Gentamicin Pharmacokinetics in Thai Neonates : Recommendation for a Dosing Guideline

SUKANYA KANTHAWATANA, M.D., Ph.D.*,
KITTICHAI URUWANNAKUL, M.D.**,
SOMPORN CHOTINARUMON, M.D.**

Abstract

A pharmacokinetic study of gentamicin was performed on 32 Thai neonates. After a single intravenous infusion of gentamicin at 2.5 mg/kg body weight, blood samples were collected at 0.5 and 12 hours. Serum gentamicin concentrations were determined with use of fluorescence polarizing immunoassay. None of the neonates with < 28 weeks post conceptional age (PCA), contrary to most of the more mature neonates, achieved the recommended therapeutic peak concentrations. The volume of distribution (V_d) and elimination half-life ($T_{1/2}$) of gentamicin were found to reversely correlate with the PCA, with significantly larger V_d and longer $T_{1/2}$ values observed among the premature neonates. Our findings were similar the results previously reported in Caucasians, and thus strongly indicated the necessity of gentamicin dosage adjustment among Thai neonates according to their PCA. A gentamicin dosing guideline for Thai neonates has been proposed, nonetheless, with higher doses and longer dosing intervals recommended among premature neonates.

Gentamicin is one of the most commonly used drugs in the neonatal nursery for treatment of neonatal sepsis. A large volume of distribution (V_d) together with a low clearance of gentamicin from the body observed among neonates have resulted in a prolonged elimination half-life ($T_{1/2}$) and thus increased the risk of drug accumulation during treatment[1,2]. Several published guidelines for gentamicin dosing are primarily based on gestational and/or postnatal age and on body weight[3-8] since the development of renal function has been shown to closely correlate with post conceptional age[9-11]. Nonetheless, there has been no general consensus among physicians providing care for the neonates, of the most appropriate empiric gentamicin dosage regimen for neonates in clinical practice. Some of the gentamicin dosing recommendations have been demonstrated to produce trough

* Department of Pharmacology,
** Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

concentrations above 2 mg/L,[1,12] thus increasing the risk of the drug toxicity[13,14]. Moreover, these published dosing guidelines are based on the pharmacokinetic studies of gentamicin in Caucasians; therefore, the validity of these guidelines for Thai neonates still needs to be explored. The purpose of this research work was to study the pharmacokinetics of gentamicin among Thai neonates and to determine an appropriate dosing guideline.

METHOD

Thirty-two neonates admitted to the Neonatal Unit at the Maharaj Nakhon Chiang Mai Hospital between March and September of 1995, with an indication for gentamicin treatment, were recruited in the study. Patients were classified into 3 groups according to their post conceptional age (PCA): < 28 weeks, between 28-34 weeks, and > 34 weeks. Neonates with severe birth asphyxia or with the apgar score of less than 2 at 5 minutes, unstable vital signs, severe septicemia, and those receiving indomethacin therapy during the study period, were excluded from the study. Each neonate received a single dose of gentamicin at 2.5 mg/kg body weight by an intravenous infusion drip over 30 minutes. Serum concentrations of gentamicin were determined with the use of the TDx Fluorescent Polarizing Analyzer (Abbott Laboratories, U.S.A), at 0.5 and 12 hours after the end of the drug infusion. Pharmacokinetic analyses were performed using gentamicin serum concentrations collected on all study patients. These calculations were performed based on a one-compartment, first-order model using the method described previously[15]. Using each patient's calculated pharmacokinetic parameters, peak and trough serum concentrations were simulated[2,15] to determine the dosing regimens that would result in the recommended therapeutic peak (4-10 mg/L) and trough (< 2 mg/L) concentrations for the treatment of neonatal sepsis[16,17]. One-way Analysis of Variance for non-repeated measurement was used to detect a difference in the $T_{1/2}$ and V_d values among the groups. P values of less than 0.05 were considered statistically significant. The study was approved by the Medical Ethics Committee of the Chiang Mai University Faculty of Medicine. The mother of each neonate signed the written informed consent prior to the study enrolment.

RESULTS

Of the thirty-two neonates who were recruited in the study, six were < 28 weeks, ten were between 28-34 weeks, and sixteen were > 34 weeks PCA. All neonates had an appropriate birth weight for gestational age (AGA) with the mean post natal age (PNA) of 0.8±1.3 days. There was no significant difference in the apgar score at 5 minutes among the three groups (Table 1). Serum concentrations of gentamicin after a single intravenous infusion at 2.5 mg/kg body weight are shown in Table 2. None of the neonates with PCA < 28 weeks achieved the therapeutic peak plasma concentrations of 4-10 mg/L, whereas, most of the more mature neonates in the other groups achieved the therapeutic peak concentrations. The elimination $T_{1/2}$, as well as V_d, were significantly increased among the more premature neonates compared to those with PCA > 34 weeks. Both the $T_{1/2}$ and V_d values were shown to reversely correlate with the PCA, with the coefficient of correlation of 0.97 and 0.87, respectively. There was no significant difference in the mean values of $T_{1/2}$ and V_d among neonates within the group despite some difference in birth weight: ≤ 1500 *vs* > 1500 g for the 28-34 weeks PCA, and ≤ 2500 *vs* > 2500 g for the > 34 weeks PCA groups. The simulated peak and trough concentrations of gentamicin at steady-state condition using each patient's calculated pharmacokinetic parameters revealed that higher doses and longer intervals would be necessary for the premature compared to the more mature neonates, in order to achieve the therapeutic gentamicin concentrations (Table 3).

Table 1. Demographic data of the neonates enroling in the study.

Post-conceptional age	Sex (M/F)	Apgar score at 5 minutes
< 28 week	2/4	10[a] (5-10)[b]
28-34 week	7/3	10 (7-10)
> 34 week	5/11	10 (6-10)

[a] mode
[b] range

Table 2. Gentamicin serum concentrations and estimated plasma elimination half-life and volume of distribution values after a single intravenous infusion of gentamicin at 2.5 mg/kg body weight. Data represent mean ± SD.

Post conceptional age	Serum conc. (mg/L)		Estimated	
	0.5 h	12 h	$T_{1/2}$ (h)	V_d (L/kg)
< 28 week (n = 6)	2.9 ± 1.3 * (0)[a]	1.5 ± 0.1	17.9 ± 10.7*ε	3.1 ± 2.3*ϕ
28-34 week (n = 10)	4.5 ± 1.8 (7)	2.1 ± 0.8	12.6 ± 7.6*	1.4 ± 0.9*
> 34 week (n = 16)	5.0 ± 1.3 (12)	1.4 ± 0.4	6.4 ± 1.7	0.7 ± 0.2

[a] Number of patients with level ≥ 4 mg/L.
* p < 0.5 *vs* PCA > 34 week
ε p < 0.5 *vs* PCA 28-34 week
ϕ p = 0.5 *vs* PCA 28-34 week

Table 3. Recommended gentamicin dosing guideline and predicted peak and trough concentrations at steady-state.

Post conceptional age	Dose (mg/kg)	Interval (h)	Predicted conc. (mg/L)	
			peak	trough
< 28 week	4.5	q 18	4.0 ± 2.0[a]	1.2 ± 0.2
28-34 week	3.0	q 18	4.2 ± 1.6	1.3 ± 0.6
> 34 week	2.5	q 12	4.8 ± 1.2	1.4 ± 0.5

[a] Mean ± SD

DISCUSSION

Even though previously published empiric neonatal gentamicin dosing regimens were designed to achieve predictable therapeutic concentrations, some were published[1,18] when very limited information regarding neonatal gentamicin pharmacokinetics was available and the survival rate of very premature neonates was still rather low. Thus, the neonates being treated were of considerably higher birth weight than at present. Subsequent guidelines recommended some adjustments in dosing intervals for premature neonates,[2,8,19] nonetheless, significant difference in dosing regimens remained (Table 4). In this study, we determined the pharmacokinetics of gentamicin in Thai neonates and our findings that PCA reversely correlated with T_{1-2} or V_d were similar to the results previously reported[1-7]. With use of individual's calculated pharmacokinetic parameters, we determined an appropriate dosing regimen for each individual. Our neonatal gentamicin dosing guideline classified neonates accordingly based on their PCA because it best described maturity of renal function[9,11]. Interestingly, we found that a higher dose and longer dosing interval would be required for those more premature neonates to achieve the therapeutic serum gentamicin concentrations (Table 3) comparing to previous published guidelines (Table 4). Nonetheless, this recommended guideline was not designed to replace routine monitoring of serum gentamicin concentrations, especially in those with unstable conditions, deterioration of renal function, fluid and electrolyte imbalance, or

Table 4. Previously published neonatal gentamicin dosing guidelines.

Source	Age	Dose
Szefler et al[2]	< 35 week GA[a]	2.5 mg/kg q 18 h
	≥ 35 week GA[a]	2.5 mg/kg q 12 h
Miranda et al[5]	< 34 week PCA	2.5 mg/kg q 18 h
	> 35 week PCA	2.5 mg/kg q 12 h
Lopez-Samblas et al[8]	< 30 week PCA	3.0 mg/kg q 24 h
	30-37 week PCA	2.5 mg/kg q 18 h
Pediatric drug Handbook[19]	premature: < 1 week PNA[a]	2.5 mg/kg q 18 h or 3.5 mg/kg/dose (dosing interval by formula) dosing interval = 50.5-0.76 x GA in weeks
McCracken and Nelson[18]	< 1 week PCA[a]	2.5 mg/kg q 18 h
	> 1 week PCA	2.5 mg/kg q 8 h

[a] Guidelines are for the first week of life only.
GA = gestational age; PCA = post conceptional age; PNA = postnatal age

acidosis, which could result in unexpected variations of the pharmacokinetics. These conditions might lead to lower than desirable peak serum concentration and thus undertreatment or, on the other hand, to excessive increases in trough concentrations and thus, toxicity. Gentamicin serum concentrations should be routinely monitored for individualization of treatment schedules, thus increasing safety and efficacy of this drug for clinical use especially in neonates.

(Received for publication on September 4, 1996)

REFERENCES

1. Assael BM, Gianni V, Marini A, et al. Gentamicin dosage in preterm and term neonates. Arch Dis Child 1977; 52: 883-6.
2. Szefler SJ, Wynn RJ, Clarke DF, et al. Relationship of gentamicin serum concentration to gestational age in preterm and term neonate. J Pediatr 1980; 97: 312-5.
3. Hindmarsh KW, Nation RL, Williams GL, et al. Pharmacokinetics of gentamicin in very low birth weight preterm infants. Eur J Clin Pharmacol 1983; 24: 649-53.
4. Koren G, Leeder S, Harding E, et al. Optimization of gentamicin therapy in very low birth weight infants. Pediatr Pharmacol 1985; 5: 79-87.
5. Miranda JC, Schimmel MM, James LS, et al. Gentamicin kinetics in the neonate. Pediatr Pharmacol 1985; 5: 57-61.
6. Kasik JW, Jenkins S. Postconceptional age and gentamicin elimination half life. J Pediatr 1985; 106: 502-5.
7. Thompson AH, Way S, Bryson SM, et al. Population pharmacokinetics of gentamicin in neonates. Dev Pharmacol Ther 1988; 11: 173-9.
8. Lopez-Samblas AM, Torres CL, Wang H, et al. Effectiveness of a gentamicin dosing protocol based on postconcentional age: comparison to published neonatal guidelines. Annals Pharmacother 1992; 26: 534-2.
9. Arant BS. Developmental pattern of renal functional maturation compared in the human neonate. J Pediatr 1978; 92: 705-12.
10. Chow-tung E, Young S, McCollock K, et al. Developmental pharmacokinetics of gentamicin in neonates: relationship to post-conceptional age and renal function. Clin Pharmacol Ther 1985; 37: 187-91.
11. Leake RD, Trystad CW, Oh W. Inulin clearance in the newborn infant: relationship to gestational age and postnatal age. Pediatr Res 1976; 10: 759.
12. Mullhall A, De Louvois J, Hurley R. Incidence of potentially toxic concentrations of gentamicin in the neonate. Arch Dis Child 1983; 58: 897-900.

13. Rajchgot P, Prober CG, Soldin S, et al. Aminoglycoside-related nephrotoxicity in the premature newborn. Clin Pharmacol Ther 1984; 35: 395-401.
14. Davey P. Aminoglycosides and neonatal deafness (letter). Lancet 1985; 2: 612.
15. Sawchuck RJ, Zaske DE, Cipolle RJ, et al. Kinetic model for gentamicin dosing with the use of individual patient parameters. Clin Pharmacol Ther 1977; 21: 362-9.
16. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycosides therapy: importance of the peak concentration to minimal inhibitory concentration. J Infect Dis 1987; 155: 93-9.
17. Mattie H, Craig WA, Pechere JD. Determinant of efficacy and toxicity of aminoglycosides. J Antimicrob Chemother 1989; 24: 281-93.
18. McCracken GH, Nelson JD. Antimicrobial therapy for newborns. New York: Grune & Stratton 1977: 35.
19. Benitz WE, Tatro DS, eds. The pediatric drug handbook. 2nd ed. Chicago: Year Book Medical Publishers 1988: 505-6.

เภสัชจลนศาสตร์ของยาเจนตาไมซินในทารกแรกเกิดชาวไทย และแนวปฏิบัติในการให้ยา

สุกัญญา คันธาวัฒน์, พ.บ., Ph.D.,*
กิตติชัย อุรุวรรณกุล, พ.บ., สมพร โชตินฤมล, พ.บ.**

ทารกแรกเกิดชาวไทยจำนวน 32 ราย ได้เข้าร่วมในการศึกษาเภสัชจลนศาสตร์ของยาเจนตาไมซิน โดยได้รับยาในขนาด 2.5 มก. ต่อน้ำหนักตัว 1 กก./ทางหลอดเลือดดำ ตัวอย่างเลือดถูกเก็บที่เวลา 0.5 และ 12 ชั่วโมงหลังจากได้รับยา และวัดหาความเข้มข้นของยาในซีรัมโดยวิธีการทางอิมมูโนเอสเสย์ ความเข้มข้นของยาที่วัดได้ที่ 0.5 ชั่วโมงในผู้ป่วยที่มีอายุครรภ์น้อยกว่า 28 สัปดาห์ทุกรายที่ทำการศึกษามีระดับต่ำกว่าระดับที่เหมาะสมในการรักษา ในขณะที่ความเข้มข้นของยาที่วัดได้ในผู้ป่วยที่มีอายุครรภ์มากขึ้นส่วนใหญ่จะอยู่ในระดับที่เหมาะสม ค่าปริมาตรการกระจายตัวและค่าครึ่งชีวิตของยาเจนตาไมซินแปรผกผันกับอายุครรภ์โดยที่ค่าปริมาตรการกระจายตัวสูงขึ้นและค่าครึ่งชีวิตของยานานขึ้นในผู้ป่วยที่มีอายุครรภ์น้อยกว่า ผลการศึกษาที่ได้นี้คล้ายคลึงกับผลการศึกษาที่ได้ในผู้ป่วยต่างชาติ และบ่งชี้ถึงความจำเป็นในการปรับขนาดและระยะห่างของการให้ยาแก่ทารกแรกเกิดตามอายุครรภ์ ซึ่งในรายงานนี้ได้เสนอแนะถึงแนวทางปฏิบัติในการให้ยาแก่ทารกแรกเกิดชาวไทยไว้ด้วยโดยให้ยาในขนาดที่สูงขึ้นและเว้นระยะห่างของการให้ยานานขึ้นสำหรับทารกแรกเกิดที่มีอายุครรภ์ไม่ครบกำหนด

* ภาควิชาเภสัชวิทยา,
** ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่, เชียงใหม่ 50200