr Opin Nephrol Hypertens. 2008; 17:320–325.
17 Allegaert K, Anderson BJ, van den Anker JN, Vanhaesebrouck S, de Zegher F. Renal drug clearance in preterm neonates: relation to prenatal growth. Ther Drug Monit. 2007;29:284–291.
18 De Cock RF, Allegaert K, Schreuder MF, Sherwin CM, de Hoog M, van den Anker JN, et al. Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. Clin Pharmacokinet. 2012;51:105–117.
19 Koren G, James A, Perlman M. A simple method for the estimation of glomerular filtration rate by gentamicin pharmacokinetics during routine drug monitoring in the newborn. Clin Pharmacol Ther. 1985;38:680–685.
20 Tanaka A, Suemaru K, Araki H. A new approach for evaluating renal function and its practical application. J Pharmacol Sci. 2007;105:1–5.
21 Padovani EM, Pistolesi C, Fanos V, Messori A, Martini N. Pharmacokinetics of amikacin in neonates. Dev Pharmacol Ther. 1993;20:167–173.
22 Allegaert K. Aminoglycoside pharmacokinetics in neonates: the need to search for covariates of variability in addition to case descriptions. Acta Paediatr. 2009;98:1546.
23 Kenyon CF, Knoppert DC, Lee SK, Vandenberghe HM, Chance GW. Amikacin pharmacokinetics and suggested dosage modifications for the preterm infant. Antimicrob Agents Chemother. 1990;34:265–268.
24 Sawchuk RJ, Zaske DE, Cipolle RJ, Wargin WA, Strate RG. Kinetic model for gentamicin dosing with the use of individual patient parameters. Clin Pharmacol Ther. 1977;21:362–369.
25 Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987;155: 93–99.
26 Burton M, Shaw L, Schentag J, Evans W. Applied Pharmacokinetics & pharmacodynamics: principles of therapeutic drug monitoring. 4th ed. London: Lippincott Williams & Wilkins; 2006.
27 Cars O, Odenholt-Tornqvist I. The post-antibiotic sub-MIC effect in vitro and in vivo. J Antimicrob Chemother. 1993;31 Suppl D:159–166.
28 Mohamed AF, Nielsen EI, Cars O, Friberg LE. Pharmacokinetic-pharmacodynamic model for gentamicin and its adaptive resistance with predictions of dosing schedules in newborn infants. Antimicrob Agents Chemother. 2011;56:179–188.
29 De Hoog M, van den Anker J. Aminoglicosides and glycopeptides. In: Yaffe SJ, Aranda JV, editors. Neonatal and pediatric pharmacology: therapeutic principles in practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2010. p. 412–435.
30 Bleyzac N, Varnier V, Labaune JM, Corvaisier S, Maire P, Jelliffe RW, et al. Population pharmacokinetics of amikacin at birth and interindividual variability in renal maturation. Eur J Clin Pharmacol. 2001;57:499–504.
31 Anderson BJ, Holford NH. Tips and traps analyzing pediatric PK data. Paediatr Anaesth. 2011;21:222–237.
32 Bueva A, Guignard JP. Renal function in preterm neonates. Pediatr Res. 1994;36:572–577.
33 Mannan MA, Shahidulla M, Salam F, Alam MS, Hossain MA, Hossain M. Postnatal development of renal function in preterm and term neonates. Mymensingh Med J. 2012;21:103–108.
34 Langhendries JP, Battisti O, Bertrand JM, Francois A, Darimont J, Ibrahim S, et al. Once-a-day administration of amikacin in neonates: assessment of nephrotoxicity and ototoxicity. Dev Pharmacol Ther. 1993;20:220–230.