Evaluation of nephrotoxicity and ototoxicity following amikacin administration once daily or every 48 hours in neonates

Aiju Endo, MS[a],* [ID], Kazumi Hanawa, PhD[b], Atsushi Nemoto, MD, PhD[c], Takahiro Ishikawa, Bachelor of Pharmacy[a], Shizuka Kazama, Bachelor of Pharmacy[a], Yu Kagami, Bachelor of Pharmacy[a], Yuki Maebayashi, MD, PhD[c], Nobuyuki Katsumata, MD, PhD[c], Atsushi Naito, MD, PhD[c], Yoshifumi Kobayashi, Bachelor of Pharmacy[a], Yayoi Kawano, PhD[d], Takehisa Hanawa, PhD[d]

Abstract

The purpose of this study was to evaluate the effects of once daily (OD) or every 48 hours (every-48-h) administration of amikacin (AMK) on renal function and ototoxicity in neonates. We investigated the frequency of nephrotoxicity and ototoxicity in neonates who received AMK OD or every-48-h from April 2015 to March 2021 and underwent dose evaluation by therapeutic drug monitoring (TDM). In addition, the relationships among birth weight, gestational age, AMK peak and trough values, total duration of AMK administration, and total AMK dose were examined separately for nephrotoxicity and ototoxicity. AMK was administered OD in 38 patients and every-48-h in 62 patients. Nephrotoxicity was observed in 8 patients on OD versus 36 patients on every-48-h administration ($P < .001$), and ototoxicity was observed in 2 patients on OD versus 12 patients on every-48-h administration ($P = .192$). For nephrotoxicity, only the trough value was relevant ($P = .007$). In terms of ototoxicity, there were no influencing factors. The risk of nephrotoxicity was higher with every-48-h AMK administration than with OD AMK administration, with nephrotoxicity depending on the trough value. However, compared with OD, the every-48-h group had lower body weight and possibly poorer original renal function. In addition, ototoxicity did not differ by administration method. Based on these results, every-48-h administration of AMK can be used as safely as OD by performing TDM and preventing high concentrations.

Abbreviations: AGs = aminoglycosides, AMK = amikacin, BW = body weight, every-48-h = every 48 hours, GA = gestational age, IND = indomethacin, OD = once daily, PNA = post-natal-age, SCr = serum creatinine, TDM = therapeutic drug monitoring.

Keywords: amikacin, every 48 hours, nephrotoxicity, once daily, ototoxicity

1. Introduction

Aminoglycosides (AGs) are water-soluble antibiotics that act against gram-negative bacteria, synergize against beta-lactam agents, and are predominantly excreted by the kidneys.[1,2] Therefore, AGs are commonly used as empiric therapy for various infections in neonates with weak immune systems.[3,4] The therapeutic effectiveness of AGs depends on their peak blood concentrations. Side effects, such as nephrotoxicity, which depend on trough levels, have been reported.[5,6] Therefore, once-daily (OD) dosing has been common rather than multiple daily dosing, thereby making therapeutic drug monitoring (TDM) essential for AGs to ensure therapeutic efficacy and prevent toxicity.[7]

Standard dosing of 15 mg/kg OD in neonates provides an effective amikacin (AMK) concentration (peak value) of 20 to 40 µg/mL.[3,4] However, sufficient concentrations are often not achieved in low-birth-weight infants with high extracellular fluid and immature renal function.[8] Nelson's guide and the drug information resource "Lexicomp" recommend increasing the dose and extending the dosing interval 36 to 48 hours.[3,4] This also prevents AG toxicity.[9,10]

Common side effects of AGs include nephrotoxicity and ototoxicity. AGs cause renal damage by apoptosis owing to their impact on lysosomes after reabsorption in renal proximal tubular epithelial cells.[11] Therefore, a prolonged high concentration is undesirable because renal damage depends on the trough value.[12] OD administration has been reported to reduce the risk of renal injury compared with multiple daily.[13] However, similar reports for every 48 hours (every-48-h) administration are limited.

Ototoxicity caused by AGs in vitro increases with exposure to high blood concentrations.[14] The acceptable trough level of AMK in newborns is up to 10 µg/mL.[6] The risk of ototoxicity increases at trough levels above 10 µg/mL.[15] The ototoxicity caused by AGs depends on administration duration and total

dose.[16–18] However, most of these reports are based on gentamicin administration, and descriptions of AMK are limited. Our previous research on AMK did not examine the administration duration or total dose.

Therefore, based on our institutional guidelines and previous studies, in addition to administering AMK OD as described in the Methods section, we have previously administered AMK every-48-h with an increased single dose. However, the safety of our AMK administration regimen was unexamined, as there are few reports on every-48-h administration. AGs cause nephrotoxicity and ototoxicity depending on the high concentration transition and time of exposure.[5,6] We focused on the two administration regimens' side effects, especially nephrotoxicity and ototoxicity.

2. Materials and Methods

2.1. Participants and study design

We conducted a chart review of children admitted to Yamanashi Prefectural Central Hospital's NICU between April 2015 and March 2021 and treated with AMK for empiric therapy and various infectious diseases, including bacteremia on a retrospective basis. Based on Nelson and the Japanese Society of Chemotherapy regimen in our hospital, AMK is administered to patients as follows: body weight (BW) ≥ 1000 g, OD, 15 mg/kg; BW < 1000 g, every 48 h, 20 mg/kg. In addition, TDM was carried out at a steady state at least a day after starting AMK administration. The peak and trough values were measured in venous blood samples on the same day 1 to 2 hours before and after AMK administration, respectively.

The exclusion criteria were no measurement of AMK peak and trough values, no blood sampling to evaluate side effects, no evaluation of ototoxicity, and congenital hearing loss. Cases with peak values <20 μg/mL were excluded owing to untargeted concentrations and the possibility of erroneous data. If a patient was administered more than one course of AMK during hospitalization, the duration and dose were calculated as the sum values. If multiple AMK blood measurements were performed, the highest trough value was used (peak values were used from the same day as its trough values). The blood AMK concentration was measured based on the kinetic interaction of microparticles in a solution (SRL Inc., Tokyo, Japan).

2.2. Survey contents

We investigated the number of applicable cases, gestational age (GA), birth BW, and post-natal-age (PNA) at the start of the AMK administration, AMK administration period until blood sampling, peak and trough values, total duration and dose, and occurrence of nephrotoxicity and ototoxicity. The peak values, trough values, total duration and total dose were compared between cases with and without renal and hearing impairment. The number of cases with indomethacin (IND) treatment affecting renal function in OD and every-48-h administration group was also investigated. The variation in serum creatinine (SCr) levels over time with AMK administration initiation was investigated under each administration method with and without IND. Other factors affecting hearing impairment in addition to AMK administration were recorded and evaluated.[19–21] The list of risk factors affecting hearing impairment in newborns includes Apgar score < 5 at 1 minute or < 7 at 5 minutes; hypoxemia or seizures resulting from a difficult delivery; prenatal infection with rubella, syphilis, herpes, cytomegalovirus, or toxoplasmosis; craniofacial anomalies, particularly those involving the external ear; hyperbilirubinemia (diagnosed based on: jaundice occurring within 24 hours, 1 week, or >2 weeks of birth; total serum bilirubin elevated to >5 mg/dL

per day; total serum bilirubin of >18 mg/dL; or symptoms or indication of severe disease); sepsis or meningitis via positive blood culture, spinal fluid culture, or clinical judgment by a neonatologist; respiratory dependency; use of other potentially ototoxic drugs such as vancomycin and furosemide; and familial hearing loss.

2.3. Nephrotoxicity evaluation

As SCr and creatinine clearance values are reportedly proportional after the third day of PNA, the SCr levels,[22] a proxy of renal function, were evaluated by comparing values at the start of AMK administration and the measurement of AMK concentrations. Based on previous reports and definitions by Kidney Disease Improving Global Outcomes, acute kidney injury was defined as a ≥1.5-fold or ≥0.3 mg/dL increase in SCr, or urine output <0.5 mL/kg/h for 6 hours.[23,24]

2.4. Ototoxicity evaluation

The infants underwent automated auditory brainstem response testing to evaluate ototoxicity. Infants with abnormal results underwent acoustic brainstem response testing. If newborns were suspected of having hearing abnormalities, an otolaryngologist was consulted, and hearing impairment was determined. Cases wherein AMK-associated hearing impairment could not be ruled out were used.

2.5. Statistical analyses

Fisher's exact test was performed for comparing the incidence of ototoxicity and nephrotoxicity between groups to examine the difference in side effects between the two regimens. Univariate statistics were first performed using the Mann–Whitney U test to examine the effects of AMK parameters (peak and trough values, total duration, and total dose) on nephrotoxicity and ototoxicity. If the results indicated a significant difference, logistic regression analysis was performed (dependent variable: toxicity, independent variables: AMK parameters). Next, the Kruskal–Wallis test was used to analyze the difference in SCr values in each administration regimen and over time, and in the IND non-treated group. Finally, Fisher's exact test was performed to investigate other confounders of hearing impairment. We calculated 95% confidence intervals using the IBM SPSS Statistics 26 software (IBM Japan, Ltd., Tokyo, Japan). Differences were considered significant at $P < .05$.

2.6. Ethical considerations

The Institutional Clinical and Genome Research Ethics Review Committee approved the study (registration number: 2021-18). To ensure confidentiality, unique identifiers, such as names, were not recorded. Instead, data were stored in a password-protected computer provided by the principal investigator.

3. Results

3.1. Cases and parameters for AMK administration

There were 163 cases in the current study period, with peak and trough values measured in 110 cases. Of these, in total, 100 cases (51 males and 49 females) fit the criteria (Table 1). The median GA and median BW were 30.1 weeks and 1413 g, respectively. AMK was administered OD in 38 cases and every-48-h in 62 cases. The median AMK OD and every-48-h doses were 14.9 and 20.1 mg/kg, respectively. At the start of AMK administration, the median PNA was 0 days, and the median administration period until blood sampling was 3 days.

Demographics, cases, and values (median [IQR]) related to AMK administration.

Characteristics	Cases and values
Number of cases (male/female)	100 (51/49)
GA (wk)	30.1 (27.0–34.8)
Birth BW (g)	1413 (854–2028)
AMK administration method	
OD (case)	38
Every-48-h (case)	62
AMK dose	
OD (mg/kg)	14.9 (14.1–15.5)
Every-48-h (mg/kg)	20.1 (16.6–21.4)
PNA at the AMK start (d)	0 (0–4)
Administration period until AMK blood sampling (d)	3 (3–5)
Total duration of AMK administration (d)	6 (4–7)

AMK = amikacin, BW = body weight, GA = gestational age, IQR = inter-quartile range, OD = once-daily, PNA = post-natal age.

3.2. Nephrotoxicity and SCr values

Nephrotoxicity was observed in 8 (21%) and 36 (58%) patients receiving AMK OD and every-48-h, respectively ($P < .001$; Table 2). Moreover, 4 (11%) and 31 (50%) patients received IND in the OD and every-48-h groups, respectively ($P < .001$). The median difference between patients with and without nephrotoxicity, respectively, was peak AMK level, 33.5 µg/mL versus 29.9 µg/mL ($P = .086$); trough value, 4.2 µg/mL versus 2.4 µg/mL ($P = .002$); total duration of treatment, 7 days versus 6 days ($P = .420$); and total dose, 64.2 mg/kg versus 76.9 mg/kg ($P = .188$).

The difference in SCr values at the start of AMK administration and the concentration measurement in all patients was divided by each method (Fig. 1A). There was no difference in the SCr value at the start of AMK administration between the two regimens ($P = .655$). Conversely, the SCr value at the time of concentration measurement was higher in the every-48-h group than in the OD group ($P < .001$). There was no difference in SCr values in the OD group between the start of AMK administration and measurement ($P = .444$). However, in every-48-h administration, there was an increase at the time of measurement compared with that at the start ($P < .001$). When the same comparison was performed in the IND non-treatment group, at the start of AMK administration, the SCr value was not different in the OD versus every-48-h group ($P = .238$); at the time of AMK concentration measurement, the SCr level was higher in the every-48-h group than in the OD group ($P = .014$; Fig. 1B). In the OD group, the SCr level was not different at the start of

AMK administration versus at the time of concentration measurement ($P = .573$); in the every-48-h group, the SCr level was higher during concentration measurement than at the start ($P < .001$).

3.3. Ototoxicity

Ototoxicity was observed in 2 (5%) and 10 (16%) patients receiving AMK OD and every-48-h, respectively ($P = .192$; Table 3). The median difference between the groups with and without ototoxicity, respectively, was peak AMK level, 31.0 µg/mL versus 31.5 µg/mL ($P = .815$); trough value, 1.8 µg/mL versus 3.1 µg/mL ($P = .592$); total duration of treatment, 6.5 versus 6 days ($P = .781$); and total dose, 82.7 mg/kg versus 74.3 mg/kg ($P = .664$).

Other factors between the groups with and without hearing impairment, respectively, were: Apgar score < 5 at 1 minute after birth, 2 versus 24 cases ($P = .725$); Apgar score < 7 at 5 minutes after birth, 2 versus 13 cases (small sample size; not evaluated further); hypoxemia or seizures resulting from a difficult delivery, 0 versus 2 cases (small sample size; not evaluated further); hyperbilirubinemia, 11 versus 71 cases ($P = .688$); bacteremia, 3 versus 14 cases ($P = .424$); respiratory dependency, 6 versus 23 cases ($P = .101$); furosemide administration, 10 versus 46 cases ($P = .062$); vancomycin administration, 1 versus 9 cases (small sample size; not evaluated further); familial hearing loss, 0 versus 1 case (small sample size; not evaluated further; Table 4). There was no meningitis, craniofacial anomaly, prenatal infection with syphilis, rubella, herpes infection, cytomegalovirus infection, or toxoplasmosis.

4. Discussion

Neonates with incredibly immature renal function at GA < 34 weeks and with a low BW < 1000 g, are likely to accumulate high AMK levels.[15,25] The relative distribution volume of AG tends to be larger in neonates with BW < 1000 g; hence, a high dose is necessary to reach the peak value for therapeutically effective concentration. If such dosing occurs, the dosing interval should be extended to prevent side effects. However, the safety of an every-48-h regimen compared with the OD regimen is unknown. Therefore, based on institutional guidelines and past reports, we focused on the side effects of AMK administered OD and every-48-h.

Although biomarkers to accurately assess drug-induced renal injury in neonates has not been identified, we used SCr values to assess AMK-induced renal injury. We assumed that renal function could be evaluated by the variation in SCr value following each administration method because SCr and creatinine

Nephrotoxicity cases and parameters, and IND cases.

	AMK administration method					
	OD		Every-48-h		P value	
A (cases)						
Nephrotoxicity	8 (21%)		36 (58%)		<.001	
IND administration	4 (11%)		31 (50%)		<.001	
B (value)		Nephrotoxicity			P value	Odds ratio
		−		+		
	Average ± SD	Median (IQR)	Average ± SD	Median (IQR)		
AMK peak concentration (µg/mL)	30.6 ± 5.8	29.9 (27.0–33.4)	34.7 ± 9.5	33.5 (30.4–39.7)	.086	1.063
AMK trough concentration (µg/mL)	2.7 ± 1.9	2.4 (1.4–3.6)	5.2 ± 4.5	4.2 (2.5–5.9)	.002	1.440
Total duration of AMK administration (d)	7.7 ± 4.9	6 (4–9)	7.3 ± 4.7	7 (5–7)	.420	1.133
Total AMK dose (mg/kg)	105.8 ± 84.2	76.9 (53.8–127.4)	85.1 ± 68.5	64.2 (45.6–86.4)	.188	0.986

A: Cases of nephrotoxicity based on AMK administration method. Analysis using Fisher's exact test. Significant differences calculated with 95% confidence intervals (CIs).
B: Average and median values of various parameters based on nephrotoxicity. Analysis using a logistic regression model. Significant differences calculated with 95% CIs.
AMK = amikacin, CI = confidence intervals, IND = indomethacin, IQR = inter-quartile range, OD = once-daily, SD = standard deviation.
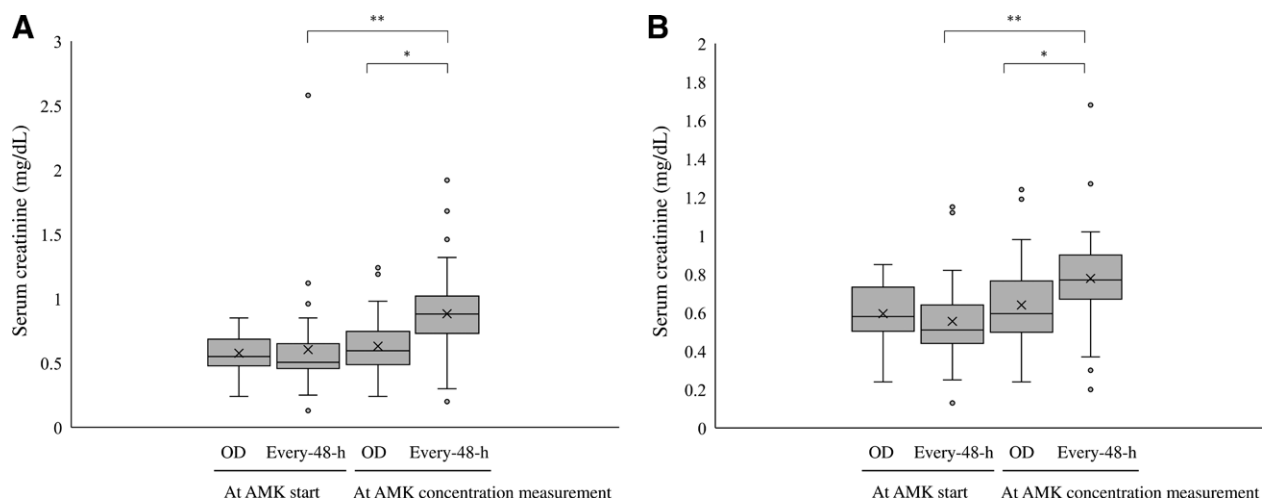
Figure 1. SCr values in once daily (OD) and every-48-h groups at the start of amikacin (AMK) administration and at the time of concentration measurements. (A) With indomethacin (IND; n = 100). From left to right, groups at the start of AMK administration, first: OD (n = 38); second: every-48-h (n = 62); groups at the time of AMK measurement, third: OD (n = 38); fourth: every-48-h (n = 62). (B) Without IND (n = 65). From left to right, groups at the start of AMK administration, first: OD (n = 34); second: every-48-h (n = 31); groups at the time of AMK measurement, third: OD (n = 34); fourth: every-48-h (n = 31). *P < .05; **P < .05; analysis using the Kruskal–Wallis test. SCr = serum creatinine.

Table 3

Various cases and parameters in ototoxicity.

	AMK administration method				
A (cases)	**OD**		**Every-48-h**		**P value**
Ototoxicity	2		10		.192
B (value)		Ototoxicity			**P value**
	−		+		
	Average ± SD	Median (IQR)	Average ± SD	Median (IQR)	
AMK peak concentration (µg/mL)	32.2 ± 7.0	31.5 (27.5–36.6)	33.8 ± 13.0	31.0 (27.3–34.6)	.815
AMK trough concentration (µg/mL)	3.6 ± 2.4	3.1 (2.1–4.3)	5.28 ± 7.7	1.8 (1.2–6.3)	.592
Total duration of AMK administration (d)	7.5 ± 4.8	6.0 (4–8)	7.7 ± 5.1	6.5 (5–8)	.781
Total AMK administration dose (mg/kg)	95.6 ± 79.2	73.5 (45.7–106.4)	104.3 ± 71.2	82.7 (44.5–165.7)	.664

A: Cases of ototoxicity based on AMK administration method. Analysis using Fisher's exact test. Significant differences calculated with 95% confidence intervals (CIs).
B: Average and median values of various parameters based on ototoxicity. Analysis using the Mann–Whitney U test. Significant differences calculated with 95% CIs.
AMK = amikacin, IQR = inter-quartile range, OD = once daily, SD = standard deviation.

Table 4

Comparison of risk factors for hearing impairment.

	Hearing impairment		
	−	**+**	**P value**
Administration method			
OD	36 (94.7%)	2 (5.3%)	.125
Every 48 h	52 (83.9%)	10 (16.1%)	
Apgar score after birth: 1 min (<5)	24 (92.3%)	2 (7.7%)	.725
Apgar score after birth: 5 min (<7)	13 (86.7%)	2 (13.3%)	NS
Hypoxemia or seizures	2 (100%)	0 (0%)	NS
Hyperbilirubinemia	71 (86.6%)	11 (13.4%)	.688
Bacteremia	14 (82.4%)	3 (17.6%)	.424
Respiratory dependency	23 (79.3%)	6 (20.7%)	.101
Furosemide administration	46 (82.1%)	10 (17.9%)	.062
Vancomycin administration	9 (90%)	1 (10%)	NS
Familial hearing loss	0 (0%)	1 (100%)	NS

There was no meningitis, craniofacial anomaly, prenatal infection with syphilis, rubella, herpes infection, cytomegalovirus infection, or toxoplasmosis.
Analysis using Fisher's exact test. Significant differences calculated with 95% confidence intervals (CIs).
NS = not significant, OD = once daily.

clearance values are reportedly proportional after the third day of PNA.[22] In our case, we thought the median SCr value could be used to evaluate renal function since it was measured on the third day of treatment. In the first examination, we found that cases of acute kidney injury were more frequent with every-48-h administration than with OD. The trough values were correlated with renal impairment, and the median value was ≥4 µg/mL. Second, the every-48-h group showed a significant increase in SCr values between the start and measurement times. However, in some cases, IND was administered simultaneously, and the possibility of acute kidney injury caused by it was considered. IND was often administered at PNA for 1 to 3 days (data not shown), and many of the times coincided with the time of AMK administration. Therefore, we first examined the differences in SCr values in the groups with and without IND administration (data not shown). The results found no difference at the start of AMK treatment but a significant increase in the IND group at the measurement time. This may indicate renal damage by IND. Thus, when we examined 65 cases in which IND administration cases were excluded, we found that SCr levels predominantly increased every-48-h group compared with OD group. Although there was no difference in SCr values in the OD group at the measurement time compared with those at the start of AMK administration, a significant increase was observed in the every-48-h group. This result suggests that AMK affected the rise in SCr level and every-48-h administration significantly affected nephrotoxicity.

This study did not compare the SCr values with those of the AMK non-treated group. Therefore, the SCr values in 96 AMK non-treated children of similar GA and weight in the study period were used for comparison (data not shown). The SCr values in the every-48-h group at the start of AMK administration and at the time of measurement showed no difference. The results for the non-treated group of INDs were similar. Based on these results, we believe that the every-48-h group was administered in BW < 1000 g infants. Their immature renal function delayed the excretion of AMK, resulting in high trough values. It is possible that the difference between OD and every-48-h dosing methods may not cause renal damage. However, further study is needed as the AMK non-treatment group in this study was a collection of moderately matched cases and lacked accuracy. In addition, we could not examine the following in this study: effect of factors other than IND on renal damage, long-term observations of renal damage caused by AMK-induced elevation of SCr values, or the long-term effects of AMK administration (since, in most cases, the administration was performed for ≤ 14 days). As AGs are generally known to cause renal damage at high trough concentrations, adult guidelines from the American Thoracic Society and Japanese Society of Chemotherapy recommend a target trough concentration of AMK < 4 µg/mL. Remaining within this low trough value and ensuring a short treatment period may reduce the chance of chronic renal injury in most cases.

Based on the results of our study and those of Engler et al,[6,15] ototoxicity is more likely to occur at high trough values (≥10 µg/mL). No significant effect was observed when the peak and trough values were compared between groups with and without ototoxicity (Table 3). In contrast, AMK-related ototoxicity is considered irreversible, mainly because of damage due to long-term exposure to the cochlea,[26] as AGs accumulate in the inner ear.[27] Therefore, the total exposure duration and AMK dose were examined for their effects on ototoxicity but showed no effects in the present study. Based on these results, plots of the duration of AMK administration and trough values in the two groups with and without ototoxicity showed similar trends (Fig. 2). However, both groups' median treatment duration was within 7 days. Most cases were within 14 days, with trough values <10 µg/mL (range shown in the gray area in Fig. 2). Moreover, in cases outside the gray area, even when the
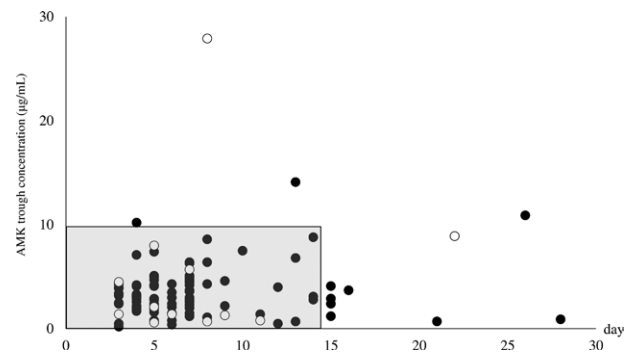
Figure 2. Relationship between administration of amikacin (AMK) trough values and total treatment duration. Vertical axis, AMK trough concentration; horizontal axis, AMK total administration duration; ○ = ototoxicity (n = 12); ● = no ototoxicity (n = 88).

trough value of AMK was ≥10 µg/mL, the administration period was short, and vice versa. Furthermore, we found no significant differences between OD and every-48-h administration for hearing impairment. No associations were found with other risk factors for hearing impairment. However, we could not investigate mitochondrial polymorphisms common in Asians.[28,29] However, if high blood concentrations are sustained for a long time (outside the gray area shown in Fig. 2), the possibility of ototoxicity cannot be excluded. The risk of ototoxicity can therefore be suppressed by selecting an appropriate administration method based on the PNA, GA, and BW, and by controlling the AMK trough concentration to <10 µg/mL while observing the blood concentration and keeping the total administration period within 14 days. This result is consistent with the review by "Lexicomp," describing that high concentrations and treatment durations longer than 14 days are unsafe.[4]

We observed no differences in side effects between the OD and every-48-h administration methods. However, we considered it necessary to note the following criteria: nephrotoxicity and ototoxicity may occur at trough values of ≥4 and ≥10 µg/mL, respectively; the duration of administration should be within 14 days. Therefore, we consider that the practice of TDM enables an early response to high AMK levels and early discontinuation of AGs, thereby reducing nephrotoxicity and ototoxicity risk. Including our criteria for AMK administration into existing guidelines will improve the treatment of neonatal infections.

Author contributions

Conceptualization: Aiju Endo, Kazumi Hanawa, Atsushi Nemoto, Takehisa Hanawa.
Data curation: Aiju Endo, Takahiro Ishikawa, Shizuka Kazama, Yu Kagami.
Formal analysis: Aiju Endo, Kazumi Hanawa, Atsushi Nemoto.
Funding acquisition: Aiju Endo, Yoshifumi Kobayashi.
Investigation: Aiju Endo, Takahiro Ishikawa, Shizuka Kazama, Yu Kagami, Yuki Maebayashi, Nobuyuki Katsumata, Atsushi Naito.
Methodology: Aiju Endo, Kazumi Hanawa, Atsushi Nemoto, Takehisa Hanawa.
Project administration: Aiju Endo, Kazumi Hanawa, Takehisa Hanawa.

References

[1] Clark RB, Pakiz CB, Hostetter MK. Synergistic activity of aminoglycoside-beta-lactam combinations against Pseudomonas aeruginosa with an unusual aminoglycoside antibiogram. Med Microbiol Immunol. 1990;179:77–86.

[2] Giamarellou H. Aminoglycosides plus beta-lactams against gram-negative organisms. Evaluation of in vitro synergy and chemical interactions. Am J Med. 1986;80:126–37.

[3] Bradley JS, Nelson JD. Nelson's Pediatric Antimicrobial Therapy. 19th ed. Tokyo, Japan: Igaku-Shoin Ltd; 2013.

[4] Taketomo CK, Hodding JH, Kraus DM. Pediatric and Neonatal Dosing Handbook. 22nd ed. Hudson, OH: Lexi-Comp Inc; 2016.

[5] Gonzalez L, SpencerJP, III. Aminoglycosides: a practical review. Am Fam Phys. 1998;58:1811–20.

[6] Engler D, Schellack N, Naude A, et al. A pilot study on the use of amikacin in neonates: who should be monitored for ototoxicity? South Afr J Infect Dis. 2015;30:72–6.

[7] Bertino JS, Jr, Rodvold KA, Destache CJ. Cost considerations in therapeutic drug monitoring of aminoglycosides. Clin Pharmacokinet. 1994;26:71–81.

[8] Gálvez R, Luengo C, Cornejo R, et al. Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity. Int J Antimicrob Agents. 2011;38:146–51.

[9] Pacifici GM. Clinical pharmacokinetics of aminoglycosides in the neonate: a review. Eur J Clin Pharmacol. 2009;65:419–27.

[10] Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JPA. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics. 2004;114:e111–8.

[11] Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother. 1999;43:1003–12.

[12] Swan SK. Aminoglycoside nephrotoxicity. Semin Nephrol. 1997;17:27–33.

[13] Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ. 1996;312:338–45.

[14] Huth ME, Ricci AJ, Cheng AG. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. Int J Otolaryngol. 2011;2011:937861.

[15] Endo A, Nemoto A, Hanawa K, et al. Relationship between amikacin blood concentration and ototoxicity in low birth weight infants. J Infect Chemother. 2019;25:17–21.

[16] Ahmed RM, Hannigan IP, MacDougall HG, Chan RC, Halmagyi GM. Gentamicin ototoxicity: a 23-year selected case series of 103 patients. Med J Aust. 2012;196:701–4.

[17] Ariano RE, Zelenitsky SA, Kassum DA. Aminoglycoside-induced vestibular injury: maintaining a sense of balance. Ann Pharmacother. 2008;42:1282–9.

[18] Black FO, Pesznecker S, Stallings V. Permanent gentamicin vestibulotoxicity. Otol Neurotol. 2004;25:559–69.

[19] Fischel-Ghodsian N. Genetic factors in aminoglycoside toxicity. Pharmacogenomics. 2005;6:27–36.

[20] Karaca CT, Oysu C, Toros SZ, Naiboğlu B, Verim A. Is hearing loss in infants associated with risk factors? Evaluation of the frequency of risk factors. Clin Exp Otorhinolaryngol. 2014;7:260–3.

[21] US Preventive Services Task Force. Universal screening for hearing loss in newborns: recommendation statement. Am Fam Physician. 2010;81:185–6.

[22] van Donge T, Allegaert K, Gotta V, et al. Characterizing dynamics of serum creatinine and creatinine clearance in extremely low birth weight neonates during the first 6 weeks of life. Pediatr Nephrol. 2021;36:649–59.

[23] Salerno SN, Liao Y, Jackson W, et al. Association between nephrotoxic drug combinations and acute kidney injury in the neonatal intensive care unit. J Pediatr. 2021;228:213–9.

[24] James M, Bouchard J, Ho J, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61:673–85.

[25] Engler D, Schellack N, Naude A, et al. Use of amikacin in neonates and related ototoxicity. Neonatology. 2013;17:24–7.

[26] Naeimi M, Maamouri G, Boskabadi H, et al. Assessment of aminoglycoside-induced hearing impairment in hospitalized neonates by TEOAE. Indian J Otolaryngol Head Neck Surg. 2009;61:256–61.

[27] Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 13th ed. Philadelphia, PA: McGraw-Hill Medical, Inc; 2017.

[28] Wu L, Li R, Chen J, Chen Y, Yang M, Wu Q. Analysis of mitochondrial A1555G mutation in infants with hearing impairment. Exp Ther Med. 2018;15:5307–13.

[29] Bindu LH, Reddy PP. Genetics of aminoglycoside-induced and prelingual non-syndromic mitochondrial hearing impairment: a review. Int J Audiol. 2008;47:702–7.