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Standard Multiple and Single Daily Dosing of Amikacin in Premature Infants

Arash Bordbar[1], Ali Mazouri[1], Mandana Kashaki[1], Majid Kalani[1], Maryam Saboute[1], Rozita Hosseini[2], Somayeh Farhadi[1], Ali Ghassemian[1*]

1. Department of Pediatrics, Shahid Akbarabadi Hospital, Iran University of Medical Sciences, Tehran, Iran
2. Department of Pediatrics, Ali Asghar Children Hospital, Iran University of Medical Sciences, Tehran, Iran

ABSTRACT

***Background*:** Bacterial sepsis is highly prevalent among premature infants. Amikacin is an antibiotic widely recommended for the treatment of neonatal sepsis, one of the consequences of which might be nephrotoxicity. The present study aimed to compare the efficacy and nephrotoxicity of multiple daily dosing (MDD) and once-daily dosing (ODD) of amikacin in preterm infants suspected of sepsis.

Methods: This triple-blind, randomized, controlled clinical trial was conducted on 40 premature infants suspected of sepsis, who were randomly divided into two groups. In addition to ampicillin, one group was administered with the standard daily dose, and the other group received an ODD of intravenous amikacin. Maximum and minimum serum levels of amikacin and urine neutrophil gelatinase-associated lipocalin (NGAL) were measured in both groups. Data were extracted and analyzed based on the research hypothesis and literature review.

Results: No significant differences were observed between the study groups in terms of gender, gestational age, mode of delivery, birth weight, and Apgar score. After the intervention, mean plasma creatinine reduced in both groups, while the mean reduction was significantly higher in the group administered with the ODD of amikacin (P=0.0001). However, mean changes in the urine NGAL had no significant difference between the groups (P=0.635). Minimum and maximum serum levels of amikacin in the study groups indicated a more significant reduction in mean level of the infants administered with the ODD of amikacin compared to the MDD group (P=0.0001).

Conclusion: Considering the higher maximum and lower minimum levels of amikacin in the neonates receiving the daily dosage regimen, it seems that this regimen is more effective in the treatment of sepsis in preterm infants. Moreover, no significant difference was observed in the efficacy and nephrotoxicity of the daily amikacin dosing in the premature infants suspected of sepsis compared to those treated by multiple doses of amikacin.

Keywords: Amikacin, Drug regimen, Nephrotoxicity, Prematurity, Sepsis

Introduction

Bacterial sepsis is highly prevalent among newborns, especially in premature infants due to their immature immune system (1). Neonatal sepsis is the leading cause of neonatal mortality and morbidity, particularly in premature infants (2). Clinical symptoms of sepsis include the loss of reflexes, weakness and lethargy, apnea, respiratory distress, bradycardia, hypothermia and hyperthermia, seizures, and abdominal distension, which might be nonspecific for a the definitive diagnosis of neonatal sepsis (2).

Healthcare providers should have strong clinical suspicion for the early detection of sepsis in premature infants since the delayed diagnosis and treatment of this disease may lead to severe clinical consequences. As such, many neonates, particularly premature infants, are hospitalized due to the possibility of sepsis (1).

Definitive diagnosis of sepsis could be achieved through a positive bacterial infection, which is a time-consuming diagnostic method (1, 2). Aminoglycosides (e.g., amikacin) combined beta-lactam antibiotics are widely used in the treatment of sepsis (1, 2). Amikacin is a semi-

* *Corresponding author*: Ali Ghassemian, Department of Pediatrics, Shahid Akbarabadi Hospital, Iran University of Medical Sciences, Tehran, Iran. Tel: 09125483417; Email: dr_ali_ghassemian@yahoo.com

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synthetic antibiotic derived from kanamycin, which has been shown to be effective against the majority of gram-negative aerobic bacteria. There are rare reports on amikacin-resistant gram-negative bacteria compared to the other aminoglycosides (3).

Acute kidney injury (AKI) is a prevalent condition in the newborns admitted to neonatal intensive care units (NICUs), with the incidence rate estimated at 6-24% (3). Infants with AKI are at the risk of developing renal diseases, chronic renal failure, and hypertension in the future (3, 4). According to reports, the premature infants that are admitted to NICUs are highly exposed to nephrotoxic drugs, such as furosemide, ibuprofen, and especially aminoglycoside antibiotics (4).

A major clinical concern in using aminoglycosides is the risk of nephrotoxicity, which is traditionally defined as the increased serum creatinine concentration to 5.0 mg/dl or 50% of the baseline level (4). In the study by McWilliam et al. (2012), AKI was defined as the increased level of serum creatinine and decreased urinary output, while these events will not occur until the loss of 25-50% of the renal function (5).

Aminoglycosides cause certain degenerative changes in the intracellular fluid of the parenchymal cells in the kidneys; such examples are the apoptosis and necrosis of the proximal tubular epithelial cells due to mitochondrial dysfunction, free oxygen radicals, and polar accumulation of lipids in the lysosomes (i.e., myeloid bodies)(5). On the other hand, Haase et al. (2009) have stated that the changes in the serum level of creatinine are indicative of glomerular damage and are non-specific for the early detection of aminoglycoside nephrotoxicity (6). Therefore, based on the histopathological examination of aminoglycoside nephrotoxicity, the researchers concluded that the serum or urinary levels of the released molecules from the proximal tubular epithelial damaged cells could be an indication for the early detection of AKI (5).

After infancy, incidence rate of the nephrotoxicity associated with the use of aminoglycosides has been estimated at 8-30%, while it might be comparatively higher in infants (4). Despite the limited data on the incidence of aminoglycoside nephrotoxicity in premature infants, most of the studies in this regard have reported the higher and long-term incidence of this condition in infants due to immature kidneys (7).

In the literature, two main strategies have been proposed to prevent the renal damage associated with aminoglycosides, as follows (4):

1. Accurate adjustment of the dosage based on the drug concentration in the interval between two injections (drug trough level monitoring with dose adjustment);
2. Increasing the intervals between two injections (extended-interval dosing)

For the past decades, the standard administration method for aminoglycosides has been twice to three times daily (8, 9). Meanwhile, several studies have denoted that the multiple-dose daily and once-daily administration of aminoglycosides could be equally effective in various age groups (8, 9). Few studies have focused on the renal damage caused by the multiple daily dosing (MDD) and once-daily dosing (ODD) of aminoglycosides in newborns, especially premature infants (8, 9).

The present study aimed to compare the renal damage between the standard dose and ODD of amikacin in the premature infants suspected of sepsis.

Methods

This triple-blind, randomized, controlled clinical trial was conducted based on previous studies through consulting with the specialists of statistics and social medicine. In total, 40 infants were selected via convenience sampling, who were born in Shahid Akbarabadi Hospital in Tehran, Iran. After obtaining parental informed consent, the neonates who met the inclusion criteria were enrolled in the study.

Inclusion criteria of the study were the preterm neonates with the gestational age of less than 37 weeks and normal intrauterine growth who were suspected of sepsis upon birth and no evidence of asphyxia and renal anomalies in the ultrasound examination after birth. Infants presenting with the positive clinical and hematological symptoms and negative blood cultures were considered to be suspected of sepsis. Based on the diagram of weight for gestational age of the preterm infants, intrauterine growth retardation was ruled out, and asphyxia was ruled out based on the medical birth records and clinical signs of the infants.

Selected neonates were randomly divided into two groups of A and B using the blocking method (four blocks). For concealment, type of the intervention remained unknown until the beginning of the intervention. Group A received amikacin diluted in 5% dextrose water proportional to the birth weight and doses available in textbooks (ODD), which was slowly injected intravenously within 30-60 minutes (3,

10). Infants in group B were also administered with amikacin diluted in 5% dextrose water proportional to the birth weight and doses available in textbooks (standard MDD), which was slowly injected intravenously within 30-60 minutes (3, 10). In addition, all the neonates received ampicillin every 8-12 hours proportional to their birth weight (10, 11).

Serum levels of blood urea nitrogen (BUN) and creatinine were extracted from the medical records of the obstetrics ward. Prior to the treatment, blood samples of the infants were analyzed in terms of complete blood count (CBC differential) , blood culture, basic level of BUN, and serum creatinine level. During the first week of birth, all the infants underwent renal and urinary ultrasound to ensure the absence of renal anomalies. In addition, CBC, diff, and serum levels of BUN and creatinine were evaluated on the third and fifth day.

In both study groups, the serum level of amikacin measured on the third day and 30 minutes after the first injection was considered as the maximum level (C_{max}), with the optimal level determined at 20-30 µg/ml (3, 11). Moreover, the serum creatinine level was determined in the blood samples. In both study groups, the serum level of amikacin measured on the fifth day and 30 minutes before the first injection was considered as the minimum or trough concentration (TC), with optimal level determined at 2-5 µg/ml (3, 11). In addition, the serum level of creatinine was determined in the blood samples.

Protein levels of neutrophil gelatinase-associated lipocalin (NGAL) in the urine were considered as the critical biomarkers of infantile acute renal injury and measured on the first day prior to starting the treatment, as well as seven days after the treatment period (5, 6).

Infants with incomplete treatment or lack of parental consent to continue the study and those not meeting any of the inclusion criteria were excluded from further evaluation. In this study, sampling continued until the number of the infants in the study groups A and B reached 20 by the seventh day of treatment and the second assessment of urine NGAL. Throughout the sampling process, the intervention remained unknown.

Acute renal injury was assessed in both study groups. Moreover, comparison of the kidney damage caused by amikacin was performed based on the serum creatinine levels and urinary NGAL levels (5, 6). After extracting the required data, the assumptions were analyzed in SPSS.

Results

To compare the renal damage between the premature infants administered with the ODD and MDD of amikacin who were suspected of sepsis, we examined 40 neonates admitted to Shahid Akbarabadi Hospital of Tehran. All the selected neonates met the inclusion criteria of this clinical trial.

Qualitative variables of the studied infants in both groups before the intervention are presented in Table 1. Quantitative variables of the studied infants in both groups are presented in Table 2.
According to the information in Table 1, there were no statistically significant differences between the two study groups in terms of gender, mode of delivery, evidence of asphyxia, ultrasound results, and blood culture results. According to the information in Table 2, there were no statistically significant differences between the two study groups in terms of the mean birth weight, gestational age, maternal plasma level of creatinine, and the one-minute and five-minute Apgar scores. Quantitative variables of the studied infants in the two study groups after the intervention are shown in Table 3.

Mean plasma levels of creatinine within the

Table 1. Comparison of Qualitative Factors before Intervention between Study Groups

		Single Dose (N=20) N (%)	Multiple Doses (N=20) N (%)	P-value
Gender	Male	9 (45.0)	10 (50.0)	0.752
	Female	11 (55.0)	10 (50.0)	
Mode of Delivery	Natural Vaginal	4 (20.0)	4 (20.0)	1.000
	Caesarean Section	16 (80.0)	16 (80.0)	
Intrauterine Growth Restriction	Yes	0 (0.0)	0 (0.0)	-
	No	20 (100.0)	20 (100.0)	
Blood Culture	Positive	0 (0.0)	0 (0.0)	-
	Negative	20 (100.0)	20 (100.0)	
Asphyxia	Yes	0 (0.0)	0 (0.0)	-
	No	20 (100.0)	20 (100.0)	
Ultrasound Results	Normal	0 (0.0)	0 (0.0)	-
	Abnormal	20 (100.0)	20 (100.0)	

Table 2. Comparison between the newborns in two groups in terms of pre-intervention quantitative factors

	Multiple dose N=20	Single dose N=20	P-value
	Mean±SD*	Mean±SD	
Weight (gr)	2203.5±537.8	1974.1±577.1	0.201
GA** (weeks)	33.1±2.1	32.1±2.1	0.160
Maternal blood creatinine	0.81±0.07	0.82±0.11	0.421
1-minute APGAR***	8.4±0.68	7.8±0.67	0.008
5-minute APGAR	9.6±0.59	8.9±0.75	0.005

* Mean and standard deviation, ** Gestational age, *** American Pediatric Gross Assessment Record

Table 3. Comparison between the newborns in two groups in terms of post-intervention quantitative factors

		Multiple dose N=20	Single dose N=20	P-value
		Mean±SD*	Mean±SD	
WBC**	Base level	12485±3030	11160±4605	0.863
	Third day	9295±3258	9020±2787	
	Fifth day	9135±2723	94±240415	
Blood creatinin	Base level	0.75±0.07	0.81±0.13	0.0001
	Third day	0.72±0.07	0.74±0.13	
	Fifth day	0.71±0.08	0.61±0.09	
Urinary NGAL*** (ng/dl)	First day	748.8±103.9	790.6±86.1	0.635
	Seventh day	782.3±61.8	786.4±97.4	
Serum amikacin level (µg/ml)	Maximum level on the third day	16.92±8.08	24.38±10.08	0.0001
	Minimum level on the fifth day	7.04±5.03	4.31±2.96	

* Mean and standard deviation, ** White Blood Cells, *** Neutrophil gelatinase-associated lipocalin

early days of birth were an estimate of the maternal plasma creatinine, which was observed to decrease in groups A and B during the study, while the mean reduction was more significant in the group receiving single-dose amikacin compared to the infants administered with multiple-dose amikacin (P=0.0001).

After measuring the C_{max} on the third day and the minimum serum levels of amikacin (TC) on the fifth day, it was observed that the reduction in the mean serum levels of amikacin (without reducing the minimum inhibitor concentration) was significantly higher in the group receiving the ODD of amikacin compared to the MDD group (P=0.0001).

Mean changes in the urinary levels of NGAL were measured on the first and seventh day of the study, and no significant differences were observed between the groups in this regard (P=0.635). Furthermore, the urine levels of NGAL showed no nephrotoxicity in the studied neonates.

Discussion

In the study by Van Den Anker et al. (2013), C_{max} was reported to play a key role in the antibacterial effects of aminoglycosides, such as amikacin (12, 13), while the C_{max}/minimal inhibitory concentration (MIC) ratio directly affected the associated bactericidal effects (12-14). According to the results of the present study, amikacin C_{max} and C_{max}/MIC ratio were significantly higher in the ODD group (milligram per kilogram of birth weight) compared to the MDD group (milligram per kilogram of birth weight) (P=0.0001).

In the study by Catherine M.T. Sherwin et al., the MIC of amikacin was achieved at 2-3 days after intravenous therapy (3, 15). In the current research, we measured the C_{max} on the third day of the treatment as well. In order to achieve the desired bactericidal effects, an eight-folded C_{max}/MIC ratio was recommended (3, 15). Moreover, in order to achieve the desired preventive effects of the amikacin-resistant bacteria, a ten-folded C_{max}/MIC ratio was recommended (3, 14, 16), and the best C_{max}/MIC ratio to achieve both these objectives was estimated at 12 times (3, 16).

In the current research, MIC was calculated to be 3-4 mcg/dl for controlling more than 90% of the gram-negative bacteria, which were isolated from the blood cultures of the studied neonates with sepsis (11, 16). Therefore, to achieve the ten-folded C_{max}/MIC ratio, the objective of the intravenous treatment with amikacin was determined at the C_{max} of 30-40 mcg/dl (3).

In several references, the peak serum concentration of amikacin has been measured to be 20-30 mcg/dl, and the objective for the C_{max}/MIC ratio has been suggested to be eight times (3, 11, 16). In the present study, the mean C_{max} of amikacin in the ODD group was

approximately 24 mcg/dl, which was sufficient. However, in the MDD group, the mean C_{max} was estimated at 17 mcg/dl, which was less than the recommended level. Low C_{max} is considered a health risk in neonates, especially those presenting with the evidence of sepsis (3, 16, 17).

In the standard dose method (SDD), despite administering an initial dose of amikacin in neonates, if the subsequent doses are administered every 8-12 hours, the maximum therapeutic level will not be achieved for 24 hours due to the distribution volume of the drug (3, 15, 16).

In the current research, the C_{max}/MIC ratio in the ODD group was more than eight times, which resulted in the minimum bactericidal effect, while in the standard-dose group, the C_{max}/MIC ratio was less than eight times, which was lower than the proposed ratio. In the study by Catherine T.M. Sherwin et al., the most important underlying factor for treatment failure and drug resistance with amikacin in infants was the C_{max}/MIC ratio of less than eight times (3, 16).

In a meta-analysis conducted by Nestaas et al. (2005), the researchers compared the methods of amikacin administration with increased intervals using traditional multiple doses. According to the results, the optimal C_{max} could be achieved with the increased intervals (3, 8, 16). Furthermore, it was stated that in the traditional dosing, there were more concerns regarding the lack of the desirable C_{max} and C_{max}/MIC ratio (3, 8, 15, 16); our findings are consistent with the results of the mentioned study.

In the study by Catherine T. M. Sherwin et al. (2009), it was claimed that the trough concentration and serum level of aminoglycosides at the interval of two injections were a significant determinant of aminoglycoside nephrotoxicity in newborns (3, 18).

In the current research, TC was measured as the serum level of amikacin on the fifth day of treatment 30 minutes before the next injection. According to the studies in this regard, the range of amikacin TC in newborns is 2-5 mcg/dl (3, 11). In the single-dose group, TC of two newborns was less than the MIC range of amikacin (3-4 mcg/dl), while the findings of Gonzalez et al. (1998) indicated that due to the effects of post-antibiotics on aminoglycosides, they inhibit bacterial growth even when the serum concentration of antibiotics is less than the MIC (19).

In the present study, mean TC was 31.4 mcg/dl in the ODD group, which was within the recommended range, and none of the infants had a TC of <2 mcg/dl. In the study by Catherine M. T. Sherwin et al., TC was reported to be a significant influential factor in the incidence of amikacin nephrotoxicity (3, 7, 17), while in the premature infants, TC of <2 mcg/dl was observed to be effective in preventing amikacin nephrotoxicity (3, 17). In premature infants, treatment failure is often not likely with the TC of 1-2 mcg/dl and minimum C_{max}/MIC ratio of eight (3, 18, 20).

In the present study, mean TC was 4.7 mcg/dl in the MDD group, which was higher than the recommended range; on the other hand, TC of <2 mcg/dl was reported in none of the neonates. In the research by McWilliam et al. (2012), in order to provide a TC value beyond the scope of treatment (e.g., infants with the TC of 2-5 mcg/dl), a higher intracellular concentration of amikacin in the renal parenchyma was reported to increase the risk of amikacin nephrotoxicity (3, 5, 15).

In the meta-analysis by Nestaas et al. (2005), achieving a TC of lower than the optimal range was more likely in the method with increased intervals, while the risk of exceeding the therapeutic range and entering the nephrotoxic range was reported to be lower (8, 21). In the traditional method, TC was more likely to be within the recommended range; however, it was associated with the increased risk of exceeding the therapeutic range and entering the nephrotoxic range (8, 21, 22). Our findings are in line with the results of the mentioned study.

In the study by McWilliams et al. (2012), NGAL, kidney injury molecule-1, and n-acetyl glucosaminidase were introduced as the highly sensitive markers for the early detection of renal proximal tubular epithelial cell damage (5, 6). One of the main characteristics of the NGAL protein is that it causes a rapid and significant increase in the serum and urine AKI within 2-4 hours after injury and 48 hours before increasing the serum creatinine (5, 6).

In the study by McWilliams et al. (2012), the baseline level of urine NGAL in the absence of the clinical signs of the disease and nephrotoxic treatment was estimated at 4.424 ng/mg Cr (range: 3.688-6.162 ng/mg Cr), which dramatically increased during AKI. In addition, the mean increase was reported to be 7.2031 ng/mg Cr within the range of 4.1351-9.2711 ng/mg Cr (5, 23, 24).

In the current research, no significant increase was observed in the urine NGAL level on the first and seventh day of the intervention in the study groups A and B. Mean urine NGAL in the group administered with the single-dose of amikacin was 790 and 786 ng/mg Cr on the first and

seventh day of treatment. However, the mean changes in the urine NGAL level, which were measured on the first and seventh day of treatment, were not significant and showed no evidence of AKI.

According to the results of the present study,mean changes in the urine NGAL in the MDD group was about 749 ng/mg Cr on the first day and 782 ng/mg Cr on the seventh day of amikacin treatment. However, the mean changes in the urine NGAL levels, which were measured on the first and seventh day of treatment, were not significant and showed no evidence of AKI.

According to the findings of the current research, mean urine NGAL on the first and seventh day of treatment had no statistically significant difference between the two groups (P=0. 635). On the other hand, the reduction in the mean urine NGAL level in the group administered with the single-dose of amikacin changed from 790 ng/mg Cr on the first day of treatment to 786 ng/mg Cr on the seventh day of treatment, which was not considered to be statistically significant. However, measurement of the urine NGAL levels on the first and seventh day of the intervention revealed no cases of nephrotoxicity in the two study groups.

According to neonatal references, the plasma creatinine level in the early days of life is an indicator of the maternal serum creatinine level (1, 12). Due to the immaturity of the renal tubules and vascular structures of the nephrons, plasma creatinine of infants is high for their body size and muscle mass and remains high for 1-2 weeks (1, 12). In the neonates that are more premature, the serum creatinine will remain high for a longer period. In some cases, the creatinine levels of the neonatal plasma may exceed the maternal levels due to the absorption of creatinine by the immature tubules (1, 12). According to studies on nephrology, maternal plasma levels of creatinine depend on factors such as the muscle mass, glomerular filtration rate (GFR), and tubular secretion. Therefore, high and variable serum levels of creatinine are expected in infants.

In the present study, the plasma levels of creatinine in all the mothers were within the normal range. Furthermore, increased mean plasma level of creatinine was observed in none of the infants during the intervention. After the intervention, the mean plasma level of creatinine reduced in both groups, while the mean reduction was significantly higher in the ODD group compared to the MDD group. This is in congruence with the results of the previous studies performed on newborns (25, 26) and adults (21, 22).

Findings of the current research were inconsistent with some of the previous studies in this regard. For instance, Najmeddin et al. (2014) evaluated the nephrotoxicity of amikacin after seven days of treatment in 40 adult patients with sepsis, who were randomly assigned to two groups. Patients in the first group were administered with a standard dose of amikacin (5.12 mg/kg) every 12 hours, and the second group received a high dose of amikacin (25 mg/kg) every 24 hours. The obtained results showed no significant differences between the two groups regarding the changes in the GFR, serum creatinine, and frequency of AKI (P=0.342). However, the serum level of NGAL was significantly higher than the baseline level in the high-dose single daily regimen compared to the medium multiple dosing of the drug on the third and fifth day of the treatment. Moreover, the researchers stated that this phenomenon reflected a pattern of safer prescription for the traditional low multiple doses of amikacin with respect to the associated tubular damage (27).

Based on the parameters used to assess clinical effectiveness, our findings indicated that the once-daily dosing of amikacin had the same therapeutic effects as the traditional multiple-dose regimen, which is consistent with the results of the studies conducted by Mendoza et al. on infants (26) and Abdel-Hady et al. (25) on preterm infants. In addition, Kafetzi et al. performed a study on the children aged 3 months-14 years and concluded that the once-daily dosing of aminoglycosides is similar to the administration of the drug 2-3 times per day (28). Findings of the present study are also in line with the meta-analyses that have been published on infants and children, reporting the similar effectiveness and safety of single-dose aminoglycosides as compared to the multiple doses of these drugs (8, 25, 29).

Despite the general assumption that the prescribed dosing of aminoglycosides is associated with the risk of nephrotoxicity, several studies have shown that the risk of aminoglycoside nephrotoxicity is directly correlated with the intervals between the administered doses (4, 5). In this regard, Murry et al. stated that the patients who received the once-daily dosing of aminoglycosides had lower nephrotoxicity compared to those who were treated by the standard multiple doses of the drugs (30), which could be due to the shorter duration of the treatment with the once-daily dosing of aminoglycosides in some patients (30). Furthermore, the researchers reported that the

once-daily dosing of aminoglycosides may cause less nephrotoxicity for two reasons. First, aminoglycosides provide safer serum concentrations after each dose since the TC remains below the toxic levels between the intervals. Second, higher C_{max} levels lead to faster clinical improvement, thereby exposing patients to the less cumulative doses of the drugs within the shortest duration of treatment (30).

Final outcome and male gender are important factors to be considered in the patients treated by aminoglycosides. Among the other influential factors in this regard are the type of regimen (ODD or SDD), appropriate dosing, duration of the treatment, and potential nephrotoxic risk factors, such as the gestational age, age after birth, reduced creatinine clearance, poor feeding support, intensive care admission, and concomitant use of other nephrotoxic drugs (e.g., furosemide, amphotericin B, Vancomycin, and cephalosporins) (5, 7, 8, 12).

Conclusion

According to the literature and results of the present study, it could be concluded that the once-daily dosing and multiple doses of amikacin are not significantly different in terms of nephrotoxicity in the preterm infants suspected of sepsis. Considering the higher C_{max} of amikacin in the once-daily dosing administration, it seems that this method is more effective in the treatment of septic infants compared to using the multiple doses of the drug. Furthermore, once-daily dosing of amikacin was observed to be less likely to exceed the recommended therapeutic ranges of TC and nephrotoxicity, which makes it a safer method of administration in premature infants.

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