CHAPTURE IV

RESULT AND DISCUSSION

1. Characteristics of patients

Fifty-four patients who met the criteria of this study were randomized selection for twice daily and once daily treatment group. The characteristics of the patients, indication for gentamicin treatment, dose, duration and combination antibiotic were presented in table 4.1 and table 4.2. There were 27 patients in twice daily dosing group (TDD), and 27 patients in once daily dosing group (ODD). These were 14 males (51.85%) and 13 females (48.15%) in the TDD group and 16 males (59.26%) and 11 females (40.74%) in the ODD group. There was no significant difference in sex between the TDD and ODD groups ($p > 0.05$).

Comparison of patients' characteristics between the TDD and ODD groups were showed in table 4.3. The infants in TDD group had mean ± SD gestational age of 38.37 ± 2.12 weeks (35 to 43 weeks), postnatal age of 1.43 ± 1.25 days (0.04 to 4days), weight of 2,987.04 ±656.71 g (2,000 to 4,750 g), height of 49.56 ± 3.63 cm (44 to 57 cm) , Apgar scores at 1 minute of 7.48 ± 1.74 (4 to 10) , Apgar scores at 5 minutes of 9.63 ± 0.69 (8 to 10) . The infants in ODD group had mean ± SD gestational age of 38.44 ± 2.12 weeks (34 to 41 weeks), postnatal age of 0.94 ± 1.22 days (.04 to 5days) , weight of 2,924.07 ±597.65 g (2,050 to 4,300 g), height of 49.26 ± 2.68 cm(45 to 57 cm) , Apgar scores at 1 minute of 7.67 ± 1.57 (4 to 9), Apgar scores at 5 minutes of 9.26 ± 1.06 (7 to 10). There were no significant differences in mean gestational ages, postnatal ages, weights, heights, Apgar scores at 1 minute, and Apgar score at 5 minutes between the groups ($p > 0.05$). The Apgar score at 5 minutes of both groups were in the same range ≥7, representing the good condition of the infants.

Indication for gentamicin treatment in twice-daily dosing group were 3 premature rupture of membrane (PROM) (11.11%), 6 pneumonia (22.22%), 4 necrotizing enterocolitis (NEC) (14.81%), 2 sepsis (7.41%), 1 clinical sepsis (3.70%), 3 PROM with sepsis (11.11%), 2 sepsis and pneumonia (7.41%), 2 meconium aspiration syndrome (MAS) (7.41%), 1 MAS and pneumonia (3.70%), 2 respiration distress(RD) (7.41%), and 1 RD with sepsis (3.70%). Indication for gentamicin treatment in once - daily dosing group were 4 PROM (14.81%), 3 NEC (11.11%), 3 sepsis (11.11%), 2 sepsis with pneumonia (7.41), 2 pneumonia (7.41), 7 MAS (25.93%), 1 omphalitis (3.70%), and 2 RD (7.41%), 3 RD with transient tachypnea of new born (TTNB) (11.11%). The infants had mean $\pm$ SD gentamicin dose of 2.44 $\pm$ 0.16 mg/kg/12 hours (2.00 to 2.8 mg/kg/12 hours) in TDD group and 4.73$\pm$ 0.268 mg/kg/24 hours(4.17 to 5.00 mg/kg/24 hours) in ODD group ,duration of 7.96 $\pm$3.16 days(3 to18 days) in TDD group and 6.93$\pm$ 3.13 days(3 to 14 days) in ODD group. There was no significant difference in mean duration between the groups (table 4.3). Neither patients were treated with gentamicin alone, all 27 patients in TDD group were treated concomitantly with ampicillin while in the ODD group 25 patients (92.59%) were treated concomitantly with ampicillin, 1 patient (3.7%) was treated concomitantly with ampicillin (8 days) and cefotaxime (5 days), and 1 patient (3.7%) was treated concomitantly with cloxacillin. One patient (3.7%) in the ODD group the antibiotic used was changed form gentamicin combine with ampicillin to amikacin combine with cefotaxime for 3 days, and finally changed to vancomycin (the culture showed MRSA) since the condition of patient was deteriorated (pt.no 1).

Table 4.4 and 4.5 showed the disease of the patients receiving gentamicin in TDD and ODD groups respectively. Disease of the patients in TDD group were 5 birth asphyxia (18.50%), 8 hyperbilirubinemia (29.63%), 3 MAS (11.11%), 4 NEC (14.81%), 9 pneumonia (33.33%), 6 PROM (22.22%), 7 RD (25.92%), 9 sepsis (33.33%), 1 stress ulcer (3.70%), 3 TTNB (11.11%), and 7 other diseases (25.92%). Disease of the patients in ODD group were birth 6 asphyxia (22.22%), 5 hyperbilirubinemia (18.52%), 7 MAS (25.93%), 3 NEC (11.11%), 4 PROM (14.81%), 15 RD (55.55%), 5 sepsis (18.52%), 1 skin infection (3.70%), 5 TTNB (18.52%),

and 9 other diseases (33.33%). Some patients in both groups had more than one disease resulted in the average of 2.30 in the TDD group and 2.22 in the ODD group.

TABLE 4.1 Characteristics of the patients receiving twice- daily dosing of gentamicin.

Pt. NO	Sex	GA. weeks	PA. days	Wt. g	Ht. cm	AS 1 min	AS 5 min	Indication	Dose mg/kg	Duration (days)	Con. AB.
1	M	40	2.00	3,800	52	9	10	PROM >24 hr, Sepsis	2.63	7	Ampicillin
2	M	40	0.50	4,000	53	7	10	Sepsis	2.50	4	Ampicillin
3	F	40	0.04	4,000	53	7	9	Pneumonia	2.50	9	Ampicillin
4	M	39	0.29	2,900	57	8	10	PROM >24 hr, Sepsis	2.41	4	Ampicillin
5	F	37	4.00	2,000	45	9	10	NEC	2.50	8	Ampicillin
6	F	36	0.17	2,150	45	8	10	Sepsis,RD	2.33	11	Ampicillin
7	M	43	1.00	2,900	49	6	9	NEC	2.41	7	Ampicillin
8	M	34	1.00	2,050	44	8	10	Sepsis ,Pneumonia	2.00	18	Ampicillin
9	M	37	1.00	3,200	50	9	10	PROM 19hr ,Sepsis	2.50	9	Ampicillin
10	F	36	0.05	2,250	45	9	10	PROM >24 hr	2.22	11	Ampicillin
11	F	42	0.13	2,650	48	4	8	Pneumonia	2.49	8	Ampicillin
12	F	35	2.00	2,750	48	5	10	PROM >24 hr	2.55	8	Ampicillin
13	F	37	2.00	2,500	49	7	10	Clinical sepsis	2.50	3	Ampicilllin
14	M	37	4.00	2,850	48	9	10	Pneumonia	2.46	10	Ampicillin
15	M	39	0.21	3,050	47	9	10	MAS	2.46	7	Ampicillin
16	M	40	1.00	2,550	48	8	10	MAS,Pneumonia	2.35	4	Ampicillin
17	F	38	1.38	3,000	48	10	10	RD	2.50	5	Ampicillin
18	F	40	1.00	4,750	57	6	9	MAS	2.53	10	Ampicillin
19	M	39	2.00	2,550	48	9	10	NEC	2.75	8	Ampicillin
20	F	39	1.00	2,500	47	5	10	NEC	2.80	7	Ampicillin
21	M	40	0.25	3,400	50	4	10	PROM >24 hr	2.35	9	Ampicillin
22	M	38	0.29	3,350	50	5	8	Sepsis, Pneumonia	2.39	11	Ampicillin
23	M	37	0.29	3,300	50	9	10	Pneumonia	2.42	11	Ampicillin
24	F	37	1.00	2,900	48	7	8	RD	2.41	4	Ampicillin
25	F	40	2.00	3,800	52	9	10	Pneumonia	2.37	8	Ampicillin
26	F	40	4.00	2,800	49	9	10	Pneumonia	2.50	9	Ampicillin
27	M	36	2.17	2,700	48	7	9	Sepsis	2.22	5	Ampicillin
Mean ±SD (Range)		38.37± 2.12(35-43)	1.43± 1.25 (0.04-4)	2987.04 ± 656.71 (2000-4750)	49.56 ± 3.63 (44-57)	7.48± 1.74 (4-10)	9.63± 0.69 (8-10)		2.44± 0.16 (2.0-2.3)	7.96± 3.16 (3-18)	

TABLE 4.2 Characteristics of the patients receiving once-daily dosing of gentamicin.

Pt. No	Sex	GA. Weeks	PA. days	Wt. g	Ht. Cm	AS 1 min	AS 5 min	Indication	Dose mg/kg	Duration (days)	Con. AB.
1	F	38	0.17	2,800	50	7	9	Sepsis, Pneumonia	4.29	3	Ampicillin
2	F	41	0.04	3,200	45	7	9	MAS	4.38	14	Ampicillin
3	F	38	1.00	2,600	48	9	10	NEC	5.00	5	Ampicillin
4	M	37	0.83	2,050	45	9	10	Sepsis, Pneumonia	4.39	7	Ampicillin
5	F	37	1.00	2,150	45	9	10	Sepsis	4.65	10	Ampicillin
6	M	41	2.00	3,400	52	7	8	PROM >24 hr	4.41	7	Ampicillin
7	M	37	0.25	2,750	50	7	9	PROM >24 hr	4.36	4	Ampicillin
8	F	37	0.13	2,450	47	8	10	RD, TTNB	4.49	5	Ampicillin
9	M	34	0.04	2,400	47	4	7	PROM >24 hr	4.17	8	Ampicillin
10	M	39	0.08	3,950	52	9	10	RD	5.00	4	Ampicillin
11	M	35	0.08	2,250	47	9	10	RD	4.44	13	Ampicillin 8, cefotaxime 5 days
12	F	38	0.46	2,750	49	8	9	MAS	4.73	7	Ampicillin
13	M	37	3.00	3,800	51	9	10	NEC	5.00	6	Ampicillin
14	M	38	5.00	3,000	50	6	8	Omphalitis	5.00	3	Cloxacillin
15	F	41	0.21	3,500	52	4	7	MAS	5.00	5	Ampicillin
16	M	39	0.29	4,300	57	8	10	MAS	4.65	11	Ampicillin
17	F	41	0.13	2,400	47	6	9	PROM >24 hr	5.00	10	Ampicillin
18	M	40	1.00	3,700	51	9	8	RD, TTNB	4.74	3	Ampicillin
19	M	41	1.00	2,600	50	7	10	MAS	4.82	4	Ampicillin
20	M	40	0.50	2,500	49	7	10	MAS	4.80	8	Ampicillin
21	F	41	1.00	3,500	53	5	7	Pneumonia	4.86	7	Ampicillin
22	M	36	0.63	2,500	48	9	10	Sepsis	4.80	7	Ampicillin
23	M	37	4.00	3,250	50	9	10	NEC	4.92	5	Ampicillin
24	F	37	0.63	2,400	49	9	10	Sepsis	5.00	11	Ampicillin
25	F	41	0.75	2,550	48	8	10	MAS	4.71	7	Ampicillin
26	M	41	1.00	3,400	50	9	10	RD, TTNB	5.00	3	Ampicillin
27	M	36	0.21	2,800	48	9	10	Pneumonia	5.00	10	Ampicillin
Mean+ SD (Range)		38.44+ 2.12(34-41)	0.94+ 1.22 (0.04-5)	2924.07+5 97.65 (2050-4300)	49.26+ 2.68(45-57)	7.67+ 1.57 (4-9)	9.26+ 1.06 (7-10)		4.73+ 0.27 (4.17-5)	6.93+ 3.13 (3-14)	

PT.NO. = Patient number GA. = Gestational age (weeks) PA. = Postnatal age (days)

Wt. = weight (gm) Ht. = Height (cm) AS = Apgar scores

Con.AB. = Concomitant antibiotic

TABLE 4.3 Comparison of the patients between the TDD and the ODD groups.

Parameter	Mean ± SD (range) at:		P value[a]
	TDD group	ODD group	
Sex – Male	14*	16*	-
– Female	13*	11*	-
Gestration age (weeks)	38.37 ± 2.12 (35 – 43)	38.44 ±2.12 (34 – 41)	0.898
Postnatal age (days)	1.43 ± 1.25(0.04 - 4.00)	0.94 ± 1.22 (0.04 - 5 00)	0.150
Weight (g)	2,987.04± 656.71(2,000 – 4,750)	2,924.07 ±597.65 (2,050 – 4,300)	0.974
Height (cm)	49.56 ± 3.63(44 – 57)	49.26± 2.68(45 – 57)	0.221
Apgar score at 1 min	7.48 ± 1.74(4 – 10)	7.67 ±1.57(4 – 9)	0.683
Apgar score at 5 min	9.63± 0.69(8 – 10)	9.26± 1.06(7 – 10)	0.134
Duration (days)	7.96 ± 3.16(3 – 18)	6.93 ± 3.13(3 – 14)	0.230

a: P value by unpaired – t test.

*: The absolute value (not the mean ± SD)

TABLE 4.4 Disease of the patients receiving twice- daily dosing of gentamicin.

Disease	Number	percent
-Birth asphyxia	5	18.52
-Hyperbilirubinemia	8	29.63
-Meconium aspiratory syndrome(MAS)	3	11.11
-Necotizing enterocolitis (NEC)	4	14.81
-Pneumonia	9	33.33
-Premature rupture of membrane(PROM)	6	22.22
-Respiratory distress(RD)	7	25.93
-Sepsis:bacteria septicemia,menigitis	9	33.33
-Stress ulcer	1	3.70
-Transient tachypnea of new born(TTNB)	3	11.11
Orther disease	7	25.93
Total	62	
Average diseases/patient	2.30	

TABLE 4.5 Disease of the patients receiving once- daily dosing of gentamicin.

Disease	Number	percentage
-Birth asphyxia	6	22.22
-Hyperbilirubinemia	5	18.52
-Meconium aspiratory syndrom(MAS)	7	25.93
-Necotizing enterocolitis (NEC)	3	11.11
-Premature rupture of membrane(PROM)	4	14.81
-Respiratory distress(RD)	15	55.55
-Sepsis: bacteria septicemia,menigitis	5	18.52
-Skin infection	1	3.70
-Transient tachypnea of new born(TTNB)	5	18.52
Orther disease	9	33.33
Total	60	
Average diseases /patient	2.22	

2. Gentamicin Pharmacokinetic data

The pharmacokinetic data for the TDD group, and the ODD group were shown in table 4.6 and table 4.7. Pharmacokinetic data were analyzed with a one – compartment model.

The mean ± SD steady – state gentamicin peak concentration (C_{pk}) of the infants in the TDD group was 5.94 ± 1.57 mg/l (3.90 – 10.60 mg/l) while the mean ± SD C_{pk} of the infants in the ODD group was 8.92 ± 1.59 mg/l (5.70 – 12.40 mg/l). The mean ± SD of Cpk was significantly higher in the ODD group than the TDD group ($p < 0.001$). This present may be also indicated to significant clinical results, especially in patients with pneumonia. The relationship of blood levels and clinical efficacy had been studied in many clinical studies.[74-79] These studies support the importance of achieving adequate early aminoglycoside concentration in patients with gram – negative bacteremia. The adequate gentamicin concentration for septicemia UTI and wound infection was ≥ 5 mg/l , and ≥ 8 mg/l for pneumonia.[75,78] Moore et al had also found that patients with gram – negative pneumonia patients with 1 hour post infusion concentration of ≥ 7 mg/l for gentamicin more often had successful out come than those concentration less than 6 mg/ml.[79] Peak level in different range of the patients in the TDD and the ODD group were showed in table 4.8. In this study, there were 7 infants (25.93%) in the TDD group had Cpk < 5 mg/l, 24 infants (88.89%) had Cpk < 8 mg/l, and 3 infants had Cpk ≥ 8 mg/l while none of the infants in the ODD group had Cpk < 5 mg/ml, only 6 infants (22.22%) had Cpk < 8 mg/l and two of these (7.41%) had Cpk greater than 12.0 mg/l (12.1 and 12.4 mg/l). The mean ± SD C_{tr} was 1.44 ± 0.49 mg/l (0.40 – 2.70 mg/l) in the TDD group, and 0.90 ± 0.35 mg/l (0.30 – 1.70 mg/l) in the ODD group. The mean± SD C_{tr} was significantly lower in the ODD group than in the TDD group ($p<0.001$). Number and percentage of the patients whose peak serum level was subtherapeutic and trough serum level was over therapeutic for both groups were shown in table 4.9. Subtherapeutic gentamicin peak serum concentration of less than 4 mg/l was found in one patient(3.70%) in TDD group while none of the patient in the ODD group had subtherapeutic gentamicin serum peak concentration. The peak gentamicin concentration of all infants in the ODD group

were within the therapeutic range (C_{pk} were not less than 5 mg/l and not greater than 18 mg/l). Elevated trough concentration of more than 2 mg/l(2.3 anc 2.7 mg/l) were found in 2 patients (7.4%) in the TDD group while elevated trough concentration of more than 1.5 mg/l, but less than 2.0 mg/l (1.7 mg/l) was found in one patient (3.7%) in the ODD group . Dosing of gentamicin therapy were adjusted in all cases where nontherapeutic gentamicin serum concentrations were found.

The mean ± SD of the pharmacokinetic parameters of the patients in the TDD group and the ODD group were shown in table 4.10. The mean ± SD of the elimination rate constants (K) in the TDD group and the ODD group were 0.137 ± 0.031 hr^{-1} (0.085 – 0.229 hr^{-1}) and 0.105 ± 0.020 hr^{-1} (0.065 – 0.152 hr^{-1}) respectively. The mean ± SD of the elimination half – life (t1/2) was 5.30 ± 1.23 hr (3.02 – 8.17 hr) for the TDD group and 6.85 ± 1.36 hr (4.56–10.64 hr) for the ODD group. The mean ± SD of the volume of distribution (Vd) in the TDD group and the ODD group were 0.48 ± 0.13 l/kg (0.21 – 0.82 l/kg), and 0.54 ±0.12 l/kg (0.37-0.85 l/kg) respectively. The mean ± SD of the clearance of gentamicin (Cl) in the TDD group and the ODD group were 0.194 ± 0.068 l/hr (0.070 – 0.299 l/hr) and 0.167 ± 0.057 l/hr (0.094 – 0.280 l/hr) respectively. The pharmacokinetic parameters varied widely among the infants within both groups. There were no significant differences in mean Vd, and Cl between two group ($p>0.05$). The mean elimination rate constant (K) was significantly lower in the ODD group as compared to the TDD group which resulted in significantly longer the elimination half life (t1/2) in the ODD group than in the TDD group which might due in part to the less development of the kidney function of the infants shorter PA in the ODD group as could be seen from the higher mean serum creatinine concentration at the first and the third day in ODD group than in the TDD group even though it was not significant different ($p>0.05$).

Correlation by linear regression analysis between serum creatinine (SCr) in mg/dl in the third day and clearance of gentamicin (Cl) in l/hr, creatinine clearance (Clcr) in ml/min/1.73 m^2 and clearance of gentamicin (Cl) in l/hr, and creatinine clearance in l/hr and clearance of gentamicin (Cl) in l/hr were showed in table 4.11. The data and method for calculation Clcr in ml/min/1.73m^2 to Clcr in l/hr were showed in Appendix III. Figure 4,5, and 6 demonstrated the correlation between SCr in mg/dl,

Clcr in ml/min/1.73 m^2, Clcr in l/hr and Cl in l/hr respectively. The patients in TDD and ODD groups were combined because there were no differences in serum creatinine and clearance of gentamicin calculated from serum gentamicin concentration at the third day. Correlation – coefficient between SCr in mg/dl and Cl in l/hr was low (r=0.20 – 0.40=low)[80] with r = -0.362, while Clcr either in ml/min/ m^2 or l/hr was moderately correlate (r = 0.40 – 0.60 = moderate) to Cl in l/hr with r = 0.438 and r = 0.535 respectively.

Correlation by multiple regression analysis between postnatal age (PA), weight (Wt), serum creatinine (SCr) or creatinine clearance (Clcr) and clearance of gentamicin (Cl) calculated from the serum gentamicin concentration in the third day were showed in table 4 12. Three equations had been generated as followed:

The first equation

$$Cl\ (l/hr) = -0.0558 + 0.0118\ PA - 0.0630\ SCr(mg/dl) + (7.6680 \times 10^{-5})\ Wt\ (gm)$$

; r = 0.8441 (r=0.8 – 1.0 = high).

The second equation

$$Cl\ (l/hr) = -0.1007 + 0.0127\ PA + 3.7922 \times 10^{-4}\ Clcr(ml/min/1.73\ m^2) + 7.3703 \times 10^{-5}\ Wt\ (gm)$$

; r = 0.8444.

The third equation

$$Cl\ (l/hr) = -0.0883 + 0.0127\ PA + 0.0478\ Clcr\ (l/hr) + 7.0198 \times 10^{-5}\ Wt\ (gm)$$

; r = 0.8405

In clinical practice, these equations can be applied to predict the dosage for neonates using the calculated Cl and the population Vd of neonates (0.45 ±0.1 l/kg)[42] when serum gentamicin concentration were not available. From this study, the first equation was recommended because it was the most simplify, do not require any precalculation and the correlation coefficient was not significantly different from the other equations.

TABEL 4.6 Dosage, measured serum gentamicin concentrations and pharmacokinetic parameters of the patients receiving TDD treatment

Pt.No.	Dose	Cpk	Ctr	K	T1/2	Vd		Cl	Adjustment
	mg/kg	mg/l	mg/l	hr^{-1}	hr	l	l/kg	l/hr	
1.	2.63	5.5	1.0	0.161	4.30	1.79	0.47	0.288	N
2.	2.50	4.8	1.2	0.134	5.16	2.23	0.56	0.299	N
3.	2.50	6.3	1.9	0.116	5.97	1.84	0.46	0.214	N
4.	2.41	5.1	1.3	0.130	5.33	1.53	0.53	0.198	N
5.	2.50	9.2	1.5	0.166	4.17	0.53	0.27	0.089	N
6.	2.33	10.6	1.7	0.173	4.01	0.45	0.21	0.078	N
7.	2.41	4.1	1.3	0.109	6.33	2.09	0.72	0.229	N
8.	2.00	8.7	1.9	0.145	4.78	0.48	0.24	0.070	N
9.	2.50	6.7	1.6	0.136	5.08	1.29	0.40	0.176	N
10.	2.22	3.9	1.6	0.085	8.17	1.84	0.82	0.156	Y
11.	2.49	7.5	1.7	0.138	5.02	0.95	0.36	0.131	N
12.	2.55	6.2	2.3	0.094	7.34	1.52	0.55	0.143	Y
13.	2.50	5.8	1.5	0.129	5.38	1.20	0.48	0.155	N
14.	2.46	4.5	1.0	0.143	4.84	1.64	0.58	0.235	N
15.	2.45	5.6	1.2	0.147	4.72	1.40	0.46	0.205	N
16.	2.35	7.0	2.7	0.091	7.64	1.18	0.46	0.107	Y
17.	2.50	5.8	1.2	0.150	4.62	1.33	0.44	0.200	N
18.	2.53	6.1	1.4	0.140	4.94	2.10	0.44	0.294	N
19.	2.75	4.7	0.4	0.229	3.02	1.27	0.50	0.290	N
20.	2.80	6.1	1.8	0.120	5.78	1.28	0.513	0.154	N
21.	2.35	6.0	1.7	0.119	5.82	1.54	0.45	0.184	N
22.	2.39	5.0	1.0	0.153	4.52	1.63	0.49	0.250	N
23.	2.42	5.4	1.5	0.122	5.68	1.71	0.52	0.208	N
24.	2.41	4.4	0.8	0.162	4.27	1.53	0.53	0.249	N
25.	2.37	4.5	1.0	0.142	4.88	2.07	0.55	0.294	N
26.	2.50	5.8	0.9	0.179	3.88	1.08	0.38	0.193	N
27.	2.22	5.0	1.9	0.092	7.52	1.636	0.61	0.151	N
Mean ± SD (range)	2.44 ± 0.158 (2.00-2.80)	5.94 ± 1.57(3.9-10.6)	1.44± 0.49 (0.4-2.7)	0.137 ± 0.031 (0.085-0.229)	5.30± 1.23 (3.02-8.17)		0.481± 0.129 (0.21-0.82)	0.194 ±0.068 (0.070-0.299)	

TABEL 4.7 Dosage, measured serum gentamicin concentrations and and pharmacokinetic parameters of the patients receiving ODD treatment

Pt.No	Dose	Cpk	Ctr	K	t1/2	Vd		Cl	Adjustment
	mg/kg	mg/l	mg/l	hr^{-1}	hr	l	l/kg	l/hr	
1.	4.29	11.6	1.3	0.097	7.12	1.04	0.37	0.101	N
2.	4.38	8.2	0.8	0.103	6.70	1.68	0.53	0.174	N
3.	5.00	9.3	0.4	0.140	4.96	1.26	0.48	0.176	N
4.	4.39	7.3	1.0	0.089	7.79	1.28	0.62	0.113	N
5.	4.65	9.6	1.4	0.086	8.09	1.10	0.51	0.094	N
6.	4.41	8.5	0.8	0.106	6.53	1.68	0.49	0.178	N
7.	4.36	6.2	1.3	0.069	9.98	2.23	0.81	0.155	N
8.	4.49	9.9	1.0	0.102	6.80	1.10	0.45	0.112	N
9.	4.16	7.6	1.7	0.065	10.64	1.56	0.65	0.102	Y
10.	5.0	9.1	0.9	0.103	6.74	2.17	0.55	0.223	N
11.	4.44	8.5	0.9	0.100	6.94	1.17	0.52	0.117	N
12.	4.72	9.6	1.1	0.097	7.17	1.49	0.54	0.144	N
13.	5.00	8.9	0.8	0.106	6.54	2.03	0.53	0.215	N
14.	5.00	5.7	0.5	0.108	6.41	2.55	0.85	0.280	N
15.	5.00	8.0	0.6	0.116	5.95	2.01	0.58	0.235	N
16.	4.65	9.4	0.3	0.152	4.56	1.83	0.43	0.280	N
17.	5.00	8.4	1.0	0.096	7.25	1.41	0.59	0.135	N
18.	4.73	7.0	0.7	0.102	6.77	2.54	0.69	0.259	N
19.	4.81	8.9	0.4	0.138	5.03	1.32	0.51	0.182	N
20.	4.80	12.1	0.9	0.115	6.00	0.94	0.38	0.109	N
21.	4.85	9.4	0.7	0.115	6.01	1.72	0.49	0.198	N
22.	4.80	9.5	1.2	0.092	7.54	1.30	0.52	0.119	N
23.	4.92	9.5	0.4	0.141	4.92	1.51	0.47	0.210	N
24.	5.00	10.6	1.5	0.087	7.97	1.19	0.49	0.103	N
25.	4.70	7.6	0.9	0.095	7.31	1.60	0.63	0.152	N
26.	5.00	8.1	0.9	0.098	7.10	2.11	0.62	0.206	N
27.	5.00	12.4	1.0	0.111	6.19	1.08	0.38	0.128	N
Mean± SD (range)	4.73 ± 0.268 (4.167-5.00	8.92± 1.59 (5.70-12.40	0.90 ±0.35 (0.3-1.7)	0.105 ±0.020 (0.065-0.152)	6.85 ±1.36 (4.56-10.64)		0.544 ±0.115 (0.37-0.85)	0.167 ±0.057 (0.094 - 0.280)	

TABLE 4.8 Peak level in different range of the patients in the TDD and the ODD groups.

Peak level (mg/l)	Number of the patients (%)	
	TDD group	ODD group
< 5	7 (25.93)	-
<8	24 (88.89)	6 (22.22)
≥ 8	3 (11.11)	21 (77.78)
>12	-	2 (7.41)*

* 12.1 and 12.4 mg/l

TABLE 4.9 Number and percentage of the patients whose peak gentamicin serum concentrations was subtherapeutic and/or trough gentamicin serum concentration was too high.

Group	No. of subtherapeutic Patients (%)[a]	No. of over trough patients(%)[b]	Total (%)
Twice – daily group [c]	1(3.70%)	2(7.41%)	3(11.11%)
Once – daily group [d]	–	1(3.70%)	1(3.70%)

a: The meaning of subtherapeutic peak gentamicin serum concentration were < 4 μg/ml in the TDD group ,< 5 μg/ml in the ODD group.

b: The meaning of high trough gentamicin serum concentration were > 2 μg/ml in the TDD group, > 1. 5 μg/ml in the ODD group.

c: Peak serum concentration of gentamicin was 3.9 μg/ml in one patient and trough serum concentration of gentamicin in two patients were 2.3 μg/ml, and 2.7 μg/ml .

d: Trough serum concentration of gentamicin in one patients was 1.7 μg/ml.

TABLE 4.10 Comparison of the pharmacokinetic parameters between the TDD and the ODD groups.

Parameter	Mean ± SD (range) at:		p value[a]
	TDD group	ODD group	
Peak concentration (μg/ml)	5.94 ± 1.57 (3.9 –10.6)	8.92 ±1.59(5.70 – 12.40)	p<0.001
Trough concentration (μg/ml)	1.44 ± 0.49(0.4 – 2.7)	0.90 ±0.35(0.30 – 1.70)	p<0.001
Elimination rate constant (hr^{-1})	0.137 ± 0.031(0.085 – 0.229)	0.105 ±0.020(0.065 – 0.152)	p<0.001
Elimination half – life (hr)	5.30 ±1.23(3.02 – 8.17)	6.85 ± 1.36(4.56 – 10.64)	p<0.001
Volume of distribution (l/kg)	0.48 ± 0.13(0.21 – 0.82)	0.54 ± 0.12 (0.37 – 0.85)	p=0.063
Clearance of gentamicin (l/hr)	0.194 ± 0.068 (0.07 – 0.299)	0.167± 0.057(0.094 – 0.280)	p=0.115

a: P value by unpaired – t test

TABLE 4.11 Correlation between serum creatinine, creatinine clearance and clearance of gentamicin .

Equation**	Correlation coefficient (r)
Cl (l/hr) = 0.230 -0.112SCr(mg/dl)	-0.362
Cl (l/hr) = 0.134 +7.731Clcr(ml/min/1.73m^2)	0.433
Cl (l/hr) = 0.128 +0.1196Clcr(l/hr)	0.535

** Equation by Simple linear regression analysis.

Table 4.12 Correlation between postnatal age , weight , serum creatinine or creatinine clearance and clearance of gentamicin .

Equation [a]	r *	r^2 **
Cl (l/hr)= -0.0558+ 0.0118 PA^b (day) – 0.0630 SCr^b (mg/dl) + (7.6680x 10^{-5})Wt(gm)	0.8441	0.712
Cl (l/hr)= – 0.1007+ 0.0127PA^b (day)+ (3.7922x10^{-4})$Clcr^b$ (ml/min/1.73m^2) + (7.3703x10^{-5}) Wt(gm)	0.8444	0.713
Cl (l/hr) = – 0.0883 + 0.0127PA^b (day) + 0.0478 $Clcr^b$ (l/hr) + (7.0198 x10^{-5}) Wt(gm)	0.8405	0.706

* : Multiple correlation coefficient

** : r square or multiple coefficient of determination

a : Equation by multiple regression analysis

b : Obtained or calculated at the third day of gentamicin therapy

Figure 4 Linear relationship between serum creatinine (mg/dl) and clearance of gentamicin (l/hr).

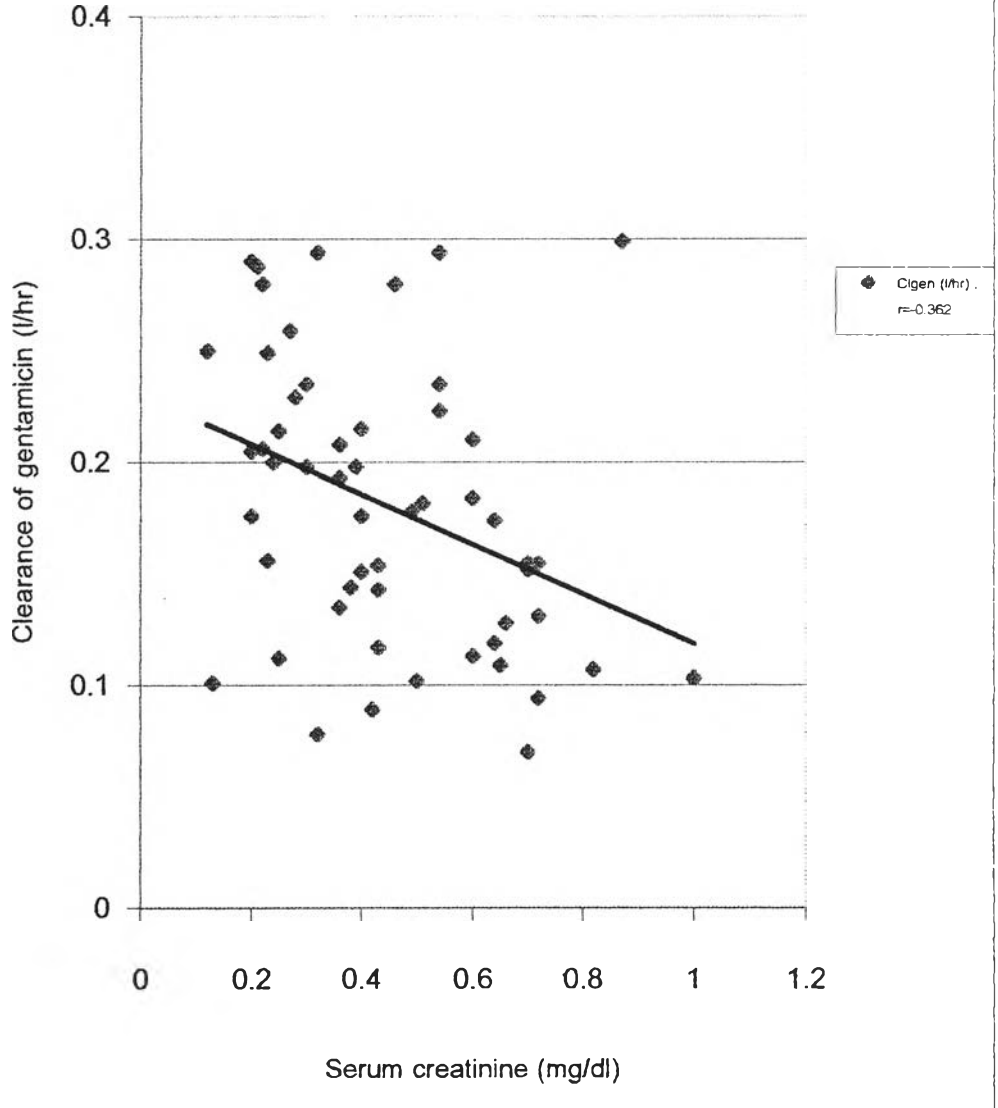


Figure 5 Linear relationship between creatinine clearance (ml/min/1.73m2) and clearance of gentamicin (l/hr).

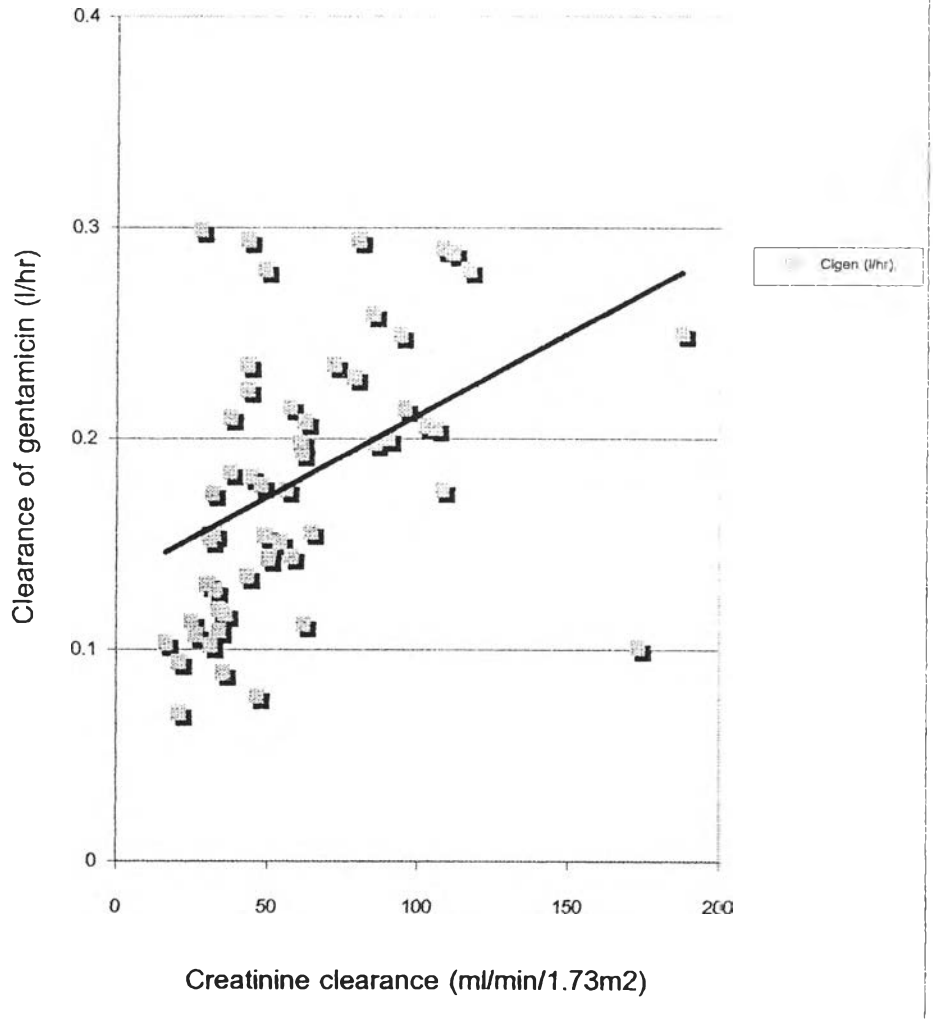
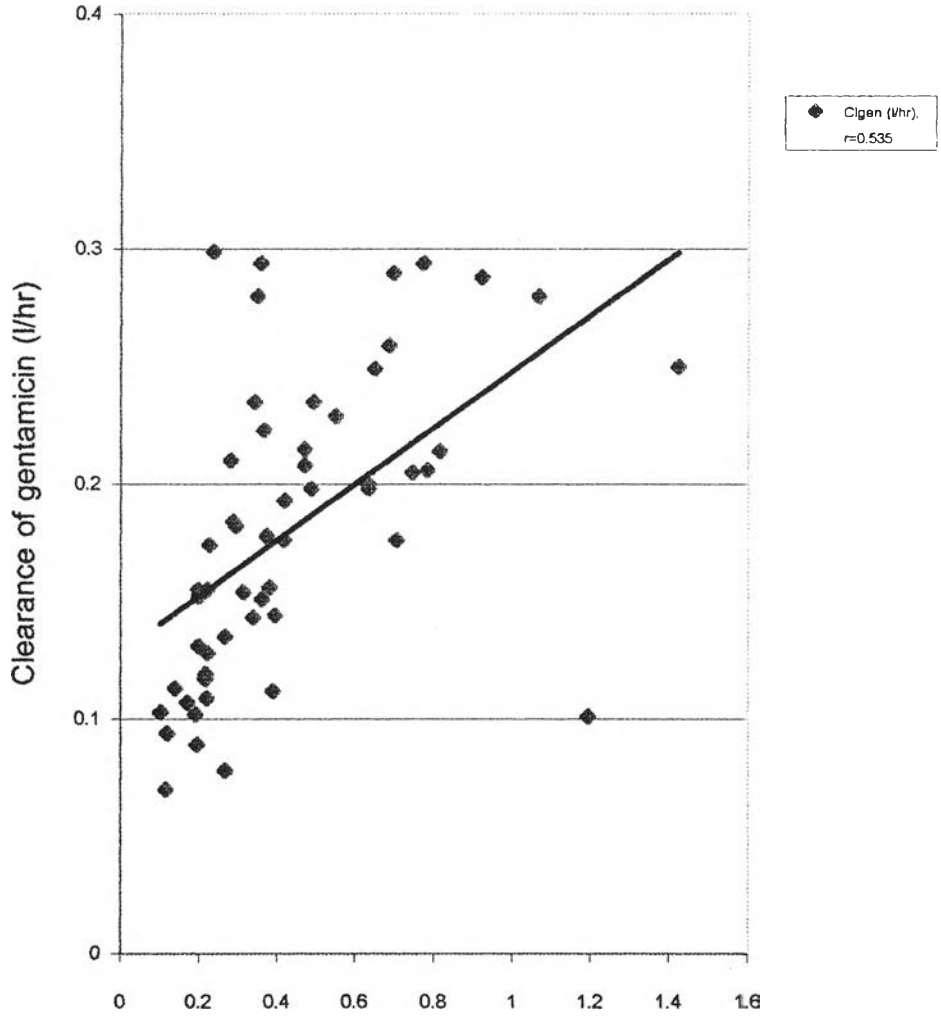


Figure 6 Linear relationship between creatinine clearance (l/hr) and clearance of gentamicin (l/hr).



3. Renal parameters

The renal parameters (e.g. serum creatinine, creatinine clearance) on the first day, third day, and discontinuous day of gentamicin therapy of the patients in the TDD and the ODD groups were shown in table 4.13 and table 4.14 respectively.

All infants in both groups had normal serum creatinine concentration during and after gentamicin treatment except for one infant in the TDD group who showed a rise in serum creatinine concentration of 1.47 mg/dl on the discontinuous day from 0.88 mg/dl on the first day of gentamicin therapy. The increment of serum creatinine concentration may be due to the effect of gentamicin interaction with indomethacin which was given 0.4 mg for 6 doses for 4 days.

The mean ± SD of serum creatinine concentration (SCr) in the TDD group on the first day of gentamicin therapy was 0.66 ± 0.23 (0.20-1.01) mg/dl on the third day was 0.41 ± 0.21(0.12-0.87) mg/dl and on the discontinuous day was 0.51± 0.25(0.20-1.47) mg/dl. The mean ± SD of serum creatinine concentration in the ODD group on the first day of gentamicin therapy was 0.73 ±0.30 (0.10-1.25) mg/dl, on the third day was 0.49±0.20(0.13-1.00)mg/dl, and on the discontinuous day was 0.52 ± 0.16 (0.19-0.76) mg /dl

Changes in serum creatinine concentration within group of the TDD or the ODD group between the first day, the third day, and the discontinuous day were analyzed by pairec- t test, and shown in table 4.15 and table 4.16 respectively. Comparison of SCr at the first day, the third day, and the discontinuous day of the patients in the TDD and the CDD groups were showed in figure 7 and figure 8 respectively. One patient (3.70%) of 27 patients in the TDD group was exclude when compared SCr between the first day, the third day, with the discontinuous day because the patient was adjusted dosing interval after the third day. Assessment by paired – t test, significant decrease in serum creatinine was observed on the third days and discontinuous day from the first day within the TDD and the ODD groups ($p< 0.05$). Significant increase in SCr was observed on the discontinuous day from the third day of gentamicin therapy in the TDD

group (p=0.012) while there was no significant increase in SCr in the ODD group (p=0.289). The similar results were observed when included and excluded the patients who had drug interaction with gentamicin. This study was not excluded the patient with furosemide because the combination of drugs was only one dose, significant of interaction is low (level 4) and the onset of interaction was delayed. The reason of the declining SCr on the third day and discontinuous day from the first day in the TDD and the ODD groups may due to the progress development in renal function of the newborn in relation to the duration of postnatal age. The renal function will rise to essentially the adult levels by the end of the first rise to essentially adult levels by the end of the first year.[81-82] Significant increase in serum creatinine concentration on the discontinuous day from the third day in the TDD group(p=0.012) while there was not significant difference in the ODD group(p=0.289).

Table 4.17 and figure 9 presented the comparison of serum creatinine concentration at the first day, third day and discontinuous day between TDD and ODD group. ANCOVA analysis were used to calculate the different of mean SCr on the third day, and discontinuous day between the TDD and the ODD groups since ANCOVA analysis reduces the effect of the first day serum creatinine concentration of the infants in both groups. There were no significant difference in SCr at the first day, third day and discontinuous day between the TDD and the ODD groups (p >0.05).

Linear relationship between the duration of gentamicin therapy and the changing of serum creatinine level at the discontinuous day from the third day of the patients in the TDD and the ODD groups were showed in figure 10 and figure 11 respectively. Correlation between the duration of gentamicin therapy and the changing of serum creatinine concentration at the discontinuous day from the third day in the TDD group was moderate correlation r = 0.612 while in the ODD there was not correlate r = 0.105 (0.00-0.20). That mean the increment of serum creatinine concentration correlated with the increment of duration of gentamicin therapy in the patient who was given twice daily dosing regimen.

Table 4.18 presented the comparison of the serum creatinine level between the third day and the discontinuous day of gentamicin therapy in the TDD and the ODD

groups. There was significant increased in serum creatinine level when using gentamicin more than eight days in the TDD group while there were no significant increased in the serum creatinine level in the ODD group. The results of the increment of serum creatinine concentration on the discontinuous day from the third day and the correlation between serum creatinine level and duration of twice daily dosage regimen might be showed that twice daily dosage regimen had an effect on renal function more than once daily dosage regimen.

TABLE 4.13 Serum creatinine ,and creatinine clearance in the TDD group.

PT. NO.	GA (weeks)	PA (day)	Duration (day)	SCr (mg/dl) day1	day3	day-off	day -off- day3	Clcr (ml/min/1.73m^2) Day1	day3	day-off
1.	40	2.0	7	0.5	0.21	0.2	-0.10	46.80	111.43	117.00
2.	40	0.50	4	0.94	0.87	0.87	0.00	25.37	27.41	27.41
3.	40	0.04	9	0.65	0.25	0.51	0.26	36.69	95.40	46.76
4.	39	0.29	4	0.70	0.30	0.30	0.00	36.64	85.50	85.50
5.	37	4.00	8	0.29	0.42	0.46	0.04	51.21	35.36	32.28
6.	36	0.17	11	0.95	0.32	0.32	0.00	15.63	46.41	46.41
7.	43	1.00	7	0.47	0.28	0.32	0.04	46.92	78.75	68.91
8.*	34	1.00	18	0.88	0.70	1.47	0.77	16.50	20.74	9.88
9.	37	1.00	9	0.55	0.40	0.48	0.08	40.91	56.25	46.88
10.	36	0.05	11	0.93	0.23	0.57	0.24	15.97	64.57	31.60
11.	42	3.00	8	0.71	0.72	0.42	-0.30	30.42	30.00	51.43
12.	35	2.00	8	1.01	0.43	0.44	0.01	21.39	50.23	49.09
13.	37	3.00	3	0.79	0.72	0.72	0.00	27.91	30.63	30.63
14.	37	4.00	10	0.37	0.30	0.34	0.04	58.38	72.00	63.53
15.	39	0.208	7	0.85	0.20	0.42	0.22	24.88	105.75	50.36
16.**	40	1.00	4	0.78	0.82	0.74	-0.08	27.69	26.34	29.19
17.	38	1.38	5	0.74	0.24	0.26	0.02	29.19	90.00	83.08
18.	40	1.00	10	0.40	0.32	0.48	0.16	64.13	80.16	53.44
19.	39	2.00	8	0.20	0.20	0.32	0.20	108.0	108.0	67.50
20.	39	1.00	7	0.38	0.43	0.33	-0.01	55.66	49.19	64.09
21.	40	0.25	9	0.81	0.60	0.45	-0.15	27.78	37.50	50.00
22.	38	0.29	11	0.57	0.12	0.50	0.38	39.47	187.50	45.00
23.	37	0.29	11	0.65	0.36	0.59	0.23	34.62	62.50	38.14
24.	37	1.00	4	0.90	0.23	0.51	0.28	24.00	93.91	42.35
25.	40	2.00	8	0.75	0.54	0.62	0.08	31.20	43.33	37.74
26.	40	4.00	9	0.43	0.36	0.61	0.25	51.28	61.25	36.15
27.	36	2.17	5	0.50	0.40	0.45	0.05	43.20	54.00	48.00
Mean± SD (range)	38.37± 2.12 (35-43)	1.43 ±1.25 (0.04-4.00)	7.96±3.16 (3-18)	0.66± 0.23 (0.2-1.01)	0.41± 0.21 (0.12-0.87)	0.51± 0.25 (0.2-1.47)	0.104± 0.198 (-0.30– 0.77)	38.22± 19.23 (15.63-108.0)	66.82± 36.30 (20.74-187.50)	50.09± 21.56 (9.88-117.0)

*: Pt. No. had drug interaction between gentamicin and indomethacin.

**: PT. No. 16 was adjusted dosing interval.

TABLE 4.14 Serum creatinine and creatinine clearance in the ODD group.

PT. NO.	GA (weeks)	PA (day)	Duration (day)	SCr (mg/dl)				Clcr (ml/min/1.73m^2)		
				day1	day3	day-off	day-off -day3	day1	day3	day-off
1.	38	0.17	3	0.14	0.13	0.01	0.37	160.71	173.08	45.00
2.	41	0.04	14	1.04	0.64	0.61	-0.03	19.47	31.64	33.20
3.	38	1.00	5	0.58	0.2	0.35	0.15	37.24	108	61.71
4.	37	0.83	7	0.53	0.60	0.57	-0.03	28.02	24.75	26.05
5.	37	1.00	10	0.58	0.72	0.63	-0.09	25.60	20.63	23.57
6.	41	2.00	7	0.91	0.49	0.53	0.04	25.71	47.76	44.15
7.	37	0.25	4	0.12	0.70	0.66	-0.04	187.5C	32.14	34.09
8.	37	0.13	5	0.76	0.25	0.50	0.25	20.41	62.04	31.02
9.	34	0.04	8	0.88	0.50	0.49	-0.01	17.63	31.02	31.65
10.	39	0.08	4	0.93	0.54	0.54	0.00	25.16	43.33	43.33
11.*	35	0.08	13	0.82	0.43	0.76	0.33	18.92	36.07	20.41
12.	38	0.46	7	1.15	0.38	0.41	0.03	19.17	58.03	53.78
13.	37	3.00	6	0.70	0.40	0.40	0.00	32.79	57.38	57.38
14.	38	5.00	3	0.10	0.46	0.46	0.00	225.0C	48.91	48.91
15.	41	0.21	5	1.2	0.54	0.51	-0.03	19.50	43.33	45.88
16.	39	0.29	11	0.86	0.22	0.42	0.20	29.83	116.59	61.07
17.	41	0.13	10	0.67	0.36	0.70	0.34	23.15	43.08	22.16
18.	40	1.00	3	0.40	0.27	0.19	-0.08	57.38	85.00	120.79
19.	41	1.00	4	0.93	0.51	0.51	0.00	24.19	44.12	44.12
20.	40	0.50	8	0.98	0.65	0.72	0.07	22.50	33.92	30.63
21.	41	1.00	7	0.89	0.39	0.57	0.18	26.80	61.15	41.84
22.	36	0.63	7	0.59	0.64	0.50	-0.14	36.61	33.75	43.20
23.	37	4.00	5	0.73	0.60	0.51	-0.09	30.82	37.50	44.12
24.	37	0.63	11	1.25	1.00	0.91	-0.09	12.94	16.17	17.77
25.	41	0.75	7	0.68	0.70	0.32	-0.38	31.76	30.86	67.50
26.	41	1.00	3	0.85	0.22	0.22	0.00	26.47	102.27	102.27
27.	36	0.21	10	0.56	0.66	0.63	-0.03	38.57	32.73	34.29
Mean ±SD (range)	38.44± 2.12(34-41)	0.96 ±1.21 (0.04-5.00)	6.93± 3.13 (3-14)	0.73± 0.30 (0.10-1.25)	0.49 ±0.20 (0.13-1.00)	0.52 ±0.16 (0.19-0.76)	0.034±0.163 (-0.38-0.37)	45.33 ±53.97 (12.94-225.00)	53.90 ± 35.22 16.17-173.08)	45.55 ±23.18 (17.77-120.79)

* : Pt.No.11 had drug interaction between gentamicin and cefuroxime.

GA = Gestation age (weeks **Day 1** = the first day of gentamicin therapy

PA = postnatal age (days) **Day 3** = the third day of gentamicin therapy

SCr = Serum creatinine concentration (mg/dl) **Day off** =discontinuous day of gentamicin therapy

Clcr = Creatinine clearance (ml/min/1.73 m^2)

TABLE 4.15 Comparison of serum creatinine concentration at the first day, third day, and discontinuous day within the TDD group.

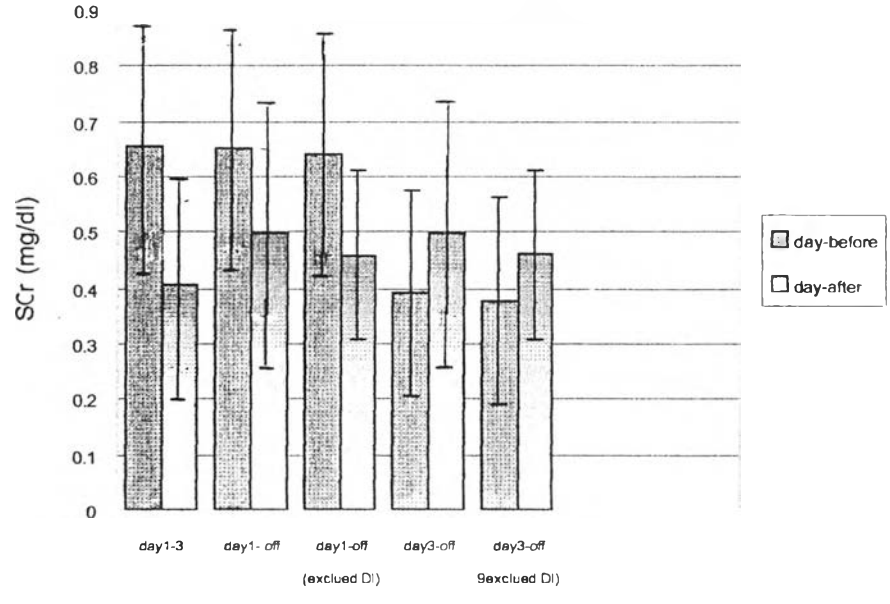
Between day	Mean ± SD (Range)	P value[a]
SCr 1 st day and 3 rd day[b]	0.656 ± 0.225 (0.20 – 1.01) and 0.406 ±0.206 (0.12 - 0.87)	P<0.001
SCr 1 st day and dis .day[c]	0.651 ± 0.228 (0.2 – 1.01) and 0.499 ±0.247 (0.20 – 1.47)	P=0.008
SCr 1 st day and dis .day[d]	0.642 ± 0.227 (0.2 – 1.01) and 0.459 ±0.151 (0.20 – 0.87)	P<0.001
SCr 3 rd day and dis .day[c]	0.390 ±0.192 (0.20 - 0.87) and 0.499 ±0.247 (0.20 – 1.47)	P=0.012
SCr 3 rd day and dis .day[d]	0.378 ±0.186 (0.12 - 0.87) and 0.460 ±0.151 (0.20 – 0.87)	P=0.015

a: P value by pair – t test. b: 27 patients were included.

c: 26 patients were included. One patient (3.70%) (Pt. No. 16) was excluded because the patient was adjusted dosage and dosing interval

d: 25 patients were included. Two patients (Pt. No. 8,16) were excluded Pt. No.8 had drug interaction between gentamicin and indomethacin after 3 days of gentamicin therapy.

Figure 7 Comparison of SCr at the first, third, and discontinuous day of the patients in the TDD group.



Significant difference in all pair.

TABLE 4.16 Comparison of serum creatinine concentration at the first day, third day, and discontinuous day within the ODD group.

Between day	Mean ± SD (Range)	P value[a]
SCr 1 st day and 3 rd day[b]	0.734 ± 0.301 (0.10 – 1.25) and 0.489 ±0.201(0.13 - 1.00)	P=0.001
SCr 1 st day and dis .day[b]	0.734 ± 0.301(0.10 – 1.25) and 0.523 ±0.158(0.19 – 0.91)	P=0.002
SCr 1 st day and dis .day[c]	0.731 ± 0.309(0.10 – 1.25) and 0.514 ±0.154(0.19 – 0.91)	P=0.002
SCr 3 rd day and dis .day[b]	0.489 ±0.201 (0.13 - 1.00) and 0.523 ±0.158(0.19 – 0.91)	P=0.289
SCr 3 rd day and dis .day[c]	0.491 ±0.204(0.13 - 1.00) and 0.514 ±0.154(0.19 – 0.91)	P=0.464

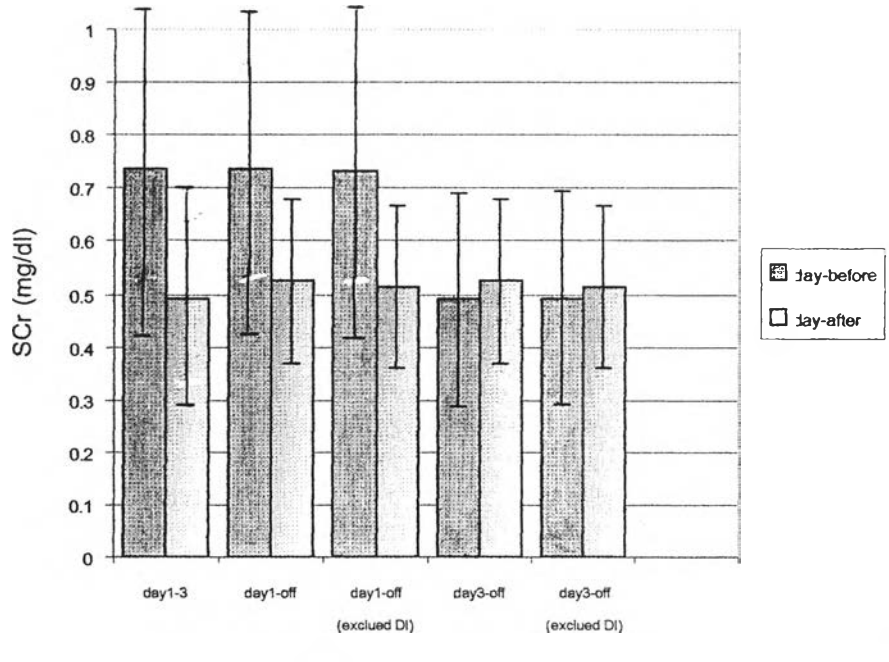
a: P value by paired t test.

b: 27 patients were included.

c: One patient (3.70%) (pt.no.11) was excluded because the patient had drug interaction between gentamicin and cefuroxime after 8 days of gentamicin therapy.

Significant difference between day1–3 and day 1–off.

Figure 8 Comparison of SCr at the first, third, and discontinuous day of the patients in the ODD group.



Significant difference between day 1 – day 3 and day 1 – day off

TABLE 4.17 Comparison of serum creatinine concentration at the first day, third day, and discontinuous day between the TDD and the ODD groups.

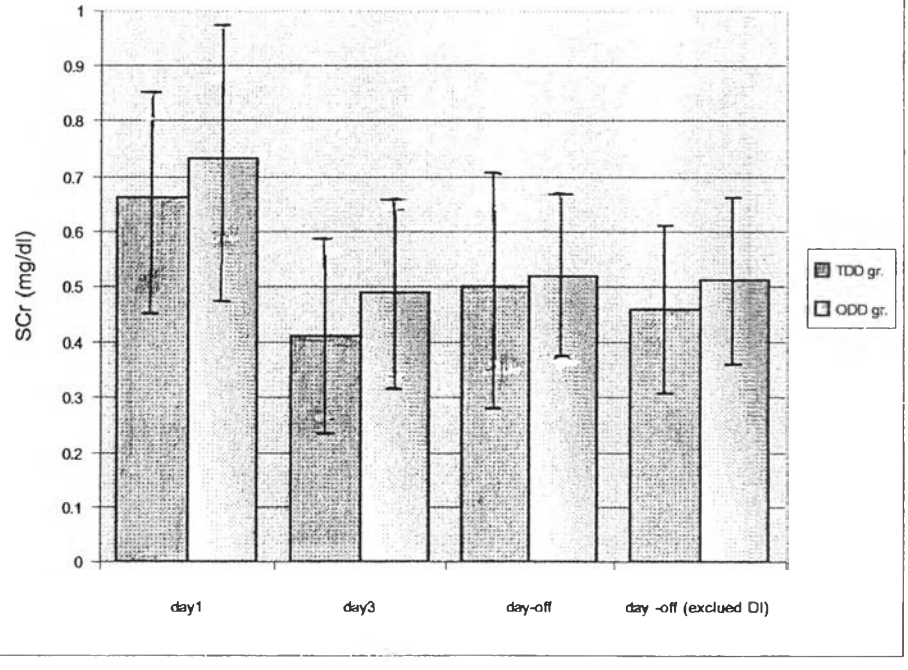
Parameter	Mean ± SD (range) at:		P value
	TDD group	ODD group	
SCr at 1st day	0.66± 0.23 (0.20 – 1.01)	0.73± 0.30 (0.10 – 1.25)	P=0.292[a]
SCr at 3rd day	0.41± 0.21 (0.12 – 0 .87)	0.49± 0.20 (0.13 – 1.00)	P=0.229[b]
SCr at discontinuous day[c]	0.50± 0.25(0.20 – 1.47)	0.52± 0.16(0.19 – 0.91)	P=0.904[b]
SCr at discontinuous day[d]	0.46 ±0.15 (0.20 – 0.87)	0.51 ±0.15(0.19 – 0.91)	P=0.334[b]

a: P value by unpaired – t test. b: P value by ANCOVA analysis

c: One patient (pt. No.16) in the TDD group was excluded because the patient was adjusted dosage and dosing interval.

d: Two patients (pt. No.16,8) in the TDD group were excluded, pt. no. 8 had drug interaction between gentamicin and indomethacin after 3 days of gentamicin therapy and one patient (pt.no.11) was excluded because the patient had drug interaction between gentamicin and cefuroxime after 8 days of gentamicin therapy.

Figure 9 Comparison of SCr at the first, third, and discontinuous day between the TDD and the ODD groups.



There were no significant difference in all pairs.

Figure10 Linear relationship between the duration of gentamicir therapy and the changing of serum creatinine level of the patients in the TDD group.

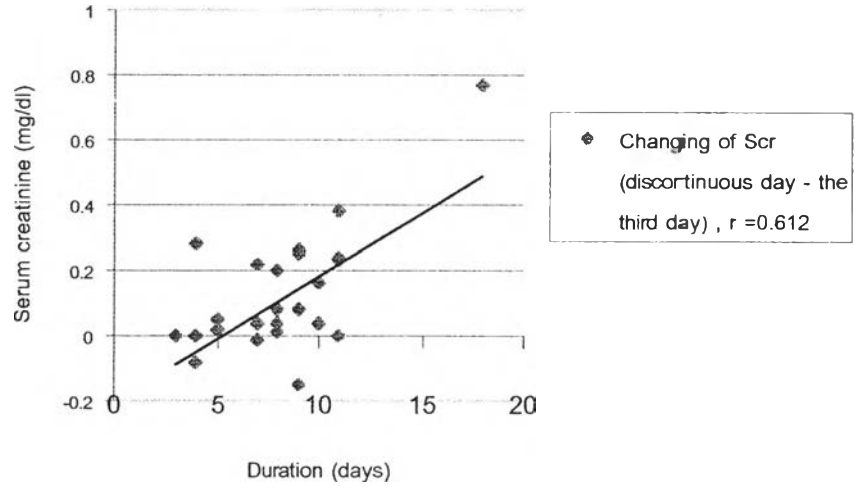


Figure11 Linear relationship between the duration of gentamicin therapy and the changing of serum creatinine level of the patients in the ODD group.

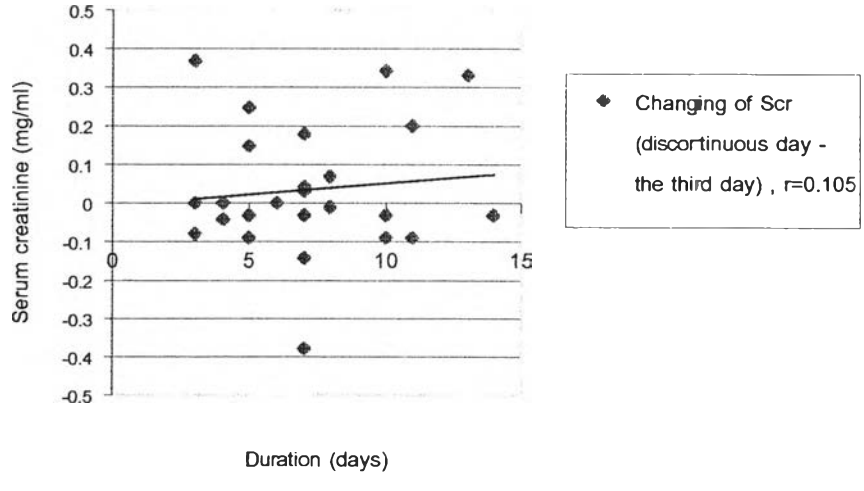


Table 4.18 Serum creatinine concentration between the third day and the discontinuous day of gentamicin therapy in the TDD and the ODD groups.

Duration (day)	N (%)	Mean ± SD of SCr (mg/dl)		P value
		Day 3	Day – off	
TDD group [a]				
4 – 5	5(19.23)	0.41± 0.269 (0.23-0.87)	0.48± 0.24 (0.26-0.87)	0.259
6 – 8	9(34.62)	0.38± 0.18 (0.20-0.72)	0.39± 0.12 (0.20-0.62)	0.826
≥ 9	11(42.31)	0.36± 0.16(0.12-0.70)	0.58± 0.31 (0.32-1.47)	0.015
≥ 9 **	10(40.00)	0.33± 0.13(0.12-0.60)	0.49 ± 0.10 (0 32 – 0.59)	0.014
ODD group [b]				
4 – 5	7(25.93)	0.48± 0.18 (0.20-0.70)	0.51± 0.09 (0.35-0.66)	0.481
6 – 8	9(33.33)	0.53± 0.12(0.38-0.70)	0.50 ±0.12 (0.32-0.72)	0.625
≥ 9	7(25.93)	0.58 ±0.26 (0.22-1.00)	0.67± 0.15 (0.42-0.91)	0.266
≥ 9 **	6(23.08)	0.60± 0.28 (0.36-1.00)	0.65± 0.16 (0.42-0.91)	0.522

a: 26 patients were included. One patient (No.16) was excluded the patient was adjust dosing interval.

b: 27 patients in ODD were included.

**: Excluded one patient in TDD and ODD because the patient had drug interaction of gentamicin with indomethacin and ceruroxime respectively.

4. Drug interaction of gentamicin

Drug interaction between gentamicin and other concurrently used drug were presented in table 4.19. Drug interactions were found in three patients in the TDD group and three patients in the ODD group. In the TDD group, the interacting drug was indomethacin in one patient and furosemide in two patients. In the ODD group, the interacting drug was cefotaxime in one patient and furosemide in two patients. Of these six cases, only one infant in the TDD group who was given indomethacin 0.4 mg 6 dose for 4 days concurrently with gentamicin presented nephrotoxicity (nephrotoxicity was defined as a rise in serum creatinine more than 0.5 mg/dl from the normal value during the period of gentamicin therapy).[19] An infant had gestation age of 34 weeks and postnatal age of 1 day, indometacin was started 5 days after gentamicin therapy. This infant showed a rise in serum creatinine concentration of 1.47 mg/dl on discontinuous day from 0.88 mg/dl on the first day of gentamicin therapy. There were two reasons that might associate with this effect.

The first reason was the effect of drug interaction between indomethacin and gentamicin in this premature infant (gestational age less than 37 weeks).[83] This interaction had significance level 2, and moderate severity. The results of this effect are elevation of plasma aminoglycoside concentration in preterm infants, and accumulation of aminoglycoside by reducing GFR.[39,66] Reduce GFR of NSAIDs is an imbalance of vasoconstrictive and vasodilatory influence on the kidney. The vasodilator activity includes renal cortical and medullary synthesis of prostacyclin (PGI_2) and prostaglandin E_2 NSAID inhibits the compensatory synthesis of prostaglandins by preventing cycloxygenation of arachidonic acid.[84] Both human (Zarfin Y, et al 1985) and animal studies (Gagliardi L.1985) support an interaction between aminoglycosides and indomethacin.[66] In this study the infant had Cpk = 8.7 mg/l and Ctr = 1.9 ml/l on the 3 th day of gentamicin therapy 2 mg/kg which could be considered as normal high level before indomethacin was given. Therefore there was a great tending that could be increased to renal toxicity level after

indomethacin was concurrently administer with gentamicin. However serum gentamicin concentration had not been measured after the interaction.

The second reason was the effect of the patient's disease status. This infant was a diagnosed as having patent ductus arteriosus (PDA) . Fluid restriction was one of the treatment options for PDA [85]. Since this infant was restricted fluid, the volume of distribution in this infant was reduced (pt No. 8 in the TDD group had Vc = 0.24 L/kg, which was much lower than the mean (4.807 $\pm$ 0.129 L/kg)).

When assessed ADR by Naranjo' s algorithm for estimating the probability of adverse drug reaction, the score (maximum score = 10) was 4 which indicated that the adverse reaction was probable caused by gentamicin (see appendix III).[86]

Table4.19 Drug interaction of gentamicin that may increase nephrotoxicity or ototoxicity of the patients in the TDD and the ODD groups.

Group	Precipitant Drug	Significance Level	Initiation of Precipitant	Dose/ Duration	No.(%)
TDD Group					
	Indomethacin	**2**			**1(3.70)**
	- 0.4 mg		5 days after started gentamicin therapy	6 coses/4 days	1(3.70)
	Furosemide	**4**			**2(7.41)**
	- 2 mg		5 days after started gentamicin therapy	1 dose/1 day	1(3.70)
	- 3 mg		in the same day	1 dose/1 day	1(3.70)
Total					**3(11.11)**
ODD group					
	Cefotaxime	**2**			**1(3.7)**
	- 7 mg q 8		8 days after started gentamicin therapy	16 dose/1 day	1(3.7)
	Furosemide	**4**			**2(7.4)**
	- 2 mg		1 day before gentamicin therapy	1 dose/1 day	1(3.7)
	- 3 mg		8 days after started gentamicin therapay	1 dose/1 day	1(3.7)
Total					**3(11.11)**

5. Efficacy

Steady state gentamicin peak serum concentration, duration, and efficacy response of gentamicin therapy in the patients with different diseases of gentamicin indication in the TDD and the ODD groups were listed in table 4.20 and table 4.21.

One patient in the TDD group was excluded since the dosing interval was adjusted after 3 days of gentamicin therapy. In the ODD group one patient was excluded because the culture of this patient showed methicillin resistant *staph. aureus* (MRSA) which naturally resistant to gentamicin, therefore the antibiotic was changed by the physician. Twenty–six patients (100%) of the patients in the TDD and the ODD groups showed the improved outcome. Even though the mean ± SD of ODD treatment (6.93 ±3.13 days) appear to be shorter than TDD treatment (7.96 ±3.16 days) these mean duration of gentamicin treatments were not statistically significant different between the TDD and the ODD groups ($P>0.05$) in except for the NEC which the duration was significantly shorter different in the ODD group than in the TDD group. However, the duration of treatment in the ODD group showed tendency to be shorter than the TDD group for most disease of gentamicin indications such as in patients with PROM and PROM with sepsis, MAS and pneumonia.

Several clinical signs of the patients were monitored to indicate efficacy responses, i.e. temperature, blood culture, white blood cell count, and other essential clinical symptoms point to improvement of the disease. Temperature and white blood cell count of the patients in the TDD and the ODD groups were showed in appendix IV. Diagnosis, evidence, and assessment of the patients in the TDD and the ODD groups were shown in table 1 and table 2 in appendix V respectively. Most of the patients had normal temperature (36.0 – 37.8 °C) at the first day before starting gentamicin therapy and throughout the course of treatment. Two patients from the TDD group and three patients from the ODD group whose temperature were not in the normal range before gentamicin therapy showed favorable signs after the therapy that is four patients whose temperature were higher than normal range had been dropped to normal and one

patient whose temperature was lower than normal range had been increased to normal within the third day of gentamicin therapy.

Most of the patients in both groups also showed normal white blood cell count (5,000 – 25,000 x 10^3 cell/cm^3) before gentamicin therapy. Six patients from the TDD group and three patients from the ODD group whose WBC were not in the normal range before gentamicin therapy showed favorable signs after the therapy that is five patients in the TDD group and two patients in the ODD group which their WBC were higher than normal range had been dropped to normal and one patient each in the TDD group and the ODD group whose WBC were lower than normal range had been increased to normal at the discontinuous day of therapy. The mean ± SD of WBC between the first day and discontinuous day within the TDD group and the ODD group were decreased significantly. In neonates, the declining of WBC especially, after the third day of life are naturally [91,92] therefore the significant decrease of WBC might not presented the improvement by treatment.

One patient in the TDD group had hemoculture positive with gram positive cocci (*S. aureus*) that no growth at the end of gentamicin therapy.

TABLE 4.20 Indication, steady state gentamicin peak serum concentration, duration and efficacy response of the patient in the TDD group.

Pt.No.	Indication	Peak level (mg//)	Duration (day)	Efficacy
1.	PROM >24 hrs,Sepsis	5.5	7	Y
2.	Sepsis	4.8	4	Y
3.	Pneumonia	6.3	9	Y
4.	PROM >24 hrs ,Sepsis	5.1	4	Y
5.	NEC	9.2	8	Y
6.	Sepsis, RD	10.6	11	Y
7.	NEC	4.1	7	Y
8.	Sepsis, Pneumonia	8.7	18	Y
9.	PROM 19 hrs, Sepsis	6.7	9	Y
10.*	PROM >24 hrs	3.9	11	Y
11.	Pneumonia	7.5	8	Y
12.*	PROM >24 hrs	6.2	8	Y
13.	Clinical sepsis	5.8	3	Y
14.	Pneumonia	4.5	10	Y
15.	MAS	5.6	7	Y
16.*	MAS, Pneumonia	7.0	4	**
17.	RD	5.8	5	Y
18.	MAS	6.1	10	Y
19.	NEC	4.7	8	Y
20.	NEC	6.1	7	Y
21.	PROM >24 hrs	6.0	9	Y
22.	Sepsis, Pneumonia	5.0	11	Y
23.	Pneumonia	5.4	11	Y
24.	RD	4.4	4	Y
25.	Pneumonia	4.5	8	Y
26.	Pneumonia	5.8	9	Y
27.	Sepsis	5.0	5	Y
Mean ± SD (range)		5.94 ±1.57(3.9-10.6)	7.96 ±3.16(3-18)	

** One patient in the TDD groups was excluded since the patient was adjusted dosing interval after 3 days of gentamicin therapy.

TABLE 4.21 Indication, steady state gentamicin peak serum concentration, duration and efficacy response of the patient in the ODD group.

Pt.No.	Indication	Peak level (mg//)	Duration (day)	Efficacy
1.	Sepsis, Pneumonia	11.6	3	-**
2.	MAS	8.2	14	Y
3.	NEC	9.3	5	Y
4	Sepsis, Pneumonia	7.3	7	Y
5	Sepsis	9.6	10	Y
6.	PROM >24 hrs	8.5	7	Y
7.	PROM >24 hrs	6.2	4	Y
8.	RD, TTNB	9.9	5	Y
9.	PROM >24 hrs	7.6	8	Y
10.*	RD	9.1	4	Y
11.	RD	8.5	13	Y
12.*	MAS	9.6	7	Y
13	NEC	8.9	6	Y
14	Omphalitis	5.7	3	Y
15.	MAS	8.0	5	Y
16.*	MAS	9.4	11	Y
17.	PROM >24 hrs	8.4	10	Y
18.	RD, TTNB	7.0	3	Y
19.	MAS	8.9	4	Y
20.	MAS	12.1	8	Y
21.	Pneumonia	9.4	7	Y
22.	Sepsis	9.5	7	Y
23.	NEC	9.5	5	Y
24.	Sepsis	10.6	11	Y
25.	MAS	7.6	7	Y
26.	RD, TTNB	8.1	3	Y
27.	Pneumonia	12.4	10	Y
Mean ± SD (range)		8.92 ±1.59(5.70-12.40)	6.93±3.13 (3-14)	

** One patient in the ODD group was excluded since the patient was changed antibiotic due to the culture showed MRSA.

Table 4.22 Steady state gentamicin peak serum concentration, duration and efficacy response in different disease of the patient in the TDD and the ODD groups.

Indication	No. Pt. (%)*		Mean±SD of Peak con.(μg/ml)			Mean ±SD of duration(day)			No. Pt. with favorable Response(%)	
	TDD	ODD	TDD	ODD	p	TDD	ODD	p	TDD	ODD
PROM and PROM with Sepsis	6	4	5.57 ±.99	7.68± 1.06	0.012	8.0± 2.37	7.25± 2.5	0.644	6	4
Sepsis and Sepsis with RD	4	3	6.55± 2.73	9.9± 0.61	0.097	5.75± 3.59	9.3± 2.08	0.188	4	3
Pneumonia	6	2	5.67± 1.15	10.90± 2.12	0.003	9.17± 1.17	8.50± 2.12	0.574	6	2
Sepsis with Pneumonia	2	1	6.80± 2.62	7.3	-	14.50 ±4.95	7	-	2	1
MAS	2	7	5.85± 0.354	9.11± 1.51	0.023	8.50± 2.12	8.0± 3.46	0.856	2	7
NEC	4	3	6.03± 2.28	9.23± 0.31	0.064	7.5± 0.58	5.33± 0.58	0.004	4	3
RD	2	2	5.1± 0.99	8.80± 0.42	0.08	4.50± 0.71	8.50± 0.63	-	2	2
RD with TTNB	-	3	-	8.33± 1.46	-		3.67± 1.15	-	-	3

Figure 12 Comparison of mean steady state peak level of gentamicin between the TDD and the ODD groups.

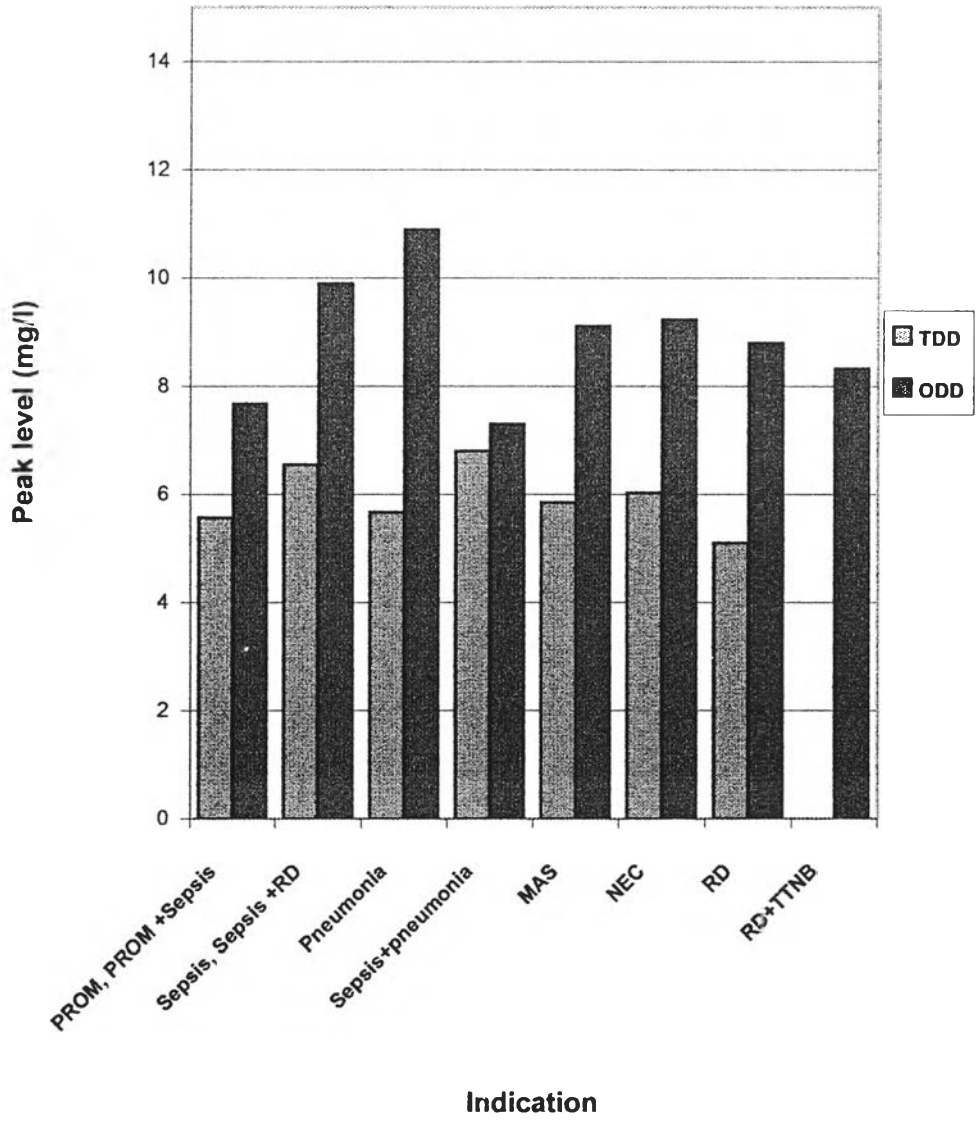


Figure 13 Comparison of the mean of duration of gentamicin therapy between the TDD and the ODD groups.