ORIGINAL ARTICLE

A Retrospective Study of Amikacin Dosage Adequacy Based on Therapeutic Drug Monitoring in Neonates in a Tertiary Care Hospital in Kelantan, Malaysia.

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Abstract

Body weight, age, and kidney function especially in neonates, significantly influence amikacin distribution and/or clearance, causing large pharmacokinetics variability, which directly effects minimum and maximum concentrations (C_{min} and C_{max}, respectively) when coupled with amikacin dose regimen. This study aims to investigate amikacin dose adequacy based on therapeutic drug monitoring (TDM) results obtained from neonatal patients. A retrospective study was conducted from July to September 2020 at Hospital Raja Perempuan Zainab II, Kelantan, Malaysia. A total of 229 blood samples were collected from neonates who were prescribed amikacin and had TDM performed from 1st January to 31st December 2019. The data is analysed using Statistical Package for Social Sciences (SPSS) version 25.0. The significance level is set at $p<0.05$. Out of the total, 113 (49.3%) neonates were prescribed amikacin doses of <7.5 mg/kg/day, while another 110 neonates (48.0%) received doses between 7.5 to 15 mg/kg/day. The remaining 2.7% (n = 6) of neonates received doses above 15 mg/kg/day. The results showed that 95.2% (n = 218) neonates achieved therapeutic C_{min} of <5 mg/L. Most neonates (80.8%) had inadequate C_{max} with only 19.2% (n = 44) accomplishing therapeutic C_{max} of ≥20 mg/L. Preterm neonates were shown to achieve the most therapeutic C_{max} (61.4%) followed by term neonates (38.6%). Neonates who achieved the target C_{max} were prescribed a dosing regimen of 7.5 to 15 mg/kg/day (12.2%) with a mean ± SD amikacin dose of 9.39 ± 3.01 mg/kg/day in this study. Almost 50% of amikacin doses prescribed for the study population were below the recommendations in the common dose guidelines, contributing to amikacin dosage inadequacy. Future detailed studies are needed to further investigate other factors associated with amikacin dose adequacy in neonates and to develop neonatal population pharmacokinetics model of amikacin.

Keywords: *Amikacin; dosage adequacy; C_{min}; C_{max}; neonates.*

Introduction

Amikacin is commonly prescribed for empiric treatment of suspected and severe hospital-acquired infections in neonates [1]. It is a concentration-dependent antibiotic with rapid and potent bactericidal activity against several Gram-negative bacilli and Gram-positive cocci [2]. Attainment of therapeutic maximum concentration of amikacin in plasma is strongly correlated with a diminution in mortality resulting from infections [3] [4].

Nephrotoxicity and ototoxicity, defined as cochlear or vestibular damage could occur if amikacin C_{trough} exceeded 5 mg/L [5]. The risk of toxicity is even higher if amikacin is administered for more than 10 days, given subsequently with a diuretic such as frusemide or following treatment of another aminoglycoside [5]. However, amikacin is less toxic to the neonatal kidney compared to gentamicin or netilmicin, and plausibly less ototoxic [6]. Amikacin efficacy and toxicity have a strong positive relationship with C_{peak} and C_{trough}, therefore an optimum amikacin dosage is required owing to inter-individual variability in the pharmacokinetics of the neonatal population [1].

The common amikacin dose used in practice for neonates is 10 mg/kg intravenous load followed by 5 to 7.5 mg/kg every 8 to 12 hours up to 15 mg/kg/day [7]. Another dosing guideline used for amikacin in preterm neonates is a stat dose of 15 mg/kg followed by 7.5 mg/kg (gestational age <30 weeks) or 10 mg/kg (gestational age of 30 to 35 weeks) or 15 mg/kg (for term neonates aged <1 week) daily (8). Once-daily administration of amikacin was better tolerated and had better pharmacodynamic advantages than the conventional schedules in adults and children [9] [10]. Once-daily dosing amikacin was able to achieve higher C_{peak} and lower C_{trough} and did not cause more nephrotoxicity than a twice daily dosing regimen in presumed or confirmed sepsis in neonates ≥36 weeks of gestational age who weighed more than 2.5kg [11].

The dose adequacy of amikacin is defined in this study as the attainment of both targeted therapeutic amikacin maximum and minimum concentrations. Currently, there is no specifically published data on the neonates' amikacin dose adequacy in Malaysia. This study not only aimed at determining whether amikacin doses based on the commonly recommended dose guidelines [7[[8] [12] were adequate for neonates to achieve the targeted concentration level but also to determine amikacin pharmacokinetics parameters such as mean rate of elimination (Ke), half-life ($t_{½}$) and volume of distribution (V_d) in Malaysian neonates admitted to Hospital Raja Perempuan Zainab II (HRPZII), Kelantan.

Materials and methods

Study design and population

A retrospective, observational study was conducted to include blood samples that satisfies every inclusion and exclusion criteria. Sample size calculation and specific sampling methods were not performed, as all eligible blood samples from the year 2019 were incorporated into this study. The inclusion criteria were that neonates must have received amikacin for more than 3 days and have been reviewed by the therapeutic drug monitoring (TDM) unit between 1st January to 31st December 2019. Meanwhile, patients with incorrect sampling times and insufficient monitored levels were excluded.

Neonatal patients were categorized into two subgroups: preterm and term. Preterm is defined as neonates of gestational age <37 weeks and term is ≥37 weeks [13]. The C_{min} monitored was categorized into two renditions: toxic and therapeutic. Toxic dose was defined as a calculated C_{min} of ≥5mg/L and conversely, a therapeutic dose was defined as a C_{min} below this threshold. [7]. The maximum concentration (C_{max}) achieved was defined as adequate if the sample was able to attain the C_{max} of >20mg/L; otherwise, it was deemed inadequate. [7]

Data collection

The information collected from TDM request forms were patient's demographic variables data such as race, age, body weight, gender, and amikacin regimen in addition to the calculated pharmacokinetics data such as volume of distribution (V_d), rate of elimination (K_e), half-life ($t_{½}$), maximum (C_{max}), and minimum (C_{min}) concentrations.

Statistical analyses

The gathered data was tabulated and analysed using SPSS version 25.0. All demographic and clinical characteristics collected via data collection form were analysed using descriptive statistics such as mean, standard deviation (SD), frequency (n), and percentage (%). The associations between demographic data and amikacin concentrations were tested using Chi-square and independent t-test. A p-value of <0.05 was considered statistically significant.

Ethical approval

This research is registered with the National Medical Research Registry (NMRR-20-1194-54684) and approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. Permission to conduct the study at the facility was granted by the Director of HRPZ II.

Results

Characteristics of the study population

A total of 229 blood samples which comprised 48.5% (n = 111) females and 51.5% (n = 118) males were obtained within the study period. The mean ± SD age for neonates is 14.14 ± 10.18 days and they were mostly Malay (n = 215, 93.9%). The mean ± SD body weight for preterm and term neonates were 1.62 ± 0.50 kg and 3.06 ± 0.57 kg, respectively. The mean ± SD doses of amikacin prescribed for preterm and term neonates in this study are 8.13 ± 2.24 mg/kg/day and 8.46 ± 2.44 mg/kg/day, respectively. A total of 113 (49.3%) neonates were prescribed doses of <7.5 mg/kg/day while another 110 (48.0%) neonates were administered with amikacin doses of 7.5 to 15 mg/kg/day. The remaining 2.7% (n = 6) of neonates received amikacin doses of >15 mg/kg/day. For the renal profile, preterm neonates have higher mean ± SD serum creatinine (SCr) level which corresponded to lesser mean ± SD creatinine clearance (CrCl) when compared with term neonates (Table 1).

Monitored therapeutic concentration of amikacin and pharmacokinetics parameters among the study population

The analysed result demonstrated that 95.2% (n = 218) of neonates had achieved therapeutic C_{min} <5 mg/L and only a small percentage of C_{min} blood samples (n = 11, 4.8%) were toxic. The majority of neonates (n = 185, 80.8%) had inadequate C_{max} with only 19.2% (n = 44) of neonates managed to achieve adequate therapeutic C_{max} of ≥20 mg/L. It is noted that with the prescribed amikacin dose of ≤15 mg/kg/day (93.0%), the neonates are unable to attain adequate $C_{max.}$ Neonates who achieved adequate amikacin C_{max} ≥20 mg/L had a mean ± SD amikacin dose of 9.39 ± 3.01 mg/kg/day, meanwhile those who attained inadequate amikacin C_{max} had mean ± SD amikacin dose of 8.01 ± 2.06 mg/kg/day. According to the analysis, the mean ± SD K_e for preterm and term neonates are quite similar (0.11 ± 0.04 hr^{-1} and 0.12 ± 0.03 hr^{-1}, respectively). As for the V_d, its mean ± SD is slightly larger among preterm neonates when compared with term neonates (0.80 ± 0.52 L/kg and 0.76 ± 0.52 L/kg, respectively). Meanwhile, the mean ± SD t½ of amikacin in preterm neonates is greater than the term neonates (8.18 ± 5.02 hr and 6.47 ± 3.90 hr, respectively) (Table 2).

Association between the characteristics of the study population and amikacin concentrations

When tested using inferential statistics, it was found that there is no significant association between the characteristics of the study population and amikacin dose adequacy except for the amikacin doses received by the neonates (p=0.022) (Table 3).

Discussion

Amikacin therapeutic use requires caution due to its narrow therapeutic spectrum and high inter-individual variability [1]. Neonates represent a particularly fragile population where adequate dosing is crucial yet challenging to achieve due to significant inter-individual variability associated with developmental processes and other pathological factors such as sepsis or burns [1] [14].

Elevated C_{trough} levels of amikacin have been associated with renal toxicity, especially in neonates [15]. Amikacin causes transient, commonly non-oliguric, renal failure in 10% to 30% of patients and is the cause of most drug-induced acute nephrotoxicity [16] [17], along with irreversible ototoxicity [18]. Due to its hydrophilic nature, amikacin is primarily eliminated through glomerular filtration (GFR), which matures after birth and continue to develop until around 2 years of age (14, 19). Elimination half-lives were 7 to 14 hours in infants, with a post menstrual age of less than 30 weeks, and 4 to 7 hours at a post menstrual age of 40 weeks (20).

This study revealed that preterm neonates, with a mean $\pm$ SD weight of 1.55 ± 0.93 kg are able to achieve adequate C_{max} with a mean $\pm$ SD amikacin dose of 8.86 ± 2.91 mg/kg/day. Meanwhile, term neonates who achieved adequate C_{max} had a mean $\pm$ SD weight of 3.05 ± 0.58 kg and received a mean $\pm$ SD amikacin dose of 8.46 ± 2.44 mg/kg/day. According to Berger et al. (2004), an amikacin dosing and monitoring protocol of a loading dose of 10 mg/kg followed by a maintenance dose of 7.5 mg/kg every 24 hours enabled targeted C_{peak} and C_{trough} in a high percentage of very low birth-weight infants with nosocomial infection after the first week of life, except for extremely low birthweight infants weighing <0.70 kg and/or with a gestational age of $\leq$24 weeks [21] which aligns by our findings.

In this study, the toxic level is defined as $C_{min} \geq$ 5mg/L, consistent with findings from other studies [22] [23] except for a study done by Hughes et al. (2017) where a C_{trough} >8mg/L was designated as toxic for amikacin pharmacokinetics comparison in neonates [24]. Engler et al. (2015) reported the acceptable trough level of amikacin in newborns was up to 10 mg/L [25]. Amikacin blood concentrations >10mg/L in vitro could increase the risk of ototoxicity [26] [27] which was demonstrated by Arshad et al. (2011). The ototoxicity caused by amikacin mostly depended on duration of therapy and the total dose administered [28]. Deafness, tinnitus or dizziness were not observed in the study by Javadi et al (2011) [29]. The mean $\pm$ SD toxic C_{min} of the neonates investigated in this study is 6.37 $\pm$ 2.04 mg/L, which is lower than the acceptable C_{min} that has ever been reported [30] [33]. This is likely because the amikacin regimen prescribed in our settings is primarily low dose.

Our study showed that 95.2% of neonates achieved therapeutic C_{min} <5mg/L, while only a small percentage of C_{min} blood samples (4.8%) were toxic. Marik et al. (1991) reported similar findings, as all paediatrics' patients included in their research who received once-daily dosing of amikacin had C_{trough} <5 mg/L (31). However, the majority of neonates in our study received doses of <7.5mg/kg/day (49%), and only 48% of them being administered doses within the range of 7.5 to 15mg/kg/day as per the guidelines [7] [8] [12]. Since amikacin toxicity is dose-dependent [22] [32], it could be inferred that the lower doses of amikacin received by most neonates in this study led to non-toxic C_{min} levels of amikacin.

Interestingly, our data demonstrated that out of 13 neonates who had toxic C_{min}, seven of them were preterm neonates, consistent with the investigation by Siddiqi et al. (2009). In their study, the majority of preterm infants (62.0%) receiving amikacin in a once-daily dosage regimen had toxic C_{min} levels, while approximately 23.0% had subtherapeutic levels when compared to term infants (21.0%)[33]. Siddiqi et al. (2009) found that preterm infants had significantly higher median (range) serum amikacin levels of 11.33 (1.50-42.60) µg/ml compared to term babies with levels of 8.5 (2.8-33.0) µg/ml ($p<0.05$) [33].

Several studies have documented the clinical and microbiological efficacy of once-daily dosing of amikacin in combination with β-lactams [34]. Amikacin antibacterial effect is best affiliated with C_{max} and the ratio of C_{max} to minimal inhibitory concentration (MIC) for specific bacteria. A C_{max}/MIC ratio >8 is necessary for optimum bactericidal effects [19] [35] thus improving the patients' clinical outcome, especially in cases involving highly resistant bacteria in severe infections [36]. Amikacin dose adequacy is defined in this study as blood samples collected achieving C_{max} of $\geq$20 mg/L (adequate) and vice versa. Since amikacin is a dose-dependent drug, no maximum peak concentration has ever been documented or studied previously [22].

A highly water-soluble compound such as amikacin has a larger V_d in neonates [37], especially in more preterm infants [38], largely attributed to their body weight as compared to children [39]. This larger mean V_d necessitates a higher daily dose requirement of amikacin in neonates and infants to achieve the targeted therapeutic range [6]. Paediatrics' renal function would naturally reach maturation level within two years of age. Therefore, amikacin clearance started with a sharp increase during the first month of life, followed by gradual rise until the patient reached the age of seven years old [40]. Thus, it is predictable that the neonatal population would have a longer mean t½ and a low mean K_e [6]. Kramer et al. (1979) insinuated that t½ variability of amikacin in children was unquestionably due to the administration route, age, kinetic model used, and analytical technique [41]. The t½ has been reported to be prolonged in paediatrics being inversely proportional to the birth weight [30]. A longer t½ and low K_e in neonates indicated less frequent dosing for C_{max} to achieve adequate therapeutic concentration due to an increase in drug rate of elimination thus supporting the use of a single daily dosing regimen [42].

Extended-interval dosage strategies (15 to 18 mg/kg every 24 to 48 hours) implementing either fixed or individualized dosage based on post menstrual age and postnatal age have resulted in more frequent accomplishment of desired C_{max} of 20 to 35 mg/L in neonates [24]. It is known that intravenous administration of amikacin when given in a dose of 7.5 mg/kg over one hour for every 12 hours consistently produces C_{max} within the therapeutic range during neonates' first two weeks of life [43]. Standard dosing of 15 mg/kg once-daily in neonates delivered an effective amikacin C_{max} of 20 to 40 mg/L (44, 45). According to Smits et al. (2015), an early C_{max} of >24 mg/L (90.5%) and C_{min} of <3 mg/L (60.2%) can be achieved with a loading dosage of 20 mg/kg of amikacin followed by once-daily individualized dosing according to postnatal age and birthweight of 15 to 20 mg/kg amikacin every 24 to 36 hours. However, our research found that 20.1% of neonates were able to reach the appropriate therapeutic Cmax > 20 mg/L at a mean ± SD amikacin dose of 8.28 ± 2.33 mg/kg/day, which is less than the dosing suggested by Smits et al. (2015).[46]

The majority of neonates who achieved adequate C_{max} were in the dose group of 7.5 to 15mg/kg/day with mean $\pm$ SD amikacin dose of 9.39 ± 3.01 mg/kg/day. However, these only accounted for 12.2% of all neonates included in the investigation. The neonates who had inadequate C_{max} had a mean $\pm$ SD amikacin dose of 8.01 $\pm$ 2.06 mg/kg/day. These inadequate C_{max} produced from our study could be due to the prescribed dosing regimens being much less than the dosage recommended by the guidelines [7[[8] [12]. Therefore, it may be appropriate to initiate an amikacin dose of 10mg/kg/day in neonates for them to accomplish adequate amikacin treatment efficacy in our population.

Amponsah et al. (2017) research found no disparities in amikacin C_{max} between 270 term and preterm infants of post menstrual, postnatal ages, and birth-days of 35 weeks (range 25 to 44), 1.23 days (range 0.16 to 21.75), and 2.30 kg (range 0.90 kg to 5.20 kg), respectively.[47] These findings corroborate our study's finding that there is no significant relationship between

gestational age and amikacin dose adequacy. Based on our research, we established that amikacin dosage adequacy is unaffected by gender or race.

Our study had some limitations. Due to its retrospective nature, the data availability is restricted only to the electronic medical record. Other factors affecting the pharmacokinetics of amikacin such as duration of treatment, septic parameters, and indications including patient conditions such as burn, renal impairment, liver diseases, and parenteral nutrition (PN) were not included. Therefore, a much-detailed investigation encompassing all necessary predictors with a larger and balanced sample size is needed for a better perspective on the amikacin pharmacokinetics data obtained.

Conclusion

Our study aimed to determine the amikacin pharmacokinetic parameters in neonates admitted to HRPZ II. We found that almost 50% of amikacin doses prescribed for the study population were below the recommendations in the common dose guidelines, which contributed to amikacin dosage inadequacy. It has been observed that an amikacin dose initiated at 10 mg/kg/day in neonates is more likely to achieve the desired $C_{max.}$ Based on these findings, we recommend revising the amikacin dosage guidelines for neonates in our tertiary care setting. However, further comprehensive research is warranted to investigate factors associated with amikacin dose adequacy in neonates and to configure a pharmacokinetic model of amikacin specific for the neonatal population.

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Conflict of interest

The authors certified that there is no conflict of interest to declare from this research publication.

Table 1. Characteristics of the study population (n=229).

Characteristics	Gestational Age		
	Preterm (n=129) n (%)	Term (n=100) n (%)	Total n (%)
Gender			
Male	59 (45.7)	59 (59.0)	118 (51.5)
Female	70 (54.3)	41 (41.0)	111 (48.5)
Race			
Malay	124 (96.1)	91 (91.0)	215 (93.9)
Non-Malay	5 (3.9)	9 (9.0)	14 (6.1)
Age (day)[a]	13.94 ± 10.28	14.41 ± 10.09	14.14 ± 10.18
Body weight (kg)[a]	1.62 ± 0.50	3.06 ± 0.57	2.24 ± 0.89
Amikacin dose (mg/kg/day) [a]	8.13 ± 2.24	8.46 ± 2.44	8.28 ± 2.33
Range dose of amikacin received (mg/kg/day)			
<7.5	66 (51.2)	47(47.0)	113 (49.3)
7.5-15.0	60 (46.5)	50 (50.0)	110 (48.0)
>15.0	3 (2.3)	3 (3.0)	6 (2.7)
Renal profile			
SCr (µmol/L) [a]	46.15 ± 21.06	35.50 ± 19.30	41.50 ± 20.95
CrCl (ml/min) [a]	40.08 ± 18.88	67.96 ± 38.44	52.25 ± 32.15

Non-Malay= Chinese, Siamese and Orang Asli; CrCl = creatinine clearance calculated based on Cockcroft-Gault equation

[a]Mean ± SD

Table 2. Monitored amikacin concentrations and related pharmacokinetics parameters according to study population (n=229).

	Gestational Age					
	Preterm (n=129) n (%)	**Term (n=100) n (%)**	**Total n (%)**	**Preterm (n=129) Mean ± SD**	**Term (n=100) Mean ± SD**	**Total Mean ± SD**
Amikacin concentrations						
C_{min}						
Toxic (≥5 mg/L)	7 (5.4)	4 (4.0)	11 (4.8)			
Therapeutic (<5 mg/L)	122 (94.6)	96 (96.0)	218 (95.2)			
C_{max}						
Inadequate (<20 mg/L)	102 (79.1)	83 (83.0)	185 (80.8)			
Adequate (≥20 mg/L)	27 (20.9)	17 (17.0)	44 (19.2)			
Pharmacokinetics parameters						
K_e (hr^{-1})				0.11 ± 0.04	0.12 ± 0.03	0.11 ± 0.04
$V_d(L)$				1.27 ± 0.80	2.19 ± 1.12	1.67 ± 1.06
V_d (L/kg)				0.80 ± 0.52	0.76 ± 0.52	0.78 ± 0.52
$t½$ (hr)				8.18 ± 5.02	6.47 ± 3.90	7.43 ± 4.63
C_{max} (mg/L)				15.96 ± 11.01	15.09 ± 6.68	15.58 ± 9.37
C_{min} (mg/L)				1.59 ± 1.50	1.18 ± 1.66	1.41 ± 1.58

C_{min} = minimum trough concentration achieved; C_{max} = maximum concentration achieved; K_e = rate of elimination; V_d= volume of distribution; t½ = half-life

Table 3. Association between characteristics of the study population and amikacin concentrations (n=229).

Characteristics	Amikacin concentrations			
	n	Adequate (%)	Inadequate (%)	p-value
Gender				
Male	118	26 (22.0)	92 (78.0)	0.264[a]
Female	111	18 (16.2)	93 (38.3)	
Gestational age				
Preterm	129	27 (20.9)	102 (79.1)	0.454[b]
Term	100	17 (17.0)	83 (83.0)	
Race				
Malay	215	39 (18.1)	176 (81.9)	0.152[a]
Non-Malay	14	5 (35.7)	9 (64.3)	
Gestational age				
Preterm	129	27 (20.9)	102 (79.1)	0.454[b]
Term	100	17 (17.0)	83 (83.0)	
CrCl (ml/min)	229	55.15 (43.70)	51.56 (28.85)	0.600[c]
Range dose of amikacin (mg/kg/day)				
<7.5	113	14 (6.1)	99 (43.2)	**0.022[b]**
7.5-15.0	110	28 (12.2)	82 (35.9)	
>15.0	6	2 (0.8)	4 (1.7)	

Non-Malay = Chinese, Siamese, and Orang Asli; CrCl = creatinine clearance calculated based on the Cockcroft-Gault equation.

[a]Pearson chi-square test for independence; [b]Fisher exact test; [c]Independent t-test.

References

[1]. Illamola SM, Sherwin CM, van Hasselt JC. Clinical pharmacokinetics of amikacin in pediatric patients: a comprehensive review of population pharmacokinetic analyses. Clinical pharmacokinetics. 2018;57(10):1217-28.

[2]. Kumana CR, Yuen KY. Parenteral aminoglycoside therapy. Drugs. 1994;47(6):902-13.

[3]. Isaksson B, Nilsson L, Maller R, Sör´ n L. Postantibiotic effect of aminoglycosides on gram-negative bacteria evaluated by a new method. Journal of Antimicrobial Chemotherapy. 1988;22(1):23-33.

[4]. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. Journal of Infectious Diseases. 1987;155(1):93-9.

[5]. Pacifici G, Marchini G. Clinical Pharmacology of amikacin in infants and children. Clinical and Medical Investigations. 2019;5.

[6]. Allegaert K, Anderson BJ, Cossey V, Holford NH. Limited predictability of amikacin clearance in extreme premature neonates at birth. British journal of clinical pharmacology. 2006;61(1):39-48.

[7]. Committee CPW. Clinical Pharmacokinetics Pharmacy Handbook Second Edition. 2 ed. Pharmacy Practice and Development Division: Ministry of Health Malaysia; 2019.

[8]. Shann F. Drug Doses Frank Shann. 17th ed. University of Melbourne, Australia: Professorial Fellow Department of Paediatrics University of Melbourne; 2017.

[9]. Best EJ, Gazarian M, Cohn R, Wilkinson M, Palasanthiran P. Once-daily gentamicin in infants and children: a prospective cohort study evaluating safety and the role of therapeutic drug monitoring in minimizing toxicity. The Pediatric infectious disease journal. 2011;30(10):827-32.

[10]. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics. 2004;114(1):e111-e8.

[11]. Alhadab AA, Ahmed MA, Brundage RC. Amikacin pharmacokinetic-pharmacodynamic analysis in pediatric cancer patients. Antimicrobial agents and chemotherapy. 2018;62(4).

[12]. Abel S. Amikacin (systemic): Pediatric Drug Information. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on January 11,2024).

[13]. Thomas E, Young O. Neofax: A manual of drugs used in Neonatal Care. Raleigh, NC: Acorn Publishing. 2007.

[14]. Illamola SM, Colom H, van Hasselt JC. Evaluating renal function and age as predictors of amikacin clearance in neonates: model-based analysis and optimal dosing strategies. British journal of clinical pharmacology. 2016;82(3):793-805.

[15]. Sumpter A, Anderson BJ. Pediatric pharmacology in the first year of life. Current Opinion in Anesthesiology. 2009;22(4):469-75.

[16]. de Duve C. International Institute of Cellular and Molecular Pathology. BioMed Central; 1997.

[17]. Arshad A, Rehman S, Zaka M, Mahmood KT. Rational use of amikacin in children. Journal of pharmaceutical sciences and research. 2011;3(1):995.

[18]. Benet L, Sheiner L. Design and optimization of dosage regimens. Pharmacokinetic Data. 1990:1675-84.

[19]. Downes KJ, Hahn A, Wiles J, Courter JD, Vinks AA. Dose optimisation of antibiotics in children: application of pharmacokinetics/pharmacodynamics in paediatrics. International journal of antimicrobial agents. 2014;43(3):223-30.
[20]. Pacifici GM, Marchini G. Clinical Pharmacology of amikacin in infants and children. Clin Med Invest. 2020;5:1-14.
[21]. Berger A, Kretzer V, Gludovatz P, Heinze G, Haiden N, Pollak A. Evaluation of an amikacin loading dose for nosocomial infections in very low birthweight infants. Acta Paediatrica. 2004;93(3):356-60.
[22]. Belfayol L, Talon P, Eveillard M, Alet P, Fauvette F. Pharmacokinetics of once-daily amikacin in pediatric patients. Clinical Microbiology and Infection. 1996;2(3):186-91.
[23]. Alqahtani S, Abouelkheir M, Alsultan A, Elsharawy Y, Alkoraishi A, Osman R, et al. Optimizing amikacin dosage in pediatrics based on population pharmacokinetic/pharmacodynamic modeling. Pediatric Drugs. 2018;20(3):265-72.
[24]. Hughes KM, Johnson PN, Anderson MP, Sekar KC, Welliver RC, Miller JL. Comparison of amikacin pharmacokinetics in neonates following implementation of a new dosage protocol. The Journal of Pediatric Pharmacology and Therapeutics. 2017;22(1):33-40.
[25]. Engler D, Schellack N, Naude A, Gous A. A pilot study on the use of amikacin in neonates: Who should be monitored for ototoxicity? Southern African Journal of Infectious Diseases. 2015;30(3):114-8.
[26]. Huth M, Ricci A, Cheng A. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. International journal of otolaryngology. 2011;2011.
[27]. Endo A, Nemoto A, Hanawa K, Maebayashi Y, Hasebe Y, Kobayashi M, et al. Relationship between amikacin blood concentration and ototoxicity in low birth weight infants. Journal of Infection and Chemotherapy. 2019;25(1):17-21.
[28]. Endo A, Hanawa K, Nemoto A, Ishikawa T, Kazama S, Kagami Y, et al. Evaluation of nephrotoxicity and ototoxicity following amikacin administration once daily or every 48 hours in neonates. Medicine. 2022;101(43).
[29]. Javadi MR, Abtahi B, Gholami K, Moghadam BS, Tabarsi P, Salamzadeh J. The incidence of amikacin ototoxicity in multidrug-ResistantTuberculosis patients. Iranian Journal of Pharmaceutical Research: IJPR. 2011;10(4):905.
[30]. Pejović B, Ranković-Janevski M, Božinović-Prekajski N. Aminoglycoside trough levels in neonates. Srpski arhiv za celokupno lekarstvo. 2010;138(1-2):50-5.
[31]. Marik P, Havlik I, Monteagudo F, Lipman J. The pharmacokinetics of amikacin in critically ill adult and paediatric patients: comparison of once-versus twice-daily dosing regimens. Journal of antimicrobial chemotherapy. 1991;27(suppl_C):81-9.
[32]. Beringer P. Winter's basic clinical pharmacokinetics: Lippincott Williams & Wilkins; 2023.
[33]. Siddiqi A, Khan D, Khan F, Razzaq A. Therapeutic drug monitoring of amikacin in preterm and term infants. Singapore medical journal. 2009;50(5):486.
[34]. Boidin C, Bourguignon L, Cohen S, Roger C, Lefrant J-Y, Roberts JA, et al. Amikacin initial dose in critically ill patients: a nonparametric approach to optimize a priori pharmacokinetic/pharmacodynamic target attainments in individual patients. Antimicrobial agents and chemotherapy. 2019;63(11):e00993-19.
[35]. Boucher BA, Coffey BC, Kuhl DA, Tolley EA, Fabian TC. Algorithm for assessing renal dysfunction risk in critically ill trauma patients receiving aminoglycosides. The American journal of surgery. 1990;160(5):473-80.
[36]. Sadeghi K, Hamishehkar H, Najmeddin F, Ahmadi A, Hazrati E, Honarmand H, et al. High-dose amikacin for achieving serum target levels in critically ill elderly patients. Infection and drug resistance. 2018;11:223-8.

[37]. Rosenbaum SE. Basic pharmacokinetics and pharmacodynamics: An integrated textbook and computer simulations: John Wiley & Sons; 2016.
[38]. Friis-Hansen B. Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth. Pediatrics. 1971;47(2):264-74.
[39]. Howard JB, McCracken GH. Pharmacological evaluation of amikacin in neonates. Antimicrobial Agents and Chemotherapy. 1975;8(1):86-90.
[40]. Sherwin CM, Svahn S, Van Der Linden A, Broadbent RS, Medlicott NJ, Reith DM. Individualised dosing of amikacin in neonates: a pharmacokinetic/pharmacodynamic analysis. European journal of clinical pharmacology. 2009;65(7):705.
[41]. Kramer WG, Cleary T, Frankel LS, Kohl S, Pickering LK. Multiple-dose amikacin kinetics in pediatric oncology patients. Clinical Pharmacology & Therapeutics. 1979;26(5):635-40.
[42]. Winter ME. Basic clinical pharmacokinetics: Lippincott Williams & Wilkins; 2004.
[43]. Prober CG, Yeager AS, Arvin AM. The effect of chronologic age on the serum concentrations of amikacin in sick term and premature infants. The Journal of Pediatrics. 1981;98(4):636-40.
[44]. Taketomo CK, Hodding J, Kraus D. Pediatric and neonatal dosing handbook. Hudson, OH: Lexi-Comp Inc; 2016.
[45]. Bradley JS. Nelson's pediatric antimicrobial therapy: American Academy of Pediatrics Grove Village; 2012.
[46]. Smits A, De Cock R, Allegaert K, Vanhaesebrouck S, Danhof M, Knibbe C. Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice. Antimicrobial agents and chemotherapy. 2015;59(10):6344-51.
[47]. Amponsah SK, Adjei GO, Enweronu-Laryea C, Bugyei KA, Hadji-Popovski K, Kurtzhals JA, et al. Population pharmacokinetic characteristics of amikacin in suspected cases of neonatal sepsis in a low-resource African setting: A prospective nonrandomized single-site study. Current Therapeutic Research. 2017;84:e1-e6.