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Pharmacokinetics of amikacin in premature neonates at Pramongkutklao Hospital

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Introduction : *Amikacin has wide inter and intra-patient pharmacokinetic variabilities. Nevertheless, the pharmacokinetics of amikacin in premature neonates has never been studied in Thailand.*

Objective : *To study the pharmacokinetics of amikacin in Thai premature neonates.*

Setting : *Pramongkutklao Hospital*

Research design : *A prospective study*

Patients : *Premature neonates with suspected infection at the Neonatal Intensive Care Unit, Pramongkutklao Hospital during the 8-month period.*

Methods : *Thirty-seven premature neonates, whose gestational age were under 30 weeks, 31-33 weeks and 34-36 weeks, were given amikacin as an empirical treatment by intravenous infusion for 30 minutes at the dose of 18 mg/kg every 48 hours, 16 mg/kg every 48 hours and 15 mg/kg every 24 hours, respectively. Peak concentration was measured at 30 minutes after complete infusion; the second concentration was measured at either 18th hours or 36th hours after administration depending on the dosing interval of each patient, while trough concentration was derived from calculation.*

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Results : *Mean peak concentration at steady state of neonates with gestational age not greater than 30 weeks, 31-33 weeks and 34-36 weeks were 28.49 ± 8.63, 24.22 ± 5.99 and 24.91 ± 5.73 μg/ml, respectively. While mean trough concentration at steady state of neonates with gestational age not greater than 30 weeks, 31-33 weeks and 34-36 weeks were 1.75 ± 1.32, 1.16 ± 2.13 and 2.21 ± 1.20 μg/ml, respectively. Mean peak and trough concentration were not significantly different among the groups ($p > 0.05$). Besides, the mean peak concentration of every group was within the desired therapeutic range (20-30 μg/ml) and mean trough concentration of every group were not greater than the desired range (2-5 μg/ml). Elimination rate constant and clearance of amikacin were significantly different among the groups and it was also in good proportional correlation with their gestational age ($p < 0.05$).*

Conclusion : *Pharmacokinetics parameters of amikacin in Thai premature neonates are similar to data previously published from other countries. The dosage regimen of amikacin used in premature neonates at Phramongkutklao Hospital were mostly within the range of peak and trough in therapeutic levels.*

Keywords : *Amikacin, Pharmacokinetics, Premature neonate.*

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บทนำ : *เภสัชจลนศาสตร์ของยาอะมิโนไกลโคไซด์มีความแตกต่างกัน ในผู้ป่วยแต่ละคน อีกทั้งยังไม่มีการศึกษาเภสัชจลนศาสตร์ของยาอะมิกาซินในทารกแรกเกิดคลอดก่อนกำหนดในประเทศไทย*

วัตถุประสงค์ : *เพื่อศึกษาเภสัชจลนศาสตร์ของยาอะมิกาซินในทารกไทยแรกเกิดและคลอดก่อนกำหนด*

สถานที่ที่ทำการศึกษา : *โรงพยาบาลพระมงกุฎเกล้า*

รูปแบบการวิจัย : *การศึกษาแบบไปข้างหน้า*

ผู้ป่วยที่ได้ทำการศึกษา : *ทารกแรกเกิดคลอดก่อนกำหนดที่สงสัยว่ามีภาวะติดเชื้อ ณ หอผู้ป่วยวิกฤตทารกแรกเกิด โรงพยาบาลพระมงกุฎเกล้าในช่วงระยะเวลานาน 8 เดือน*

วิธีการศึกษา : *ทารกแรกเกิดคลอดก่อนกำหนดที่สงสัยว่ามีภาวะติดเชื้อจำนวน 37 ราย ได้รับยาอะมิกาซินเพื่อรักษาแบบคาดการณ์ โดยทารกที่มีอายุในครรภ์น้อยกว่าหรือเท่ากับ 30 สัปดาห์จะได้รับยา 18 มก./กก./ครั้ง ทุก 48 ชั่วโมง ทารกที่อายุในครรภ์ 31-33 สัปดาห์จะได้รับ 16 มก./กก./ครั้งทุก 48 ชั่วโมง และทารกที่อายุในครรภ์ 34-36 สัปดาห์ จะได้ยา 15 มก./กก./ครั้ง ทุก 24 ชั่วโมง โดยให้ยาทางหลอดเลือดดำแบบต่อเนื่องเป็นเวลา 30 นาที และวัดระดับยาในเลือดที่ภาวะคงที่ 2 ค่าคือ เมื่อสิ้นสุดการให้ยาแล้ว 30 นาที เพื่อเป็นระดับยาสูงสุดและที่ชั่วโมงที่ 18 หรือ 36 หลังให้ยา เพื่อใช้คำนวณหาระดับยาต่ำสุดและค่าตัวแปรทางเภสัชจลนศาสตร์*

ผลการศึกษา : *ระดับยาเฉลี่ยสูงสุดในเลือดที่ภาวะคงที่ของทารกแรกเกิดที่มีอายุในครรภ์ $\leq$30 สัปดาห์, 31-33 สัปดาห์และ 34-36 สัปดาห์ เท่ากับ 28.49 $\pm$ 8.63, 24.22 $\pm$ 5.99 และ 24.91 $\pm$ 5.73 ไมโครกรัม/มล. ตามลำดับ และระดับยาเฉลี่ยต่ำสุดที่ภาวะคงที่เท่ากับ 1.65 $\pm$ 1.28, 1.13 $\pm$ 2.11 และ 2.01 $\pm$ 1.12 ไมโครกรัม/มล. ระดับยาสูงสุดและต่ำสุดนี้ไม่แตกต่างกันระหว่างกลุ่มอย่างมีนัยสำคัญทางสถิติ ($p > 0.05$) ระดับยาเฉลี่ยสูงสุดนี้อยู่ในช่วงของการรักษาที่เหมาะสมคือ 20 - 30 ไมโครกรัม/มล. และระดับยาต่ำสุดไม่เกินช่วงที่เหมาะสมคือ 2-5 ไมโครกรัม/มล. ค่าคงที่ในการขจัดออกของยา และค่าการขจัดออกของยาในทารกมีความแตกต่างกันระหว่างกลุ่มและสัมพันธ์กับอายุในครรภ์มารดา อย่างมีนัยสำคัญ ($p < 0.05$)*

วิจารณ์และสรุป : *ค่าตัวแปรทางเภสัชจลนศาสตร์ของยาอะมิกาซินในทารกไทยแรกเกิดที่คลอดก่อนกำหนด ไม่แตกต่างจากผลการศึกษาในต่างประเทศ อีกทั้งข้อกำหนดขนาดของยาที่โรงพยาบาลพระมงกุฎเกล้าสามารถให้ระดับยาสูงสุดและต่ำสุดในช่วงที่รักษาโรคได้*

คำสำคัญ : *อะมิกาซิน, เภสัชจลนศาสตร์, ทารกแรกเกิดคลอดก่อนกำหนด*

Infection is a major cause of morbidity and mortality in the neonatal period; the mortality rate of which is about 10 - 50 %. [1,2] Since the signs and symptoms of infection are nonspecific, the antibiotics used as an empirical treatment need to be started as soon as the infection is suspected. However, the treatment must be safe because only a small proportion of the neonates have real infection. The most common infectious organisms are namely, *E. coli*, group B streptococci and *L. monocytogenes*. Aminoglycosides are generally used as the first-line antibiotics, either alone or combined with beta-lactams or third generation cephalosporins for neonatal infection, and amikacin is identified as an effective agent against resistant strains. Because of their narrow therapeutic index, potential complications from aminoglycosides such as nephrotoxicity or ototoxicity may occur. In the mean time, therapeutic drug monitoring may be necessary to avoid their toxicities.

Several studies indicate that aminoglycosides have wide inter- and intra-patient pharmacokinetic variabilities. [3,4] Pharmacokinetic parameters are determined by many factors such as gestational age, weight, disease conditions and renal function.[3,5-7] Even there are recommendations that all patients receiving aminoglycosides should have their dosing regimens prospectively individualized by determination of appropriate pharmacokinetic parameters, it is almost impossible to have individual dosage regimens in every hospital. [8] Accordingly, it is important to develop alternate approaches to individualize therapy for various groups of population.

Because of the differences in body composition and the development of renal functions, adult dosage regimens may not be well adapted to neonates. [5,8,9] Kenyon *et al.* suggested that using aminoglycosides for the treatment of infection in neonates should be administered at larger doses and longer dosing interval to obtain the same therapeutic serum level as in adults because of the larger volume of distribution (V_d) and smaller renal clearance of neonates. [8] Gallini *et al.* also revealed that the development of renal function was associated with gestational age and postnatal age. [10] From these data, it is recommended that dosage regimens in neonates should be based on gestational age, birth weight and also postnatal age. Recently, several studies were attempted to create a dosing chart for neonates at birth but there was no sufficient evidence to define the optimal dosage regimen. [11,12] Neofax, a worldwide handbook used among the pediatricians, has set a guideline providing dosage regimens for aminoglycosides including amikacin. However, the recommended dosing intervals for amikacin are quite inconvenience. Phramongkutklao Hospital's Neonatal Intensive Care Unit (NICU) did some modifications from Neofax and the objectives of this research are to study the pharmacokinetics of amikacin in Thai's premature neonates and also the appropriateness of modified amikacin's dosing intervals.

Methods

This research was conducted at NICU, Pramongkutklao Hospital for a period of 8 months. The study protocol was reviewed and approved by The Ethics Committee on Human Research of the institution.

Thirty-seven premature neonates, which are defined when the subject was born with gestational age less than 37 weeks, were enrolled in this study.

Sample size was calculated based on previous amikacin study in neonates with the peak concentration and standard deviation of 30.57 ±2.81 µg/ml. Using ten percent variation from that peak concentration, the samples in each group need to be at least 4 patients. The assessment of gestational age is only based on the measurement scores described by Ballard *et al.* [13] The subjects were treated with amikacin either alone or in combination with other antibiotics because they were suspected of or documented to have infection as indicated in Table 1 which was modified from Neofax by providing intravenous infusion at constant rate for 30 minutes. After administration, 0.5-1.0 ml of blood sample was drawn as follows:

a. for subjects receiving amikacin every 24 hours, blood samples were collected for peak concentration within 30 minutes after completion of the third dose and blood samples were drawn again at the 18th hours of the third dose for calculation of trough concentration;
b. for subjects receiving amikacin every 48 hours, blood samples were collected for peak concentration within 30 minutes after completion of the second dose and blood samples were drawn again at the 36th hours of the second dose for calculation of trough concentration.

The samples were allowed to clot and serum was separated by centrifugation at 3,000 rpm for 10-15 minutes at room temperature. Then the samples were analyzed immediately or frozen at -8 to -70ºC and analyzed within 24 hours using Fluorescence Polarization Immunoassay Techniques (FPIA) by TDx Analyzer System (Abbott Laboratories).

Results

From the total of thirty-seven subjects, there were 7 patients in Group I with gestational age not greater than 30 weeks; Group II, with gestational age of 31-33 weeks, composes of 16 patients; and, Group III, with gestational age of 34-36 weeks, composed of 14 patients, respectively. Table 2 and 3 represent the patients' characteristics between gestational groups. The results from chi-square test show that there is no significant difference in sex between gestational groups ($p > 0.05$). However, there are significant differences between groups with respect to gestational age, birth weight and height ($p < 0.001$). In contrast, there is no significant difference between groups according to Apgar score at 1 minute, 5 minutes and during the treatment ($p > 0.05$). Postnatal age in smaller gestational age is shorter compared to higher gestational age. However, there is no significant difference among mean postnatal age of each group.

Table 1. Dosage regimens of amikacin.

Gestational age (weeks)	Dosage (mg/kg)	Interval (hrs)
≤30	18	48
31-33	16	48
34-36	15	24

Table 2. Comparison of mean ± SD of the patients' characteristics between gestational groups.

Characteristics	Mean ± SD (Range)				p-value*
	Group I	Group II	Group II	Total	
Gender: Male	5	7	8	20	0.452
Female	2	9	6	17	
Gestational age	28.57 ± 1.27	32.13 ± 0.81	34.57 ± 0.76	32.38 ± 2.34	0.000
(weeks)	(27-30)	(31-33)	(34-36)	(27-36)	
Birth weight	1,217.86 ± 248.02	1,733.44 ± 321.57	2,202.14 ± 409.97	1,813.24 ± 494.58	0.000
(grams)	(920-1,560)	(1,240-2,510)	(1,500-3,030)	(920-3,030)	
Height	38.00 ± 3.16	41.44 ± 2.56	44.39 ± 2.61	41.91 ± 3.51	0.000
(cm)	(34-43)	(37-47)	(41-48)	(34-48)	
Apgar score					
1 min	5.57 ± 2.51	7.25 ± 2.29	7.29 ± 1.64	6.95 ± 2.16	0.176
	(2-8)	(1-9)	(4-9)	(1-9)	
5 min	8.14 ± 1.21	8.88 ± 1.50	8.93 ± 1.00	8.76 ± 1.28	0.378
	(7-10)	(5-10)	(7-10)	(5-10)	
Duration of	7.29 ± 1.89	5.88 ± 1.26	5.93 ± 1.27	6.16 ± 1.46	0.074
Therapy (days)	(5-11)	(4-8)	(4-8)	(4-11)	

* p-value compare between 3 gestational groups analyzed by ANOVA except sex analyzed by chi-square test.

Table 3. Comparison of postnatal age between gestational groups.

Gestational age (wks), (Group, n)	Postnatal age (hrs)			
	Mean	Median	Range	Std dev.
≤30 (Group I, n = 7)	3.90	2.50	2.00-9.00	2.62
31-33 (Group II, n = 16)	4.96	2.50	1.00-23.25	5.96
34-36 (Group III, n = 14)	6.77	6.25	0.33-19.55	5.14

Pharmacokinetics data of amikacin

The pharmacokinetic parameters of amikacin were analyzed with assumption of one compartment model and first order kinetics since plasma concentrations were obtained during the elimination phase which errors from calculation would be minimized.

Table 4 presents mean SD of peak and trough concentrations of each group and of total patients. The mean ± SD of amikacin peak concentration (C_p) had no significant differences among the groups ($p > 0.05$). Mean ± SD of peak concentrations of all newborns are 25.29 ± 6.46 μg/ml which was in desired therapeutic range and similar to value reported by

Langhendries *et al.* [14] The numbers and percentage of patients whose amikacin peak concentrations were subtherapeutic (<20 μg/ml), therapeutic (20-30 μg/ml) and over-therapeutic levels (>30 μg/ml); they are shown in Table 5. Only about 54 % of all subjects had desired therapeutic levels. The highest percentages of patients achieving desired concentration are found in Group III. Subtherapeutic and over-therapeutic levels were found in about 22 % and 24 % of total patients, respectively. The results show that five of eight patients who have subtherapeutic peak concentration were in Group II. Notably, most patients in Group I had over-therapeutic peak concentrations.

Even though the second drawing for amikacin serum level was done at six to twelve hours before the next dose, six of sixteen patients in Group II had serum drug concentration less than 0.8 μg/ml. This result indicates that there was a wide variability in this group. The mean ± SD of amikacin trough concentration (C_t) of total doses is 1.77 ± 1.60 μg/ml. There is no significant difference of C_t between groups ($p > 0.05$). The numbers and percentage of patients whose amikacin trough concentration were less than 2 μg/ml, 2-5 μg/ml and over 5 μg/ml are shown in Table 6. Most subjects had C_t less than 5 μg/ml except one patient in Group II.

Table 4. Comparison of amikacin dose and serum concentration in three gestational groups.

Parameters	Mean ± SD (Range)				p-value*
	Group I (n=7)	Group II (n=16)	Group III (n=14)	Total (n=37)	
Calculated dose (mg/kg)	17.57 ± 0.49 (16.67-18.00)	15.77 ± 0.29 (15.32-16.48)	14.74 ± 0.37 (14.22-15.38)	15.72 ± 1.08 (14.22-18.00)	0.000
C_p (μg/ml)	28.49 ± 8.63 (15.45-41.40)	24.22 ± 5.99 (16.11-38.05)	24.91 ± 5.73 (13.17-36.43)	25.29 ± 6.46 (1.17-41.40)	0.343
C_t (μg/ml)	1.75 ± 1.32 (0.35-3.63)	1.16 ± 2.13 (0.05-7.17)	2.21 ± 1.20 (0.27-4.54)	1.77 ± 1.60 (0.05-7.17)	0.290

* calculate from n=10, p-value analyzed by using ANOVA

C_p = peak concentration, C_t = trough concentration

Table 5. Peak concentrations in different gestational age groups.

Peak serum level	Number of the patients (%)			
	Group I (n = 7)	Group II (n = 16)	Group III (n = 14)	Total (n = 37)
< 20 μg/ml	1 (14.29)	5 (31.25)	2 (14.28)	8 (21.62)
20-30 μg/ml	2 (28.57)	8 (50.00)	10 (71.43)	20 (54.05)
> 30 μg/ml	4 (57.14)	3 (18.75)	2 (14.28)	9 (24.33)

Table 6. Trough concentration in different gestational age groups.

Trough serum level	Number of the patients (%)			
	Group I (n = 7)	Group II (n = 16)	Group III (n = 14)	Total (n = 37)
< 2 µg/ml	4 (57.14)	15 (93.75)	6 (42.86)	25 (67.57)
2-5 µg/ml	3 (42.86)	0	8 (57.14)	11 (29.73)
> 5 µg/ml	0	1 (6.25)	0	1 (2.70)

Mean ± SD of pharmacokinetic parameters of the patients are shown in Table 7. Average mean ± SD of elimination rate constant (K_e) and elimination half life ($t_{1/2}$) are 0.094 ± 0.035 hr^{-1} and 8.90 ± 5.41 hr, respectively. Mean ± SD of K_e increases in patients with older gestational age while mean ± SD of $t_{1/2}$ decreases with gestational age. As for K_e, there was a significant difference among the groups but not for $t_{1/2}$ (p = 0.003; p = 0.057). Moreover, there is a significant difference for clearance per body weight (Cl) but not for V_d per body weight (p = 0.020; p = 0.641, respectively). Average mean ± SD of Cl and V_d were 0.058 ± 0.022 l/kg/hr and 0.6959 ± 0.231 l/kg, respectively.

Correlation between pharmacokinetics parameters and gestational age or postnatal age was analyzed by linear regression using SPSS version 10.0.1 and shown in Table 8. The results indicate that there is a significant correlation between gestational age for K_e, Cl and $t_{1/2}$ (r = 0.529, 0.454 and 0.367, respectively, $p < 0.05$). Correlation for K_e and Cl is proportional to gestational age while for $t_{1/2}$ shows inversely relationship compared to gestational age. However, there is no correlation between V_d and gestational age (r = 0.130, $p > 0.05$). There is also a significant correlation between K_e and postnatal age (r = 0.529, $p < 0.05$).

Table 7. Comparison of pharmacokinetic parameters of amikacin in three gestational groups.

Parameters	Mean ± SD (Range)				p-value*
	Group I (n=7)	Group II (n=10)	Group III (n=14)	Total (n=31)	
K_e (hr^{-1})	0.067 ± 0.023 (0.0369 - 0.0963)	0.082 ± 0.030 (0.0208 - 0.1376)	0.115 ± 0.032 (0.0789 - 0.1971)	0.094 ± 0.035 (0.0208 - 0.1971)	0.003
$t_{1/2}$ (hr)	11.41 ± 3.95 (7.20 - 18.79)	10.65 ± 8.10 (5.04 - 33.03)	6.39 ± 1.51 (3.52 - 8.79)	8.90 ± 5.41 (3.52 - 33.03)	0.057
V_d (l/kg)	0.684 ± 0.277 (0.431 - 1.1213)	0.703 ± 0.247 (0.4585 - 1.2678)	0.616 ± 0.205 (0.3950 - 1.1485)	0.659 ± 0.231 (0.3950 - 1.2678)	0.641
Cl (l/hr/kg)	0.044 ± 0.018 (0.0248 - 0.0788)	0.053 ± 0.016 (0.0264 - 0.0778)	0.069 ± 0.022 (0.0406 - 0.1091)	0.058 ± 0.022 (0.0248 - 0.1091)	0.020

* p-value analyzed by using ANOVA

K_e = elimination rate constant, $t_{1/2}$ = half-life, V_d = volume of distribution, Cl = clearance

Table 8. Correlation between pharmacokinetic parameters and gestational age.

Equations	R^2	r	p-value
K_e = 0.0074GA-0.1456	0.2801	0.529	0.002
$t_{1/2}$ = -0.7852GA+34.378	0.1348	0.367	0.042
V_d = -0.0119GA+1.0452	0.0169	0.130	0.486
Cl = 0.0039GA-0.0672	0.2064	0.454	0.010

GA = gestational age, K_e = elimination rate constant, $t_{1/2}$ = half-life, V_d = volume of distribution, Cl = clearance

Toxicity of amikacin

Renal parameters

Almost all subjects had normal serum creatinine concentration (SCr) before and after amikacin treatment. There was no patient having SCr rising equal to or greater than 0.5 mg/dl after receiving the treatment compared to baseline, except 5 patients had slightly rising SCr but not clinically significant.

Mean ± SD of SCr and CrCl at day 1 and within day 2 of the amikacin therapy discontinuation is presented in Table 9. There was no significant difference between groups in SCr and CrCl at day 1 ($p > 0.05$). In contrast, there were significant differences between groups in SCr and CrCl at day 2 after the discontinuation of therapy ($p < 0.05$).

Efficacy

Several clinical indicators such as clinical symptoms, body temperature, and white blood cell counts were monitored to indicate the efficacy of amikacin therapy. Most patients showed good response to the drug and had normal blood cell count after therapy. Indication, dose and peak concentrations at stead state, duration and efficacy

Table 9. Comparison of mean serum creatinine and creatinine clearance.

Measurement	Mean ± SD (Range)				p-value
	Group I (n=7)	Group II (n=16)	Group III (n=14)	Total (n=37)	
SCr on day 1	1.02 ± 0.19 (0.72 - 1.28)	1.09 ± 0.22 (0.62 -1.47)	1.02 ± 0.28 (0.71 - 1.67)	1.05 ± 0.24 (0.62 - 1.67)	0.718
SCr on day 2 after discontinuation	0.96 ± 0.25 (0.59 - 1.40)	0.80 ± 0.21 (0.34 - 1.11)	0.67 ± 0.19 (0.38 - 0.92)	0.78 ± 0.23 (0.34 - 1.40)	0.017
CrCl on day 1	12.56 ± 2.26 (10.05 - 16.96)	13.18 ± 3.58 (8.98 - 23.42)	15.36 ± 4.14 (8.79 - 21.85)	13.89 ± 3.71 (8.79 - 23.42)	0.161
CrCl on day 2 after discontinuation	13.78 ± 3.72 (9.19 - 20.69)	18.90 ± 7.90 (11.63 - 42.71)	23.58 ± 7.27 (15.03 - 48.02)	19.70 ± 7.77 (9.19 - 48.02)	0.016

SCr = serum creatinine, CrCl = creatinine clearance

of amikacin therapy in 3 gestational groups of preterm neonates are shown in Table 10. Herein, patient number two, who was in Group II, shows unfavorable efficacy. The subject expired due to sepsis and intracranial hemorrhage. The peak concentration in this patient was 23.51 μg/ml. There is no significant relationship between peak concentration and efficacy when analyzed by logistic regression ($r = 0.089$, $p > 0.05$).

Table 10. Indication of treatment and efficacy.

Number	Indication	Dose(mg)	C_p(mg/l)	Duration(days)	Efficacy
1	Clinical sepsis	25	18.87	4	F
2	PROM, congenital pneumonia	22	23.51	8	UF
3	Clinical sepsis	19	31.09	7	F
4	Clinical sepsis	28	27.41	5	F
5	Mild RDS	18	20.15	11	F
6	RDS, congenital pneumonia	27	41.4	8	F
7	Clinical sepsis	32	23.37	5	F
8	Clinical sepsis	22	30.59	6	F
9	RDS, clinical sepsis	21	15.45	7	F
10	RDS, congenital pneumonia	40	30.16	7	F
11	Hypoglycemia	45	21.60	8	F
12	PROM > 24 hr	32	13.17	6	F
13	Hypoglycemia	22	16.11	6	F
14	RDS	18	27.57	7	F
15	PROM > 24 hr, clinical sepsis	24	16.66	6	F
16	PROM > 24 hr, clinical sepsis	25	23.85	8	F
17	Hypoglycemia	28	34.12	5	F
18	Clinical sepsis	30	19.47	5	F
19	RDS, congenital pneumonia	22	21.26	6	F
20	Clinical sepsis	27	22.83	5	F
21	Clinical sepsis	33	24.42	5	F
22	Clinical sepsis	22	21.64	5	F
23	Clinical sepsis, RDS	30	16.29	4	F
24	RDS	16	30.05	7	F
25	PROM > 24 hr	36	26.6	7	F
26	Clinical sepsis	30	29.28	7	F
27	Clinical sepsis	30	38.05	7	F
28	Clinical sepsis, PROM> 24 hr	30	28.03	6	F
29	Clinical sepsis, PROM> 24 hr	38	26.56	7	F
30	RDS	30	36.60	6	F
31	PROM > 18 hr, clinical sepsis	40	18.71	4	F
32	Clinical sepsis	25	25.04	5	F
33	Suspected neonatal sepsis	30	23.84	5	F
34	Congenital pneumonia, RDS	30	26.80	7	F
35	PROM > 24 hr, chorioamnionitis	38	26.81	4	F
36	Birth asphyxia	32	27.20	5	F
37	RDS	24	36.43	7	F

C_p = peak concentration, F = favorable, UF = unfavorable, PROM = prolonged rupture of membrane, RDS = respiratory distress syndrome

Discussion

The pharmacokinetics of aminoglycosides varies quite widely among populations. The pharmacokinetics strongly depends on age, weight, disease condition and renal function. In neonatal period, gestational and postnatal age is also the determinants. Kenyon *et al.* showed that administration of amikacin in preterm neonates using recommended dose for adults resulting in inadequate peak concentration, while trough concentration is high. [8] They suggested the modification of trough concentration by extending the dosing interval, while the peak concentration would also be improved by increasing the dose. Regarding this recommendation, Langhendries *et al.* conducted sequential studies in neonates to access this concept. [12,14] Based on the pharmacokinetic populations, a dosing chart for neonates, which are relatively higher, doses and longer interval in small gestational group, was proposed. Besides, the validity of their recommended dosing regimen has been assessed.

According to Neofax, dosage regimens of amikacin are divided into 4 gestational groups. Dose for small gestational age is higher than larger gestational age and dosing interval in small neonates also longer. Since some dosing interval are every 36 hours which is quite inconvenience dosing period for nurses, many hospitals have extended the dosage regimen to 48-hour interval. As most studies conducted in neonates from foreign countries that might have different pharmacokinetic parameters from Thai neonates, this research was conducted to assess the validity of the new dosage regimen and obtain pharmacokinetic parameters in Thai newborns.

In this study, the peak concentrations were obtained from blood samples drawing; all trough concentrations are extrapolated concentration from the calculation. Almost all patients had true peak concentration at the exact time of 30 minutes after the completion of infusion. Only two patients, number 5 and 9, obtained blood sampling at an hour after completion of infusion due to difficulties in the blood sampling technique. Therefore, the peak concentrations in these two patients are extrapolated. The results show that mean C_p and C_t are not significantly different between the groups. Although mean C_p in Group I is the highest, post hoc analysis with Scheffe showed that there is no significant difference among all groups. Most patients in Group I had peak concentration over therapeutic range. There is an evidence of correlation between high peak concentration and therapeutic outcome; however, there is no clear evidence of the disadvantage of over therapeutic level.[15] Besides, high peak concentration does not increase renal accumulation in neonates, especially in the premature neonates because of the immature proximal tubule cells and lower number of binding sites in the neonates.[6] Nevertheless, patients in this group should be closely monitored and further research in a larger sample size needs to be performed before making any conclusions. About 54 % of total subjects had desired C_p while about 21 % had C_p in subtherapeutic range and 24 % had C_p in over therapeutic range. The percentage of patients with desired therapeutic concentration in this study is lower than the results reported by Labaune *et al.* [11] Nevertheless, Moore *et al.* showed that the peak concentration was equal to or over than 20 μg/ml related to therapeutic outcome. [15] Regarding to this

finding, 78 % of total patients had peak concentration equal to or over than 20 μg/ml.

All patients obtained C_t levels lower than 2 μg/ml except one whose C_t level was 7.17 μg/ml. Trough concentration higher than 10 μg/ml is considered nephrotoxic. [16] Therefore, C_t indicates no renal toxic in this study. However, most C_t is quite low, amikacin has postantibiotic effect that serum levels may be allowed to fall below the minimum inhibitory concentration (MIC) of pathogen without compromising antimicrobial effects. The MIC_{90} of amikacin for *E.coli*, a major microorganism in neonatal infection, is 1 μg/ml. [17] Nevertheless, most patients in this study did not have real infection at birth and they also had co-administration of ampicillin.

Laders *et al.* and Pons *et al.* suggested that pharmacokinetics during the neonatal period are dependent on the postconceptional age. [18,19] This study was conducted in patients with postnatal age less than 48 hours so only gestational age is the determinant factor. As expected, pharmacokinetic parameters from this study varies between gestational groups. K_e and Cl are different between groups and proportional related to gestational age. Significant difference between groups for K_e results from significant between Group I versus Group III and Group II versus Group III ($p = 0.007$ and 0.046, respectively). Significant difference between groups for Cl results from significant between Group I versus Group III ($p = 0.034$). K_e is not only related to gestational age but it is also significantly related to postconceptional age ($p < 0.05$). Half-life is inversely correlated with gestational age but there is no significant difference between groups. V_d is not significantly different between groups as well. Besides, there is no significant correlation between V_d and gestational age. The lack of relationship between postconceptional or gestational age might be due to the small sample size; this reflects the fluctuation state of hydration in the early days of life. V_d is considered as a physiological indicator of extracellular fluid and can show a wide variation between patients and even in each individual patient at different time. [20] Since V_d is not significantly different between groups, peak concentration in Group I is quite higher than Group II and III. Normally, V_d of preterm neonates is relatively larger than in adults. In this study, V_d is about 38 % of body weight while it is about 25 % of lean body weight in adults since there is larger extracellular fluid volume in neonates. The results in this study agree with the previously published data. [6,8,18,21]

Regarding the renal function, SCr and CrCl were not significantly different between gestational groups at day 1 while they were significantly different at day 2 of the discontinuation ($p < 0.05$). These findings might be due to SCr at birth does not all come from neonates, it partially origins from mothers. [22,23] The fact that SCr and CrCl after the discontinuation are different between groups demonstrated that the maturity of renal function after birth depends on the gestational age at birth. This finding agrees with the results reported by Rudd *et al.* and Counahan *et al.* that glomerular filtration rate was proportional to gestational age. [22,23] Even though SCr is suggested to be a more reliable indicator for glomerular filtration rate than CrCl, in this study, however, CrCl is more associated with gestational age than SCr ($r = 0.427$, 0.363, respectively). Nephrotoxicity, defined as an increasing in SCr equal to or greater than 0.5 mg/dl, is not found in this study.

In conclusion, the outcomes of this study show that the modification of dosage regimens results in peak serum concentrations equal to or greater than 20 μg/ml in most patients with trough concentration less than nephrotoxic level. We also found that amikacin pharmacokinetics of Thai preterm neonates are not different from previous studies in the West. [4,8,21]

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