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REVIEW ARTICLE

Pharmacokinetic Properties of Amikacin in Asian Neonates and Infants: A Narrative Review.

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Abstract

Amikacin (AMK) is among the narrow therapeutic index drugs that are still being used in neonates for early-onset and late-onset sepsis. The pharmacokinetic and pharmacodynamic properties of drugs in neonates vary across ages, especially in premature babies. Neonates exhibit differences in body composition and organ function, which can influence drug disposition and response. Although much literature has discussed the pharmacokinetics of AMK in neonates, this review aims to explore the pharmacokinetic properties of AMK in Asian neonates and infants. Seven articles were included in this review, with evaluation conducted on Malaysian, Japanese, Pakistani, Indian, Korean, and Thai neonates. Overall, 702 neonates were included in these studies, consisting of both preterm and term neonates, with one study focusing exclusively on low-birth-weight neonates. This review highlights that a high dose of AMK with once-daily dosing shows a better option for achieving therapeutic concentrations. Nevertheless, variability in pharmacokinetic profiles across neonatal age was observed. Factors affecting these pharmacokinetic changes need to be addressed during the initiation of AMK therapy in neonates to ensure optimal outcomes.

Keywords: *Amikacin, Asian, Neonates, Pharmacokinetic.*

Introduction

Aminoglycosides (AMGs), such as amikacin (AMK) and gentamicin (GEN), are among the narrow therapeutic index drugs that are still being used in neonates for early-onset and late-onset sepsis. They inhibit protein synthesis in susceptible bacteria by binding to 30S ribosomal subunit. AMGs have excellent coverage against most gram-negative organisms, including *Pseudomonas aeruginosa* and some *Mycobacterium* spp. They demonstrate concentration-dependent bacterial killing and have a post-antibiotic effect [1].

Blood concentration monitoring of AMK is routinely performed for dose optimization. The recommended blood sampling time is at a steady state dose (usually after 24 hours), requiring two samples for estimation of minimum concentration (Cmin) and maximum concentration (Cmax). Pre-dose sampling and post-distributional sampling are routinely done. Alternatively, two post-distributional samples, taken at least two half-lives apart can be used. Achievement of a therapeutic Cmax indicates the efficacy of AMK, while a supratherapeutic Cmin exposes patients to toxicity [2].

Nephrotoxicity and ototoxicity are the most mentioned adverse events related to AMG use. Nephrotoxicity is reversible with early detection and timely discontinuation of AMGs. Meanwhile, vestibular and auditory toxicity might occur at high doses due to the presence of oxidative free radicals, which damage the hair cells in the cochlea. This toxicity can become permanent with prolonged use of AMG. Routine hearing tests are currently performed in infants nowadays [1].

Pharmacokinetic and pharmacodynamic properties of drugs in neonates vary across ages, especially in premature babies. Neonates exhibit differences in body composition and organ function, which can influence drug disposition and response to drugs. Developmental and physiological changes continue to fluctuate throughout the first year of life [2]. Although much literature has discussed the pharmacokinetics of AMK in neonates, this review aims to explore the pharmacokinetic properties of AMK in Asian neonates and infants.

Materials and methods

Literature search

A literature search was performed using several research databases, including PubMed and Scopus, in August 2024. Relevant papers and reports within the subject area of pharmacokinetic properties of AMK were searched using a combination of the following sets of keywords: 1) Amikacin AND 2) neonate OR infant AND 3) pharmacokinetic OR 4) volume of distribution OR 5) clearance OR 6) ototoxicity OR 7) nephrotoxicity. No cut-off points of search years were applied. The selection criteria for articles were as follows; articles had to be written in English and focus on the AMK pharmacokinetics in Asian neonates and infants. Articles that were short reports, letters, written in languages other than English, or without full-text availability were excluded.

Results

Out of 124 retrieved literatures, only seven were eligible. 116 articles were excluded as the subjects were not from Asian population, and one article was published in Korean language. No duplication of articles was detected.

The retrieved literature evaluated neonates from Malaysia, Japan, Pakistan, India, Korea, and Thailand. Overall, 702 neonates were included in these studies, comprising both preterm and term neonates, with one study focusing exclusively on low-birth-weight neonates.

Amikacin dosing regimens:

A retrospective study conducted in a neonatal intensive care unit (NICU) of a Korean hospital compared standard reference-based dosing with a

revised pharmacokinetic dosing guide. The study showed that the achievement of the target Cmax (20-30 mg/L) was significantly higher in the revised pharmacokinetic dosing guide (*p*-value <0.001), while there is no significant difference in Cmin between the two groups (*p*-value = 0.086). The standard reference-based dosing ranges from 18 mg/kg every 48 hours (for neonates aged ≤7 days and gestational age (GA) of ≤27 weeks) to 15 mg/kg every 24 hours (for neonates aged ≤7 days and GA of ≥34 weeks). Doses were adjusted based on GA, postconceptional age (PCA), and postnatal age (PNA). In contrast, the revised dosing regimens were computed at 13 mg/kg for all PCA with a range of dosing intervals from every 48 hourly (neonates aged <7 days and GA of ≤29 weeks) to every 24 hours (neonates aged <7 days and GA of ≥37 weeks) [3].

Another study conducted in a tertiary hospital in the East Coast Region of Malaysia demonstrated a statistically significant association between AMK dose and the achievement of the target Cmax. Preterm neonates were prescribed with a mean ± SD AMK dose of 8.12 ± 2.24 mg/kg/day, while term neonates with 8.46 ±2.44 mg/kg/day. Neonates who started with a dose of less than 15 mg/kg/day were unable to achieve therapeutic Cmax of at least 20 mg/L. In contrast, those with adequate Cmax had a mean (± SD) AMK dose of 9.39 ± 3.01 mg/kg/day. The Cmin observed was <5 mg/L in most subjects (95.2%), regardless of the dosing regimen [4].

A study on AMK pharmacokinetics in premature neonates in a Thailand Hospital evaluating the Cmax and Cmin after initiating AMK dosing based on GA. Doses were divided into three groups: ≤30 weeks GA: 18 mg/kg every 48 hours; 31-33 weeks GA: 16 mg/kg every 48 hours; 34-36 weeks GA: 15 mg/kg every 24 hours. The reported mean (± SD) Cmin of total dose was 1.77 + 1.6 mg/L with no significant difference of Cmin among groups (p-value = 0.29). Most subjects achieved a concentration of <2 mg/L. The mean (± SD) for Cmax of all neonates was 25.29 + 6.46 mg/L, which is within therapeutic range, with no significant difference between groups as well (p-value = 0.343). A high peak concentration of >30 mg/L was most frequently reported in neonates <30 weeks GA (57.14%) [5]. The summary of the effects of dosing regimens on the attainment of Cmax and Cmin is presented in Table 1.

Pharmacokinetic (PK) Properties:

Yusof, NN et.al. (2024) analyzed the PK properties of 129 preterm and 100 term neonates. The elimination rate constant (Ke) for preterm and term neonates was similar with values of 0.11 ± 0.04 /hour and 0.12 ± 0.03 /hour, respectively. Preterm neonates tend to have a larger volume of distribution (Vd) and longer half-life (t½) (mean ± SD: 0.80 ± 0.52 L/kg and 8.18 ± 5.02 hours) compared to term neonates (mean (±SD): 0.76 ± 0.52 L/kg and 6.47 ± 3.9 hour) [4].

AMK clearance was significantly affected by PCA and PNA, showing an increasing trend as subjects aged. AMK clearance in neonates with PCA ≥ 37 weeks and PNA ≥ 8 days was fourfold higher than in neonates PCA ≤ 29 weeks and PNA ≤ 7 days. In contrast, Vd values did not show any significant differences among the subgroups [3].

The reported means (± SD) of Ke showed an increasing trend with GA; with 0.067 ± 0.023 /hour (≤30 weeks GA), 0.082 ± 0.030 /hour (31-33 weeks GA), and 0.094 ± 0.035 /hour (34-36 weeks GA). The corresponding clearance per body weight were 0.044 ± 0.018 L/kg/hour, 0.053 ± 0.016 L/kg/hour, and 0.058 + 0.022 L/kg/hour, respectively. The mean (± SD) of t½ was 8.90 ± 5.41 hours, shorter across GA, with Vd of 0.659 ± 0.231 L/kg. No significant variation was seen across groups [5]. The findings of the overall pharmacokinetic profile are summarized in Table 2.

Nephrotoxicity and Ototoxicity of Amikacin:

Endo, A et.al. (2022) defined acute kidney injury (AKI) as a ⩾ 1.5-fold or ⩾ 26.5 umol/L increase in serum creatinine, or urine output <0.5 mL/kg/hour for 6 hours. In a retrospective chart

review, AMK was dosed according to body weight: <1 kg: 20 mg/kg every 48 hours (EOD) and ≥ 1 kg: 15 mg/kg once daily (OD). Nephrotoxicity was observed in 21% of subjects receiving 15 mg/kg OD and 58% of subjects with a dose of 20 mg/kg EOD. The reported Cmax of subjects with and without nephrotoxicity was 33.5 mg/L and 29.9 mg/L, respectively, with the Cmin of 4.2 mg/L and 2.4 mg/L, respectively. This study also reported that an increment of serum creatinine was seen in EOD group on the day of AMK concentration measurement, regardless of concurrent indomethacin therapy initiation [6].

Ototoxicity was observed in 16 % subjects in the EOD dosing group while 5% in the OD group. No significant difference was seen between the groups regarding Cmax and Cmin (p = 0.815 and 0.592, respectively). The reported median (IQR) Cmax was 31.0 (27.3-34.6) mg/L for EOD group while 31.5 (27.5-36.6) mg/L for OD group, with Cmin of 1.8 (1.2-6.3) mg/L and 3.1 (2.1-4.3) mg/L, respectively. However, the total AMK dose administered was higher in EOD group compared to OD group (82.7 mg/kg and 73.5 mg/kg). Endo, A et.al. (2019) previously reported that a higher Cmin was associated with a higher risk of ototoxicity, with a cut-off value of 10 mg/L (p = <0.05) [6-7].

One study found no significant difference in serum creatinine and creatinine clearance among premature neonates across postnatal ages on Day 1 of AMK administration (p value= 0.718 and 0.161, respectively). However, a significant difference was observed in serum creatinine and creatinine clearance measured within 2 days after discontinuation of AMK (p-value= 0.017 and 0.016, respectively). A better renal profile was observed in neonates with GA 34 -36 weeks [5].

Factors that might affect the variability of Amikacin PK properties:

Endo, A et.al. (2019) examined the characteristics of neonates with a Cmin of ≥10 mg/L. Neonates with supratherapeutic Cmin neonates had a low body weight (LBW) with a mean of 0.742 kg, while those with therapeutic Cmin had a mean body weight of 1.415 kg. The overall test result was statistically significant (p = <0.05). The researchers further analyzed the volume of distribution (Vd), calculated using measured post-dose concentration and dosage, and found a significant difference between the two groups (≥10 mg/L group:0.37 L/kg, < 10 mg/L group: 0.55 L/kg, p-value = <0.05) [7]. A population pharmacokinetic modeling conducted by Saikumar Matcha et.al. (2023) also identified creatinine clearance and body weight as significant covariates influencing the pharmacokinetic properties of AMK in neonates [8].

Prematurity has been identified as a contributing factor to variability in Vd and t½, as reported in Malaysian neonates. Prolonged t½ and larger Vd were observed in neonates with GA of < 37 weeks. The study also reported that preterm neonates had a mean ± SD body weight at 1.62 ± 0.50 kg, while term neonates' mean body weight was 3.06 ± 0.57 kg [4]. A comparative study conducted at a Military Hospital in Pakistan evaluated the risk of toxicity in premature infants. Subjects were administered AMK at a dose of 15 mg/kg OD and trough concentrations were taken after 72 hours of therapy. Serum creatinine was measured at two points: on admission and on the third day. Preterm neonates with GA of 29 - 36 weeks had significantly higher median (± IQR) of Cmin at 11.33 (1.5-42.6) mg/L compared to term neonates (8.5 (2.8-33.0) mg/L, p-value = >0.01). This finding was consistent with a higher frequency of toxic concentration observed in preterm neonates. Additionally, a positive correlation was found between AMK Cmin and serum creatinine at day 3 (r = 0.48; p = <0.05). Serum creatinine at Day 3 of AMK therapy in term neonates was significantly lower compared to preterm neonates with mean ± SD of 61.4 ± 22.8 µmol/L versus 76.0 ± 28.9 µmol/L (p = 0.002) [9].

Ke was significantly seen in an increasing trend following increasing GA (p-value = 0.003) with mean ± SD of 0.0094 ± 0.035 /hour. Following this trend, the t½ was shown to be shorter in older GA neonates, with no statistical significance (p = 0.057). The Vd appeared similar across groups (mean ± SD: 0.659 ± 0.231), while the clearance per body weight was significantly differ across groups (mean ± SD: 0.058 ± 0.022; p = 0.02). There was a significant correlation between GA and Ke, clearance, and t½ (r = 0.529, 0.44 and 0.367, respectively, p <0.05). Correlation of Ke and clearance was proportionate to GA while t½ was inversely proportional to GA. Significant correlation between Ke and PNA also has been reported (r = 0.529, p <0.05) [5].

Discussion

AMK has been widely used in neonates as standard therapy for nosocomial infections. Dosing of 15 mg/kg once daily showed achievement of therapeutic Cmax and Cmin. This finding is consistent with research conducted by Abdel-Hady et.al. (2011) and Langhendries, J. P. et al (1993). These studies employed a similar study design, randomizing neonates into two groups: Group 1 received 15 mg/kg once daily dosing, while Group 2 received AMK dose at 7.5 mg/kg twice daily. Cmax achievement was higher in Group 1 compared to Group 2, with mean (± SD) of 27.7 (± 6.6) mg/L and 23.06 (± 3.30) respectively. Additionally, Group 1 showed lower Cmin than Group 2 (4.6 ± 2.5 and 2.75 ± 1.19 mg/L, respectively). Although the reported Cmin was significantly lower in the OD group, yet, all subjects in both studies were reported with Cmin of <10 mg/L. The researchers concluded that once daily dosing revealed an acceptable high peak concentration with no toxic trough concentrations [10,14].

Hughes, KM et.al. (2017) reported that the desired Cmax of 20 - 35 mg/L was achieved in neonates with AMK dose of 12 mg/kg. Higher AMK doses were reported with supratherapeutic concentrations of more than 35 mg/L, although there was no significant difference in achieving the Cmin target between the two groups [11]. This finding was consistent with the study conducted by the Korean researchers [3]. Both studies had similar baseline demographics. However, the Korean study had an uneven distribution of subjects between groups and used different subgroup divisions.

The elimination half-life and clearance of AMK were shown to be affected by GA, PCA and PNA, with an increasing trend as neonates approached term. Conversely, the half-life decreased across age groups. Preterm infants exhibited a longer elimination half-life compared to term babies. Prematurity and ill infants tend to have lower glomerular filtration rates, leading to slower clearance of drugs, including aminoglycosides. These variations in pharmacokinetic profiles across neonates were all consistent with other published studies, however, with slight differences in the reported values possibly due to dissimilar study designs, sample sizes, and regional variations [11-14].

Serum creatinine levels and urinary excretion of marker enzymes for proximal tubular kidney damage were shown to increase in neonates on AMK therapy, regardless of the dosing regimen. Similar findings have been reported in several studies, with complete recovery of renal function over time [10,14,16]. It should be noted that these studies were designed to observe nephrotoxicity in neonates with GA of ≥ 34 weeks. Additionally, all studies had small sample sizes, and larger sample sizes may be required to yield more robust outcomes.

Treatment with AMK, compared to no treatment, was shown to have an increased risk of developing hearing loss in neonates [15]. However, several studies found no evidence of ototoxicity in neonates receiving AMK therapy, suggesting that it appears to be safe even in very low birth weight neonates in the absence of other

risk factors, such as a family history of hearing loss [16-17]. Nevertheless, although most studies excluded factors that could contribute to hearing loss, the sample sizes limited the generalizability of these findings.

Conclusion

High dose with once daily dosing shows a better option for achieving therapeutic concentrations. However, variability in pharmacokinetic profiles across neonatal age groups has been observed. Factors affecting these pharmacokinetic changes need to be addressed during the initiation of AMK in neonates, to ensure optimal outcomes. Future research involving multicenter studies with larger sample sizes and diverse demographic baselines is necessary to optimize AMK treatment in neonates.

Conflict of interest

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Authors' Contributions

SNN and SM performed the literature search and manuscript preparation. All authors agreed and approved the manuscript for publication.

Table 1. Dosing regimen effects on the attainment of Cmax and Cmin

First Author (Year)	Dosage Design	Outcome on attainment of Cmax and Cmin				p-value
An SH (2014)	Standard reference-based dosing (Group 1) versus Revised-pharmacokinetic dosing guide (Group 2) (n = 107 versus 74)	Cmax (Definition: 20 – 30 mg/L)	Significant higher Cmax attainment in Group 2 (81.3% versus 50.7%)			<0.001
		Cmin (Definition: < 5 mg/L)	No significant difference between Group 1 and Group 2 (85.1% versus 87.5%)			0.621
Yusof NN (2024)	AMK dose adequacy of the current dosing regimen		Dose (mg/kg/day)			
			< 7.5	7.5 - 15	> 15	0.022
		Cmax ≥ 20 mg/L, n (%)	14 (6.1)	28 (12.2)	2 (0.8)	
		Cmax <20 mg/L, n (%)	99 (43.2)	82 (35.9)	4 (1.7)	
			Gestational Age (weeks)			
			< 37		≥ 37	
		Cmin ≥ 5 mg/L, n (%)	7 (5.4)		4 (4.0)	NA
		Cmin < 5 mg/L, n (%)	122 (94.6)		96 (96.0)	
Pomanong Aramwit (2008)	Pharmacokinetic properties of AMK in Thai premature neonates	Gestational Age (weeks)	≤ 30 (n = 7)	31 – 33 (n = 16)	34 – 36 (n = 14)	
		Dosing regime	18 mg/kg q48h	16 mg/kg q36h	15 mg/kg q24h	
		Cmax, mg/L (%) < 20	14.29	31.25	21.62	0.343
		20 – 30	28.57	71.43	54.05	
		> 30	57.14	14.28	24.33	
		Cmin, mg/L (%) < 2	57.14	93.75	42.86	0.290
		2 – 5	42.86	0	57.14	
		> 5	0	6.25	0	

NA: not available; q48h: every 48 hours; q36h: every 36 hours; q24h: every 24 hours

Table 2. Summary of PK Properties for Asian neonates

First Author (Year)	Locality	Study Population	PCA (weeks)	PNA (days)	n	Mean (± SD)		
						Vd (L/kg)	t½ (hour)	Ke (/hour)
AnSH (2014)	Korean	Preterm & Term neonates	≤ 29	0-7	8	0.60 ± 0.16	17.6 ± 4.8	0.044 ± 0.197
				>7	11	0.54 ± 0.07	9.8 ± 2.1	0.073 ± 0.017
			30-33	0-7	2	0.61 ± 0.14	12.3 ± 0.5	0.056 ± 0.002
				>7	15	0.61 ± 0.12	7.3 ± 3.2	0.112 ± 0.046
			34-36	0-7	6	0.47 ± 0.14	6.3 ± 1.4	0.114 ± 0.025
				>7	25	0.54 ± 0.14	5.2 ± 1.6	0.143 ± 0.037
			≥37	0-7	12	0.57 ± 0.16	7.4 ± 3.1	0.105 ± 0.035
				>7	55	0.55 ± 0.13	4.4 ± 2.4	0.179 ± 0.060
Yusof NN (2024)	Malaysian	Preterm & Term neonates	< 37	ND	129	0.80 ± 0.52	8.18 ± 5.02	0.11 ± 0.04
			≥ 37	ND	100	0.76 ± 0.52	6.47 ± 3.90	0.12 ± 0.03
Pomanong Aramwit (2008)	Thailand	Premature neonates	≤ 30	3.9 ± 2.62	7	0.684 ± 0.277	11.41 ± 3.95	0.067 ± 0.023
			31-33	4.96 ± 5.96	16	0.703 ± 0.247	10.65 ± 8.10	0.082 ± 0.030
			34-36	6.77 ± 5.14	14	0.616 ± 0.205	6.39 ± 1.51	0.115 ± 0.032

PCA = postconceptional age, PNA = postnatal age, t½ = half-life, Ke = elimination rate constant, V = volume of distribution, ND = No data

References

[1]. Sizar O, Rahman S, Sundareshan V. Amikacin [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430908/

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

[3]. An SH, Kim JY, Gwak HS. Outcomes of a new dosage regimen of amikacin based on pharmacokinetic parameters of Korean neonates. American Journal of Health-System Pharmacy. 2014 Jan 15;71(2):122–7.

[4]. Yusof NN, Alias NM, Nik Saffian NNN, Mustafa S, Azmi NL. A Retrospective Study of Amikacin Dosage Adequacy Based on Therapeutic Drug Monitoring in Neonates in a Tertiary Care Hospital in Kelantan, Malaysia. Asian Journal of Medicine and Health Sciences [Internet]. 2024 Jun;7(1):65–76. Available from: https://myjurnal.mohe.gov.my/public/article-view.php?id=214821

[5]. Pomanong Aramwit, Pavich Tongroach, Chanokporn Boonthanksir. Pharmacokinetics of amikacin in premature neonates at Pramongkutklao Hospital. Chulalongkorn Medical Journal [Internet]. 2008;52(1). Available from: https://he05.tci-thaijo.org/index.php/CMJ/article/view/1004

[6]. Endo A, Kazumi Hanawa, 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 (Baltimore, Md) [Internet]. 2022 Oct 28 [cited 2024 Apr 11];101(43):e31425–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9622663/

[7]. 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 Jan;25(1):17–21.

[8]. Saikumar Matcha, Jayashree Dillibatcha, Arun Prasath Raju, Bhim Bahadur Chaudhari, Sudheer Moorkoth, Lewis LE, et al. Predictive Performance of Population Pharmacokinetic Models for Amikacin in Term Neonates. Pediatric Drugs [Internet]. 2023 Mar 21 [cited 2024 Aug 28];25(3):365–75. Available from:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10097735/

[9]. Siddiqi A, Khan DA, Khan FA, Razzaq A. Therapeutic drug monitoring of amikacin in preterm and term infants. Singapore Medical Journal [Internet]. 2009 May 1;50(5):486–9. Available from: https://pubmed.ncbi.nlm.nih.gov/19495517/

[10]. Abdel-Hady E, El Hamamsy M, Hedaya M, Awad H. The efficacy and toxicity of two dosing-regimens of amikacin in neonates with sepsis. Journal of Clinical Pharmacy and Therapeutics. 2011 Jan 4;36(1):45–52.

[11]. 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 : JPPT [Internet]. 2017 ;22(1):33–40. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5341529/

[12]. Lulic-Botica M, Sheer T, Edwards D, Thomas RL, Natarajan G. Impact of small-for-gestational age (SGA) status on gentamicin pharmacokinetics in neonates. The Journal of Clinical Pharmacology. 2013 Oct 31;54(1):39–45.

[13]. Schreuder MF, Wilhelm AJ, A. Bokenkamp, Timmermans SMH, de D, J.A.E. van Wijk. Impact of Gestational Age and Birth Weight on Amikacin Clearance on Day 1 of Life. Clinical Journal of the American Society of Nephrology. 2009 Nov 1;4(11):1774–8.

[14]. Langhendries JP, Battisti O, Bertrand JM, François A, Darimont J, Ibrahim S, et al. Once-a-Day Administration of Amikacin in Neonates: Assessment of Nephrotoxicity and Ototoxicity. Developmental Pharmacology and Therapeutics. 1993;20(3-4):220–30.

[15]. Edgar Jake AA, Francisco AV. Assessment of the Ototoxic Effects of Amikacin and Meropenem among Neonates in a Tertiary Government Hospital. Philippine Journal of Otolaryngology-Head and Neck Surgery [Internet]. 2014 Dec 1 [cited 2024];29(2). Available from: https://pjohns.pso-hns.org/index.php/pjohns/article/view/411/1025#info doi:10.32412/pjohns.v29i2.411

[16]. Kotze A, Bartel P, Sommers DK. Once versus twice daily amikacin in neonates: Prospective study on toxicity. Journal of Paediatrics and Child Health. 1999 Jun 1;35(3):283–6

[17]. Nanavati RN, Hakeem MA, Gagtey N, Swar BD. Serum Amikacin Levels And Hearing In Very Low Birth Weight (VLBW) Infants. Journal of Clinical and Diagnostic Research [Internet]. 2010 Oct 12;4:3323–6. Available from: http://www.jcdr.in/article_fulltext.asp?issn=0973-709x&year=2010&volume=4&issue=6&page=3323-3326&issn=0973-709x&id=822.