Gentamicin in Neonatal Infection : Once *Versus* Twice Daily Dosage

URAIWAN CHOTIGEAT, M.D.*,
AMPORN NARONGSANTI, B.Sc.**,
DUANGCHIT PANOMVANA NA AYUDHYA, M.Sc., Ph.D.***

Abstract

Fifty-four neonates were included and completed the study. Twenty-seven neonates were given 2.0-2.5 mg/kg of gentamicin twice daily while 27 neonates were given 4.0-5.0 mg/kg of gentamicin once daily. The twice daily dose and the once daily dose group had mean steady state gentamicin peak concentrations of 5.94±1.57 mg/l and 8.92±1.59 mg/l, respectively ($p<0.05$) while their trough concentrations were 1.44±0.49 mg/l and 0.90±0.35 mg/l, respectively ($p<0.05$). There were 3 neonates (11.11%) in the twice daily dose group whose peak and trough level were not within the desirable therapeutic range, two patients with too high trough level (>2 mg/l) and one with subtherapeutic peak level (<4 mg/l). Only one patient in the once daily group had undesirable trough level that was higher than 1.5 mg/l but less than 2 mg/l. Treatment with a once daily dose did not present more nephrotoxity than a twice daily dose regimen and had the tendency to have less effect on renal function. Once daily dosage can achieve the equivalent efficacy compared to a twice-daily dosage regimen. All neonates in twice daily and once daily dosage groups showed improvement in clinical outcome.

Therefore, a once daily dose of gentamicin with 4.0-5.0 mg/kg could be an appropriate regimen in term neonates during the first 7 days of life. This regimen produces peak concentration that may have greater clinical efficacy and trough concentration with less toxicity than conventional dosing regimen.

Key word : Gentamicin, Neonatal Infection, Once-Daily, Twice-Daily

**CHOTIGEAT U,
NARONGSANTI A, PANOMVANA NA AYUDHYA D
J Med Assoc Thai 2001; 84: 1109-1115**

* Neonatal Unit, Pediatric Department, Queen Sirikit National Institute of Child Health, Bangkok 10400,
** Department of Pharmacy, Phichit Hospital, Ministry of Public Health, Phichit 66000,
*** Department of Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, 10330, Thailand.

Gentamicin is a broad spectrum antibiotic, inexpensive and one of the drugs in the Thai national drug list. It is widely used in treatment of gram-negative bacillary infection in neonates[1-3]. Therapeutic drug monitoring is required because of its narrow therapeutic range and large volume of distribution. Drug monitoring has been recommended to provide maximal potential benefit with minimal risk of toxicity.

The concept of a once daily dose (ODD) of gentamicin was introduced into clinical practice for more than 10 years[4]. The once daily dosage therapy appears to be efficacious with no increased incidence of nephrotoxicity or ototoxicity[5-8]. The result *in vitro* and clinical studies showed that the once daily dosage regimen should be reasonable because of the large volume of distribution and slow clearance of aminoglycoside in full term neonates[9-10].

There is, as yet, no reported on the once daily dose of gentamicin especially in Thai neonates. This study was designed to measure the serum gentamicin levels and pharmacological responses and efficacy and toxicity after 2.0 to 2.5 mg/kg of gentamicin was given twice daily compared to the values observed after 4.0 to 5.0 mg/kg of gentamicin was given once daily in Thai neonates. The results of this study should be appropiate for adjustment of the dosage of gentamicin for Thai neonates in the future.

Objective

To compare the serum gentamicin, side effects and clinical efficacy obtained from the two dosage regimens 2.0-2.5 mg/kg twice daily and 4.0-5.0 mg/kg given once daily in neonates.

METHOD

This clinical trial was a prospective, randomized controlled study. It was conducted in patients who were treated with gentamicin either alone or with beta-lactam antibiotics due to suspected or proved bacterial infection. We enrolled infants admitted to the neonatal unit at Queen Sirikit National Institute of Child Health from August 1st to December 31st, 1999. The institutional review board approved this study, and informed consent was obtained for each patient before the study. Infants were eligible for enrollment if their birth weight was more than or equal to 2000 g, gestational age was more than or equal to 34 weeks, age under 7 days and Apgar score of more than or equal to 4, 6 at 1 minute, 5 minutes respectively. There were no allergy to aminoglycoside, no congenital anomalies, no renal failure and no neuromuscular disorder. Serum creatinine and blood urea nitrogen were determined before gentamicin therapy, every 3 days during therapy and after therapy. Hemoculture and complete blood count were determined before gentamicin therapy. Peak serum concentration of gentamicin in the twice daily dosage regimen was drawn within 30 minutes after completion of 30 minutes intravenous infusion of the 5th dose and the trough blood sample was drawn within 30 minutes prior to the 5th dose. But in the once daily dosage regimen, blood was drawn for peak serum concentration within 30 minutes after completion of 30 minutes intravenous infusion of the 3rd dose and the trough blood sample was drawn within 30 minutes prior to the 3rd dose.

Blood serum was separated by centrifugation (3,400 rpm for 10-15 minutes) at room temperature and it was analyzed by fluorescence polarization immunoassay technology (TDx Analyzer System, Abbott). If the samples were not immediately analyzed, they were kept frozen at-24 to-30°C in the freezer until assayed within 24-48 hours.

Adjustment of gentamicin was recommended in twice daily dosage for Cpk (peak serum concentration) which was less than 4 mg/l or higher than 12 mg/l and Ctr (trough serum concentration) which was higher than 2 mg/l[11]. Adjustment of gentamicin in once daily dosage was recommended for Cpk which was less than 5 mg/l or higher than 18 mg/l or Ctr which was higher than 1.5 mg/l[12].

Statistical Analysis

Statistical analysis used mean±SD, percentage, Chi-square test, *t*-test and Fisher's exact test. Statistical significance was defined as p value <0.05.

RESULTS

Fifty-four infants were eligible for the study. Each group was composed of twenty-seven patients. There were 14 males (51.85%) in the TDD group and 16 males (59.26%) in the ODD group. The infants in the TDD group had mean±SD, gestational age of 38.37±2.12 weeks, postnatal age of 1.43±1.25 days, weight of 2,987.04±656.71 g, Apgar score at 1 minute of 7.48±1.74 and at 5 minutes of 9.63±0.69. The infants in ODD group had mean± SD gestational age of 38.44±2.12 weeks, postnatal

Table 1. Comparison between the TDD and the ODD groups.

Parameter	mean ± SD		P value[a]
	TDD group	ODD group	
Sex (male)	14*	16*	
Gestation age (week)	38.37 ± 2.12	38.44 ± 2.12	0.898
Postnatal age (day)	1.43 ± 1.25	0.94 ± 1.22	0.150
Weight (g)	2,987.04 ± 656.71	2,924.07 ± 597.65	0.974
Apgar score 1 min	7.48 ± 1.74	7.67 ± 1.57	0.683
Apgar score at 5 min	9.63 ± 0.69	9.26 ± 1.06	0.134

a : p value by unpaired *t* test
* = the absolute value

Table 2. Dosage, indication, serum gentamicin concentrations, trough concentrations, duration and dose adjustment in patients TDD group.

No	Dose mg/kg	Indication	Cpk/mg/L	Ctr/mg/L	Duration (day)	Adjustment
1	2.63	- PROM > 24 h, sepsis	5.5	1.0	7	N
2	2.50	- Sepsis	4.8	1.2	4	N
3	2.50	- Pneumonia	6.3	1.9	9	N
4	2.41	- PROM > 24 h, sepsis	5.1	1.3	4	N
5	2.50	- NEC	9.2	1.5	8	N
6	2.33	- Sepsis, RD	10.6	1.7	11	N
7	2.41	- NEC	4.1	1.3	7	N
8	2.00	- Sepsis, pneumonia	8.7	1.9	18	N
9	2.50	- PROM 19 h, sepsis	6.7	1.6	9	N
10	2.22	- PROM > 24 h	3.9	1.6	11	Y
11	2.49	- Pneumonia	7.5	1.7	8	N
12	2.55	- PROM > 24 h	6.2	2.3	8	Y
13	2.50	- Clinical sepsis	5.8	1.5	3	N
14	2.46	- Pneumonia	4.5	1.0	10	N
15	2.45	- MAS	5.6	1.2	7	N
16	2.35	- MAS	7.0	2.7	4	Y
17	2.50	- Respiratory distress	5.8	1.2	5	N
18	2.53	- MAS	6.1	1.4	10	N
19	2.75	- NEC	4.7	0.4	8	N
20	2.80	- NEC	6.1	1.8	7	N
21	2.35	- PROM > 24 h	6.0	1.7	9	N
22	2.39	- Sepsis, pneumonia	5.0	1.0	11	N
23	2.42	- Pneumonia	5.4	1.5	11	N
24	2.41	- RD	4.4	0.8	4	N
25	2.37	- Pneumonia	4.5	1.0	8	N
26	2.50	- Pneumonia	5.8	0.9	9	N
27	2.22	- Sepsis	5.0	1.9	5	N
Mean ± SD	2.44 ± 0.158	-	5.94 ± 1.57	1.44 ± 0.49	7.96 ± 3.16	

PROM = premature rupture of membrane, MAS = meconium aspiration syndrome, NEC = necrotizing enterocolitis, RD = respiratory distress, Cpk = peak concentration, Ctr = trough concentration, TTNB = transient tachypnea of newborn, N = No, Y = Yes

age of 0.94±1.22 days, weight of 2,924.07±597.65 g, Apgar score at 1 minute of 7.67±1.57 and at 5 minutes of 9.26±1.06. There was no statistical significance in demographic data of both groups as shown in Table 1.

Tables 2 and 3 show the diseases of patients in the TDD and ODD group who received gentamicin respectively. The infants had mean±SD gentamicin dose of 2.44±0.16 mg/kg/12 hours in the TDD group and 4.73±0.268 mg/kg/24 hours in the

Table 3. Dosage, indication, serum gentamicin concentrations, trough concentrations, duration and dose adjustment in patients ODD group.

No	Dose mg/kg	Indication	Cpk/mg/L	Ctr/mg/L	Duration (day)	Adjustment
1	4.29	- Sepsis, pneumonia	11.6	1.3	3	N
2	4.38	- MAS	8.2	0.8	14	N
3	5.00	- NEC	9.3	0.4	5	N
4	4.39	- Sepsis, pneumonia	7.3	1.0	7	N
5	4.65	- Sepsis	9.6	1.4	10	N
6	4.41	- PROM > 24 h	8.5	0.8	7	N
7	4.36	- PROM > 24 h	6.2	1.3	4	N
8	4.49	- RD, TTNB	9.9	1.0	5	N
9	4.16	- PROM > 24 h	7.6	1.7	8	Y
10	5.00	- RD	9.1	0.9	4	N
11	4.44	- RD	8.5	0.9	13	N
12	4.72	- MAS	9.6	1.1	7	N
13	5.00	- NEC	8.9	0.8	6	N
14	5.00	- Omphalitis	5.7	0.5	3	N
15	5.00	- MAS	8.0	0.6	5	N
16	4.65	- MAS	9.4	0.3	11	N
17	5.00	- PROM > 24 h	8.4	1.0	10	N
18	4.73	- RD, TTNB	7.0	0.7	3	N
19	4.81	- MAS	8.9	0.4	4	N
20	4.80	- MAS	12.1	0.9	8	N
21	4.85	- Pneumonia	9.4	0.7	7	N
22	4.80	- Sepsis	9.5	1.2	7	N
23	4.92	- NEC	9.5	0.4	5	N
24	5.00	- Sepsis	10.6	1.5	11	N
25	4.70	- MAS	7.6	0.9	7	N
26	5.00	- RD, TTNB	8.1	0.9	3	N
27	5.00	- Pneumonia	12.4	1.0	10	N
Mean ± SD	4.73 ± 0.268	-	8.924 ± 1.59	0.90 ± 0.35	6.93 ± 3.13	

N = No, Y = Yes

ODD group, a duration of 7.96±3.16 days in the TDD group and 6.93±3.13 days in the ODD group. There was no significant difference in mean duration between the groups (p=0.230).

We found a low peak serum concentration of gentamicin (<4 mg/L) in one case (3.70%) and a high trough of gentamicin (> 2 mg/L) in two cases (7.4%) in the TDD group but we did not find low peak serum concentration in the ODD group and only one case of high trough (> 1.5 mg/L) in the ODD group. To compare the pharmacokinetic parameters between the TDD and ODD groups, we found mean±SD of high peak serum concentration, low trough serum gentamicin and high elimination half life of gentamicin in the ODD group (<0.001) as shown in Table 4.

While comparing the ODD and TDD groups for renal complications, we found no difference in serum concentration from day 1, day 3 and the discontinuous day as shown in Table 5.

For drug interaction between gentamicin and other concurrently used drugs, we found three patients in the TDD group and three patients in the ODD group. In the ODD group the interacting drug was cefotaxime in one patient and furosemide in two patients. In the ODD group, the interacting drug was indomethacin in one patient and furosemide in two patients. All patients in both groups improved without complications and duration of treatment between ODD and TDD showed no significant difference. (ODD=6.93±3.13, and TDD=7.96±3.16).

DISCUSSION

The concept of once-daily dosage of aminoglycosides seems to be proliferating rapidly world wide at present[12]. This study showed that steady-state gentamicin peak level of the ODD group was significantly higher than the TDD group and trough level of the ODD group was significantly lower than the TDD group. The percentage of the patients

Table 4. Comparison of pharmacokinetic parameters between the TDD and ODD groups.

Parameter	mean ± SD		P value
	TDD group	ODD group	
Peak concentration (μg/mL)	5.94 ± 1.57	8.92 ± 1.59	<0.001
Trough concentration (μg/mL)	1.44 ± 0.49	0.90 ± 0.35	<0.001
Elimination rate constant (h)	0.137 ± 0.03	0.105 ± 0.02	<0.001
Elimination half life (h)	5.30 ± 1.23	6.85 ± 1.38	<0.001

Table 5. Comparison of serum creatinine concentration on the first, third and discontinuous day.

Serum creatinine	mean ± SD		P value
	TDD group	ODD group	
1st day	0.66 ± 0.22	0.73 ± 0.33	0.292
3rd day	0.41 ± 0.21	0.49 ± 0.20	0.229
Discontinuous day	0.50 ± 0.25	0.52 ± 0.16	0.904

whose peak and trough levels were not within the desired therapeutic range (peak 4-12 mg/L and trough ≤ 2 mg/L) after being treated with traditional dosage regimen or twice daily dosage regimen was 11.11 per cent (two patients with too high trough level and one patient with subtherapeutic peak level). None of the patients treated with the once daily dosage regimen resulted in undesirable trough level (> 1.5 mg/L but less than 2 mg/l).

Side effects to the kidney by monitoring serum creatinine concentration of the TDD and the ODD groups before treatment with each dosage regimen were not significantly different between the groups ($p>0.05$). There was significant increase in serum creatinine when using gentamicin for more than eight days in the TDD group while there was no significance in the ODD group. All patients in both groups showed improved outcome. The mean duration of once-daily treatment appeared to be shorter than twice-daily treatment. The result indicated that the once-daily dosage regimen can achieve at least equivalent efficacy compared to the twice-daily dosage regimen.

Concerning drug interaction, we found three patients in the TDD group and three patients in the ODD group. Of these six cases, only one infant in the TDD group was given indomethacin 0.4 mg for six doses in 4 days. Concurrently with gentamicin presented nephrotoxicity. This occurred in an infant, with a gestational age of 34 weeks and postnatal age of 1 day, indomethacin was started 5 days after gentamicin therapy. It showed a rise of serum creatinine concentration of 1.47 mg/dl on the discontinuous day from 0.88 mg/dl on the first day of gentamicin therapy. When ADR (Adverse drug reaction) was assessed by Naranjo's algorithm for estimating the probability of adverse reaction was caused by gentamicin(13,14).

In conclusion, this study confirmed the results that a once-daily dosage of intravenous aminoglycosides could achieve an efficacy equivalent to traditional regimen with no increase and possibly a decrease in toxicity in Thai neonates(5, 15). Further studies to examine whether or not the once daily dosage regimen can improve the clinical outcome in proved septicemia will be carried out.

ACKNOWLEDGEMENT

This study was supported by a research fund of the Faculty of Pharmaceutical Sciences, Chulalongkorn University.

(Received for publication on June 7, 2000)

REFERENCES

1. Fisk KL. A review of gentamicin use in neonates. Neonatal Netw 1993; 12: 19-23.
2. Evans WE. Gentamicin dosage in children. J Pediatr 1997; 94: 139-43.
3. Mc Evoy GK, (ed). Drug information. Wisconsin: American Society of Health System. Pharmacists 1997; 56-64.
4. Marra F, Partovi N, Jewesson P. Aminoglycosides administration as a single daily dose. Drugs 1996; 52: 344-70.
5. Powell SH, Thompson WL, Luthe MA, et al. Once-daily *vs* continuous aminoglycoside dosing : efficacy and toxicity in animal and clinical studies of gentamicin, netilmicin, and tobramicin. J Infect Dis 1983; 147: 918-32.
6. Prins JM, Buller HR, Kuljper EJ, et al. Once *versus* thrice daily gentamicin in patients with serious infections. Lancet 1993; 341: 335-9.
7. Skopnik H, Heimann G. Once daily aminoglycosides dosing in full term neonates. Pediatr Infect Dis J 1995; 14: 71-2.
8. Hayani KC, Hatzopoulos FK, Frank AL, et al. Pharmacokinetics of once-daily dosing of gentamicin in neonates. J Pediatr 1997; 131: 76-80.
9. Faura CC, Garcia MR, Horga JF. Changes in serum levels and pharmacokinetic parameters in the newborn in the course of treatment with aminoglycoside. Ther Drug Monit 1991; 13: 277-80.
10. Mettie H, Crig WA, Pechere JC. Determinants of efficacy and toxicity of aminoglycosides. Antimicrob Chemother 1989; 24: 281-93.
11. Shahidullah M, Talukder MQ, Chowdhury AK, et al. Serum levels of gentamicin at peak and trough in neonates and infants. Indian J Pediatr 1991; 58: 217-21.
12. Rotschafer JC, Robak MJ. Single daily dosing of aminoglycoside : A commentary. Ann Pharmacother 1994; 28: 799-801.
13. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reaction. Clin Pharmacol Ther 198; 30: 239-45.
14. Lider N, Edwards R, MeClead R, et al. Safety of vancomycin with or without gentamicin in neonates. Neonatal Netw 1993; 12: 27-30.
15. Thureen PJ, Reiter PD, Gresores A, et al. Once *versus* twice-daily gentamicin dosing in neonates ≥ 34 weeks' gestation : cost-effectiveness analyses. Pediatrics 1999; 103: 594-8.

การให้ยา gentamicin วันละครั้งเปรียบเทียบกับการให้ยาวันละสองครั้งในการติดเชื้อในทารก

อุไรวรรณ โชติเกียรติ, พ.บ.,*
*อัมพร ณรงค์สันติ, วท.บ.**, ดวงจิต พนมวัน ณ อยุธยา, วท.ม., ปร.ด.****

ทารก 54 รายได้รับการศึกษาโดยมีการให้ยา gentamicin แบบวันละ 2 ครั้งโดยทารกจำนวน 27 รายได้รับยาขนาด 2–2.5 มก.ต่อกิโลกรัมต่อครั้ง และกลุ่มให้ยาวันละครั้งขนาด 4–5 มก.ต่อกิโลกรัม อีก 27 ราย พบว่ากลุ่มทารกที่ได้รับยาวันละ 2 ครั้งและ 1 ครั้งต่อวัน มีความเข้มข้นระดับยาสูงสุดเฉลี่ย (peak serum concentration) ณ จุดคงที่มีค่า 5.94 ±1.57 มก.ต่อลิตรและ 8.92 ± 1.59 มก.ต่อลิตร ตามลำดับ ($p<0.05$) ส่วนความเข้มข้นของยาต่ำสุดก่อนให้ยาครั้งต่อไป (trough serum concentration) มีค่า 1.44 ± 0.49 มก.ต่อลิตร และ 0.90 ± 0.35 มก.ต่อลิตร ตามลำดับ ในกลุ่มทารกที่ได้รับยาวันละ 2 ครั้งและวันละครั้งตามลำดับ ($p<0.05$)

ทารกกลุ่มที่ได้รับยาวันละ 2 ครั้งมีอยู่ 3 ราย (11.11%) มีค่า peak serum concentration และ trough serum concentration ไม่อยู่ในระดับที่ต้องการ โดยมี ค่า trough serum concentration สูงกว่า 2 มก.ต่อลิตรและมี 1 รายที่มีค่า peak serum concentration ต่ำกว่า 4 มก.ต่อลิตร แต่มีเพียง 1 รายในกลุ่มที่ได้รับยาวันละครั้งมีค่า trough serum concentration สูงกว่า 1.5 มก.ต่อลิตรแต่ต่ำกว่า 2 มก.ต่อลิตร

การศึกษาครั้งนี้ไม่พบโรคแทรกซ้อนต่อไตจากการบริหารยาทั้ง 2 แบบและผลการรักษาพบว่ามีระยะสั้นในกลุ่มบริหารยาวันละครั้ง และทั้งสองกลุ่มตอบสนองดีทางคลินิกต่อการรักษา

ดังนั้นการบริหารยาวันละครั้งในขนาด 4–5 มก.ต่อกิโลกรัมต่อวัน น่าจะเหมาะสมในการนำมาใช้ในทารกช่วง 7 วันแรก ซึ่งจะได้ peak serum concentration ที่จะได้ผลในทางประสิทธิภาพทางคลินิกที่ดีกว่าและให้ trough serum concentration ที่ต่ำกว่าการบริหารแบบมาตรฐานที่ใช้อยู่

คำสำคัญ : gentamicin, การติดเชื้อในทารก, การให้ยาวันละครั้ง, การให้ยาวันละสองครั้ง

อุไรวรรณ โชติเกียรติ, อัมพร ณรงค์สันติ, ดวงจิต พนมวัน ณ อยุธยา
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 1109–1115

* หน่วยทารกแรกเกิด, สถาบันสุขภาพเด็กแห่งชาติมหาราชินี, กรุงเทพ ฯ 10400
** กลุ่มงานเภสัชกรรม, โรงพยาบาลพิจิตร, พิจิตร 66000
*** ภาควิชาเภสัชกรรม, คณะเภสัชศาสตร์, จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330