CHAPTER IV

RESULT AND DISCUSSION

1. Theophylline Therapeutic Drug Monitoring

Thirty three preterm infants admitted at Queen Sirikit National Institute of Child Health and met the criteria were studied. Table 3 showed the patients demographic data., ie., sex, gestation age, apgar score, indication for theophylline treatment, age and weight at the beginning of theophylline treatment and the major diagnosis during theophylline therapy.

Aminophylline which was theophylline salt was used for intravenous administration. Aminophylline dosage regimen used in this study was the traditional dosage regimen used at Queen Sirikit National Institute of Child Health. Table 4 showed aminophylline dosage regimen, theophylline serum concentration after loading dose and during steady state of all patients and factors that effected theophylline pharmacokinetics. Mean aminophylline loading dose was 5.63 ± 0.86 mg/kg and mean aminophylline maintenance dose was 3.01 ± 1.16 mg/kg/day. Theophylline serum concentrations were determined at 6th and 12th hour after loading dose and during steady state. The two non-steady state theophylline serum concentrations were used to predict for the serum concentration during steady state. The maintenance dose of some patients might required adjustment if the predicted steady state theophylline serum concentration was subtherapeutic level with inadequate clinical response or the predicted steady state theophylline serum concentration was overtherapeutic level. However, the adjustment of aminophylline maintenance dose was based on the final decision of the physician. In this study, the first theophylline serum concentration was obtained at 6.02 ± 1.38 hours and the second concentration was obtained at 12.27 ± 0.74 hours after the initiation of aminophylline treatment. The mean time between the first and the second theophylline serum concentration was 6.24 ± 1.67 hours. The third theophylline serum concentration was obtained at trough during steady state.

The maintenance dose of eight patients (24.24%) were adjusted before the steady state serum concentrations were determined, because the predicted steady state theophylline serum concentrations were subtherapeutic level and clinical response was inadequate in 5 patients and the predicted steady state theophylline serum concentrations were overtherapeutic level in 3 patients. One of the 3 patients whose predicted theophylline serum concentration were overtherapeutic level showed rapid heart rate during the

third day after starting the traditional maintenance dose. The heart rate in this patient was decreased to normal when the maintenance dose was adjusted (Table 5).

Table 6 showed percentage of the patients whose theophylline serum concentration after loading dose and during steady state were within, under or over therapeutic range. The data obtained indicated that the traditional aminophylline dosage regimen used at Queen Sirikit National Institute of Child Health resulted in theophylline serum concentrations which were lower than the recommended therapeutic range in most patients either after loading dose or after maintenance dose when steady state was reached.

At 6 hours after traditional loading dose, 66.67% of the patients had their theophylline serum concentrations in subtherapeutic level and increased to 69.70% at 12 hours after loading dose before initiation of the maintenance dose. Appropriate loading dose should resulted in theophylline serum concentration which was within the therapeutic level until the maintenance dose was given, that is theophylline serum concentration should be maintained to equal to or more than 6 mcg/ml before starting the maintenance dose. The result obtained from the step-wise multiple regression analysis revealed the correlation between postnatal age (PNA), the loading dose and theophylline serum concentration at 12th hour after loading dose to be as follow :

$$C_{LD12} = 1.11LD - 0.69PNA - 0.84 \ , \ (\ r = 0.65 \ , \ p = 0.001)$$

C_{LD12} was theophylline serum concentration at 12th hour after loading dose (mcg/ml) , LD was aminophylline loading dose (mg/kg) , PNA was age of the patient at the beginning of theophylline therapy (weeks). If the target theophylline serum concentration at 12th hour was 6 mcg/ml, the aminophylline loading dose could be suggested in correspond with PNA as :

$$LD = 6.16 + 0.62PNA$$

. The age of most preterm infants with apnea who used the drug was during the first 2 weeks after birth. The recommended aminophylline loading dose should be about 6.5 mg/kg for patients used the drug during the first week of life (the PNA was taken as 0.5 week) and about 7.0 mg/kg for the patients used the drug during the second week of life (the PNA was taken as 1.5 weeks). This recommended aminophylline loading dose was closed to the loading dose recommended by Aranda et al (1976) which studied in the apneic premature newborns 3 to 15 days of age. The aminophylline loading dose recommended by Aranda et al was 6.9 mg/kg in order to give peak theophylline serum concentration approximately 8 mcg/ml. In clinical practice, the maintenance dose usually is given 8 to 12 hours after the loading dose, if this

recommended aminophylline maintenance dose is given 8 hours after the loading dose, the theophylline serum concentration before starting the maintenance dose will be approximately 6.5 mcg/ml. However, the loading dose should be adjusted when the patients have factors that could affect on theophylline pharmacokinetics, such as, severe birth asphysia or the patients received continuous furosemide before the loading dose was given. These factors might lead to higher theophylline serum concentration, resulted in acute adverse reaction in the patients when the loading dose was not adjusted.

The aminophylline maintenance dose used in preterm infants at Queen Sirikit Nation Institute of Child Health was within the dose range recommended by FDA (Gillman and Gal, 1986) and Aranda et al (1992). However, the mean maintenance dose used in this study was at the low end of the range (Aminophylline 3.01 mg/kg/day : Theophylline base 2.41 mg/kg/day). Theophylline serum concentration of 66.67% of the patients was in the subtherapeutic range, 27.27% was within therapeutic range and 6.06% was overtherapeutic range when the steady state was reached. The correlation between the trough steady state theophylline serum concentration , age at the beginning of theophylline treatment and aminophylline maintenance dose was as equation :

$$C_t = 1.49MD - 1.36PNA + 2.79 \text{ , } (\text{ } r = 0.58 \text{ , } p = 0.001 \text{)}$$

C_t was the trough steady state theophylline serum concentration (mcg/ml) , MD was aminophylline maintenance dose (mg/kg/day) , PNA was age at the beginning of theophylline treatment (weeks).

If the target level during steady state was kept at 8 mcg/ml, the maintenance dose could be calculated based on postnatal age of the patient to produce this target level by the equation :

$$\text{Maintenance dose (mg/kg/day)} = 3.50 + (0.91 \times PNA \text{ in wks})$$

Several studies have evaluated theophylline pharmacokinetics in preterm infants with apnea and published the equation for calculating the maintenance dose of theophylline to produce the target steady state serum concentration of approximately 8 mcg/ml.

Hendeles equation have been evaluated along with the equations suggested by Nassif et al and Hatzopoulos et al in the year of 1993 by Hogue and Phelps and they concluded that Hendeles equation was preferred for treatment of apnea and bradycardia in the preterm infants. However, Bhatt-Mehta et al published their equation based on gestation age and postnatal age in the year of 1995. They evaluated their

equation in prospective study and found that their equation resulted in the steady state serum concentrations which were within the target level in 74% of the patients (Bhatt-Mehta et al, 1996).

The published equations together with the recommended equation of this study were used to determine the recommended maintenance dose for each patients. The predicted steady state theophylline serum concentration was then calculated for each patient based on the observed theophylline clearance dunng steady state and using equation 6. The published equations evaluated were as follow :

1. FDA : Preterm infants 40 weeks postconception age (PCA) or younger

Maintenance dose (mg/kg/day) = 2.5

2. Hendeles equation (Hendeles et al, 1986) :

Maintenance dose (mg/kg/day) = (0.2×PNA in wks) + 5

3. Bhatt-Mehta equation (Bhatt-Mehta et al, 1995) :

Gestation age 27 - 30 weeks

Maintenance dose (mg/kg/day) = 5.81 – (0.02×PNA in wks)

Gestation age 31 – 34 weeks

Maintenance dose (mg/kg/day) = 4.82 + (0.28×PNA in wks)

** Maintenance dose : Aminophylline base

Table 7 showed the baseline data of the patient, the maintenance dose recommended by each equations and their corresponding predicted steady state theophylline serum concentration, table 8 showed percentage of the predicted steady state theophylline serum concentration corresponded to the maintenance dose recommended by different equations which was within subtherapeutic, therapeutic and overtherapeutic range and figure 2 showed scatterplot of calculated theophylline serum concentration versus aminophylline recommended dose for FDA, Hendeles, Bhatt-Mehta and new equations.

The results obtained demonstrated that the maintenance dose recommended by FDA produced the predicted steady state serum concentration which was subtherapeutic in most patients (63.16%) while the maintenance dose recommended by Hendeles and Bhatt-Mehta resulted in predicted steady state theophylline concentration which was higher than 6 mcg/ml in most patients. However, approximately 40% of

the predicted steady state theophylline serum concentration resulted from Hendeles and Bhatt-Mehta equations was higher than the recommended therapeutic range. For the recommended equation from this study, 57.90% of the predicted steady state theophylline serum concentration was in the therapeutic range, approximately 20% of the predicted steady state theophylline serum concentration was subtherpeutic and approximately 20% of the predicted steady state theophylline serum concentration was higher than therapeutic range. Among the different equations, the recommended equation from this study was the best equation for calculating the optimal theophylline maintenance dose used in Thai preterm infants with apnea or bradycardia. Hendeles and Bhatt-Mehta equation might be the better equations for the infant with brochopulmonary dysplasia (BPD) or asthma who needs higher therapeutic range (10 – 20 mcg/ml). From this study, approximately 80% of the predicted steady state theophylline serum concentration resulted from the maintenance dose recommended by Hendeles and Bhatt-Mehta was within 6-20 mcg/ml. However, the reason might due in part to the source of data used which was taken from our study that our equation was preferred when compared to other published equations. Consequently, this equation should be evaluated in prospective study and should be performed in the larger group of patients. Nevertheless, in clinical practice, the recommended theophylline maintenance dose (aminophylline base) from our study should be about 4.0 mg/kg/day for the patients received the drug during the first week of life (the PNA was taken as 0.5 week) and about 4.75 mg/kg/day for the patients received the drug during the second week of life (the PNA was taken as 1.5 weeks). For the patients who are older than 2 weeks of age, the recommended maintenance dose should be 2 mg/kg every 8 hours. However, theophylline serum concentration monitoring combined with clinical response monitoring should be performed for appropriate treatment in the patients.

Table 3 : Patients Demographic Data

no.	sex	GA	apgar Score		Indication for	Age[1]	Weight[1]	Major diagnosis during theophylline
		(weeks)	1 min	5 min	Theophylline	(days)	(g)	therapy
1	Female	33	4	7	Apnea	2	1,460	RDS, Hyperbilirubinemia, Pneumonia
2	Female	33	6	10	Apnea	2	1,560	Hyperbilirubinemia, NEC, Polycythemia
3	Female	30	9	10	Apnea	3	1,310	Hyperbilirubinemia, Pneumonia, NEC
4	Male	29	9	10	Adjunct to wean	7	1,200	RDS, Hyperbilirubinemia, Pneumonia
5	Female	34	8	10	Apnea	27	1,500	Hyperbilirubinemia, Pneumonia, Diarrhea
6	Female	34	8	10	Apnea	6	1,630	RDS, Hyperbilirubiemia, GI bleeding R/O NEC, RUL atelectasis
7	Female	31	6	9	Apnea	4	1,160	RDS, Hyperbilirubinemia, Pneumonia, IVH grade I
8	Female	33	8	9	Apnea	3	1,540	RDS, Hyperbilirubinemia, R/O NEC
9	Male	32	9	10	Apnea	3	1,620	RDS, Hyperbilirubinemia, AOP

Continued

no.	sex	GA (weeks)	apgar score		Indication for Theophylline	Age[1] (days)	Weight[1] (g)	Major diagnosis during theophylline therapy
			1 min	5 min				
10	Male	32	**BBA	-	Apnea	4	1,220	RDS, Hyperbilirubinemia, AOP
11	Female	30 (SGA)	4	9	Adjunct to wean	2	1,200	RDS, Hyperbilirubinemia, AOP
12	Female	29	5	6	Apnea	2	1,600	RDS, Hyperbilirubinemia, AOP
13	Male	31	9	10	Adjunct to wean	7	1,450	RDS, Pneumonia, RLL atelectasis
14	Female	32	6	10	Apnea	6	1,400	RDS, AOP
15	Male	30	9	10	Apnea	7	1,350	RDS, Pyoderma
16	Male	32	10	10	Apnea	4	1,780	Hyperbilirubinemia, Hepatosplenomegaly R/O congenital infection
17	Male	28	6	9	Adjunct to wean	3	975	RDS, Hyperbilirubinemia, Pneumonia
18	Male	31	9	10	Apnea	16	1,450	Sepsis, R/O NEC, IVH
19	Female	28	1	3	Adjunct to wean	10	1,040	RDS, Hyperbilirubinemia, PDA

Continued

no.	sex	GA (weeks)	apgar score		Indication for Theophylline	Age[1] (days)	Weight[1] (g)	Major diagnosis during theophylline therapy
			1 min	5 min				
20	Male	28	4	5	Adjunct to wean	5	950	RDS, Hyperbilirubinemia
21	Male	32	9	10	Adjunct to wean	8	2,000	RDS, Hyperbilirubinemia
22	Male	33	0	7	Adjunct to wean	5	1,720	RDS, Brain death
23	Female	28	6	8	Adjunct to wean	4	800	RDS, Hyperbilirubinemia, Polycythemia
24	Male	27	3	4	Adjunct to wean	2	1,090	RDS, Hyperbilirubinemia
25	Male	30 (SGA)	9	10	Adjunct to wean	5	960	RDS, Hyperbilirubinemia, Pneumonia
26	Male	33	8	10	Apnea	7	1,750	RDS, AOP
27	Female	32	9	10	Adjunct to wean	5	1,430	Hyperbilirubinemia, Sepsis with minigitis
28	Female	35	9	10	Adjunct to wean	3	2,000	RDS, Hyperbilirubinemia
29	Male	33	9	10	Apnea	3	1,650	Hyperbilirubinemia, AOP
30	Male	33	9	10	Apnea	2	1,520	RDS, Hyperbilirubinemia, AOP

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| no. | sex | GA | apgar score | | Indication for | Age[1] | Weight[1] | Major diagnosis during theophylline |
		(weeks)	1 min	5 min	Theophylline	(days)	(g)	therapy
31	Male	32	7	9	Adjunct to wean	7	1,800	RDS, Hyperbilirubinemia
32	Female	32 (SGA)	9	10	Adjunct to wean	8	880	RDS, Hyperbilirubinemia
33	Female	32	9	10	Apnea	2	1,590	Hyperbilirubinemia, Septicemia
X±SD	Male=17	31.27 ± 2.04	7.06 ±	8.91 ± 1.92*	Apnea = 18	5.58 ± 4.84	1,411.67 ±	
	Female=16		2.58*		Adjunct to wean = 15		315.10	
range		27 - 34	0 - 10	3 - 10		2 - 27	800-2,000	

[1] At the beginning of theophylline therapy

GA = Gestation age (weeks) , SGA = Small gestation age

**BBA : Born before arrival

* n = 32 , 1 case was not known apgar score.

Table 4 : The data of theophylline serum concentrations in all patients

Pt. no	Loading dose (mg/kg)	Theophylline serum conc. after loading dose (mcg/ml)		Maintenance dose (mg/kg/day)	Theophylline serum conc. during steady state[c] (mcg/ml)	Factors that affected on theophylline pharmacokinetics
		6th hour	12th hour			
1[a]*	4.79	4.06	3.29	(1) 1.92	-.	-
				(2) 2.11	4.55	-
2[a]*	5.13	5.56	4.28	(1) 1.92	-	-
				(2) 2.12	7.44	-
3[a]	6.21	6.80	6.07	2.44	4.05	-
4[b]	5.21	5.09	4.21	2.08	4.60	-
5[a]*	6.00	4.13	3.04	(1) 4.00	-	-
				(2) 6.00	5.28	-
6[a]	6.13	5.80	5.15	2.45	5.36	-

Continued

Pt. no	Loading dose (mg/kg)	Theophylline serum conc. after loading dose (mcg/ml)		Maintenance dose (mg/kg/day)	Theophylline serum conc. during steady state[c] (mcg/ml)	Factors that affected on theophylline Pharmacokinetics
		6th hour	12th hour			
7[a]	5.17	3.76	3.26	(1) 3.45	(1) 4.15	-
				(2) 5.17	(2) 5.89	-
8[a]*	4.54	5.82	5.05	(1) 5.84	-	-
				(2) 3.90	10.45	-
9[a]	6.48	5.53	4.94	(1) 2.47	4.43	-
				(2) 3.09	-	-
10[a]	5.33	4.37	3.80	(1) 4.92	15.64	-
				(2) 3.28	6.61	-
11[b]	6.25	8.57	7.49	2.50	4.80	-

Continued

Pt. no	Loading dose (mg/kg)	Theophylline serum conc. after loading dose (mcg/ml)		Maintenance dose (mg/kg/day)	Theophylline serum conc. during steady state[c] (mcg/ml)	Factors that affected on theophylline pharmacokinetics
		6th hour	12th hour			
12[a]	5.00	5.94	4.98	2.50	3.79	-
13[b]	2.97	2.47	2.17	2.41	6.31	Acidosis[2]
14[a]	6.43	5.93	5.52	2.50	8.22	-
15[a]*	6.22	7.10	6.81	(1) 3.33	-	-
				(2) 1.93	-	-
				(3) 1.11	3.57	-
16[a]	6.18	6.30	5.30	2.25	2.81	-
17[b]	6.15	5.40	5.21	4.10	4.26	-

Continued

Pt. no	Loading dose (mg/kg)	Theophylline serum conc. after loading dose (mcg/ml)		Maintenance dose (mg/kg/day)	Theophylline serum conc. during steady state[c] (mcg/ml)	Factors that affected on theophylline Pharmacokinetics
		6th hour	12th hour			
18[a]	6.21	5.86	4.92	2.76	1.88	-
19[b]	3.85	10.07	8.92	1.92	5.08	severe birth asphyxia[1]
20[b*]	6.32	5.78	5.44	(1) 4.21	-	-
				(2) 2.10	8.07	-
21[b]	6.25	5.57	4.19	3.00	3.55	Lasix[2]
22[b]	6.54	11.89	10.30	2.50	6.01	severe birth asphyxia[1]
23[b]	6.25	7.52	6.17	2.50	5.97	-
24[b]	6.24	12.25	11.45	1.83	5.76	lasix, severe birth asphyxia[1]

Continued

Pt. no	Loading dose (mg/kg)	Theophylline serum conc. after loading dose (mcg/ml)		Maintenance dose (mg/kg/day)	Theophylline serum conc. during steady state[c] (mcg/ml)	Factors that affected on theophylline Pharmacokinetics
		6th hour	12th hour			
25[b]*	5.21	3.26	2.72	(1) 2.08	-	-
				(2) 4.69	16.20	acidosis[2]
				(3) 3.12	3.82	-
26[a]	5.14	3.94	3.49	2.29	5.33	-
27[b]	5.59	4.23	3.47	2.10	5.57	-
28[b]	6.25	6.95	6.14	2.50	5.67	-
29[a]	6.06	4.94	4.34	2.42	8.16	-
30[a]	5.92	11.31	8.41	3.95	8.86	-
31[b]	6.11	5.53	4.63	2.22	5.43	-

41

Continued

Pt. no	Loading dose (mg/kg)	Theophylline serum conc. after loading dose (mcg/ml)		Maintenance dose (mg/kg/day)	Theophylline serum conc. during steady state[c] (mcg/ml)	Factors that affected on theophylline Pharmacokinetics
		6th hour	12th hour			
32[b]	5.68	8.39	7.32	(1) 3.41	5.04	-
				(2) 5.20	12.02	-
				(3) 4.50	10.70	-
33[a]*	3.93	4.28	3.78	(1) 1.58	-	-
				(2) 3.92	6.25	-
n	33	33	33	48	38	
X ± SD	5.63 ± 0.86	6.19 ± 2.39	5.34 ± 2.13	3.01 ± 1.16	6.36 ± 3.14	
range	2.97 - 6.54	2.47 - 12.25	2.17 - 11.45	1.11 - 6.00	1.88 - 16.20	

Loading dose and maintenance dose were aminophylline form which could converse to theophylline base by multiply the dose of aminophylline with factor 0.8.

* The patients whose maintenance dose were adjusted before theophylline serum concentration during steady state was obtained.

[a] The patients who used theophylline for apnea

[b] The patients who used theophylline as an adjuvant to weaning

[c] The trough concentrations

[1] Factor occurred during non-steady state serum concentrations.

[2] Factor occurred during steady state serum concentrations.

Table 5 :   The patients whose aminophylline maintenance doses were adjusted before the steady state theophylline serum concentrations were obtained, the traditional and the recommended maintenance doses and their corresponding predicted and observed theophylline serum concentration during steady state

Pt. No.	Traditional MD. (mg/kg/day)	Predicted1* (mcg/ml)	Recommended MD. (mg/kg/day)	Predicted 2* (mcg/ml)	Observed value (mcg/ml)
1[a]	1.92	3.56	2.11	4.13	4.55
2[a]	1.92	3.64	2.12	4.28	7.44
5[a]	4.00	2.21	6.00	3.71	5.28
8[a]	5.84	12.97	3.90	8.65	10.45
15[a]	3.33	23.43	1.11	6.18	3.57
20[b]	4.21	15.45	2.10	8.40	8.07
25[b]	2.08	1.79	4.69	4.25	16.20
33[a]	1.58	3.44	3.92	6.88	6.25

MD : Maintenance dose

[a] Patients used theophylline for apnea.

[b] Patients used theophylline as an adjuvant to weaning.

Predicted 1 : The predicted theophylline serum concentrations corresponded to the traditional maintenance dose.

Predicted 2 : The predicted theophylline serum concentrations corresponded to the recommended maintenance dose.

* predicted steady state theophylline serum concentration based on the non-steady state, individual pharmacokinetic parameters. Equations used were equation 1, 2, 3.2, and 5.2.

The maintenance dose of pt.no. 1, 2, 5, 25, and 33 was adjusted because the predicted steady state theophylline serum concentration was at subtherapeutic level and the clinical response was inadequate.

The maintenance dose of pt.no. 8, 15, and 20 was adjusted because the predicted steady state theophylline serum concentration was at overtherapeutic level and pt.no. 15 had rapid heart rate during the 3rd day after the original maintenance dose was given.

Table 6 : Percentage of the patients whose trough theophylline serum concentrations after loading dose and during steady state were within subtherapeutic, therapeutic and overtherapeutic range

Theophylline serum Concentration	Number of the patients (%)					
	After loading dose				Steady state	
	6th hour		12th hour			
	Apnea	weaning	apnea	weaning	apnea	weaning
Subtherapeutic range	14 (77.78)	8 (53.33)	15 (83.33)	8 (53.33)	11 (61.11)	11 (73.33)
(< 6 mcg/ml)	22 (66.67)		23 (69.70)		22 (66.67)	
Therapeutic range	4 (22.22)	6 (40.00)	3 (16.67)	7 (46.67)	6 (33.33)	3 (20.00)
(6 – 12 mcg/ml)	10 (30.30)		10 (30.30)		9 (27.27)	
Overtherapeutic range	-	1 (6.67)	-	-	1 (5.56)	1 (6.67)
(> 12 mcg/ml)	1 (3.03)		-		2 (6.06)	

** Total (N) = 33 cases

        patients used theophylline for apnea   :   18 cases

        patients used theophylline as an adjuvant to weaning :   15 cases

Table 7 : The baseline data, aminophylline maintenance dose recommended by each equations and their corresponding predicted steady state theophylline serum concentration

Pt.no	PNA (days)	GA (weeks)	Observed Cl	MD1	MD2	MD3	MD4	Css1	Css2	Css3	Css4
1	2	33	15.45	2.50	5.06	4.90	3.76	5.39	10.91	10.57	8.11
2	2	33	9.47	2.50	5.06	4.90	3.76	8.80	17.80	17.25	13.23
3	3	30	20.11	2.50	5.09	5.80	3.89	4.14	8.43	9.61	6.45
4	7	29	15.10	2.50	5.20	5.79	4.41	5.52	11.48	12.78	9.74
5	27	34	37.88	2.50	5.77	5.90	7.01	2.20	5.08	5.19	6.17
6	6	34	15.26	2.50	5.17	5.06	4.28	5.46	11.30	11.05	9.35
7(1)	4	31	27.70	2.50	5.11	4.98	4.02	3.01	6.15	5.99	4.84
7(2)	4	31	29.27	2.50	5.11	4.98	4.02	2.85	5.82	5.67	4.58
8	3	33	12.43	2.50	5.09	4.94	3.89	6.70	13.64	13.25	10.43
9	3	32	18.58	2.50	5.09	4.94	3.89	4.49	9.12	8.86	6.98
10(1)	4	32	10.48	2.50	5.11	4.98	4.02	7.95	16.27	15.84	12.79
10(2)	4	32	16.53	2.50	5.11	4.98	4.02	5.04	10.31	10.04	8.11
11	2	30	17.36	2.50	5.06	5.80	3.76	4.80	9.71	11.14	7.22
12	2	29	21.99	2.50	5.06	5.80	3.76	3.79	7.67	8.79	5.70
13	7	31	12.75	2.50	5.20	5.10	4.41	6.54	13.59	13.33	11.53
14	6	32	10.14	2.50	5.17	5.06	4.28	8.22	17.00	16.63	14.07

Continued

Pt.no	PNA (days)	GA (weeks)	Observed Cl	MD1	MD2	MD3	MD4	Css1	Css2	Css3	Css4
15	7	30	8.30	2.50	5.20	5.79	4.41	10.04	20.88	23.25	17.71
16	4	32	26.66	2.50	5.11	4.98	4.02	3.13	6.39	6.23	5.03
17	3	28	32.10	2.50	5.09	5.80	3.89	2.60	5.28	6.02	4.04
18	16	31	48.91	2.50	5.46	5.46	5.58	1.70	3.72	3.72	3.80
19	10	28	12.62	2.50	5.29	5.78	4.80	6.60	13.96	15.27	12.68
20	5	28	8.69	2.50	5.14	5.80	4.15	9.59	19.73	22.25	15.92
21	8	32	28.17	2.50	5.23	5.14	4.54	2.96	6.19	6.08	5.37
22	5	33	13.87	2.50	5.14	5.02	4.15	6.01	12.36	12.06	9.97
23	4	28	13.96	2.50	5.11	5.80	4.02	5.97	12.21	13.85	9.60
24	2	27	10.61	2.50	5.06	5.80	3.76	7.85	15.89	18.22	11.81
25(1)	5	30	9.65	2.50	5.14	5.80	4.15	8.64	17.76	20.03	14.34
25(2)	5	30	27.27	2.50	5.14	5.80	4.15	3.06	6.29	7.09	5.07
26	7	33	14.30	2.50	5.20	5.10	4.41	5.83	12.12	11.89	10.28
27	5	32	12.55	2.50	5.14	5.02	4.15	6.64	13.66	13.33	11.02
28	3	35	14.70	2.50	5.09	4.94	3.89	5.67	11.53	11.20	8.82
29	3	33	9.90	2.50	5.09	4.94	3.89	8.42	17.12	16.63	13.10

Continued

Pt.no	PNA (days)	GA (weeks)	Observed Cl	MD1	MD2	MD3	MD4	Css1	Css2	Css3	Css4
30	2	33	14.85	2.50	5.06	4.90	3.76	5.61	11.35	11.00	8.44
31	7	32	13.64	2.50	5.20	5.10	4.41	6.11	12.71	12.46	10.78
32	8	32	22.55	2.50	5.23	5.14	4.54	3.70	7.73	7.60	6 71
32	8	32	16.39	2.50	5.23	5.14	4.54	5.08	10.63	10.45	9.23
32	8	32	15.93	2.50	5.23	5.14	4.54	5.23	10.94	10.76	9.50
33	2	32	16.77	2.50	5.06	4.90	3.76	4.97	10.05	9.74	7.47
mean	5.58	31.27	17.97	2.50	5.16	5.29	4.23	5.53	11.39	11.71	9.21
SD	4.84	2.04	8.82	0.00	0.13	0.39	0.59	2.12	4.34	4.71	3.45

Total number of drug concentrations, N = 38

1 : FDA recommendation   3 : Bhatt-Mehta equation

2 : Hendeles equation   4 : New equation

Cl : Clearance, ml/hr-kg

MD : Maintenance dose, mg/kg

Css : Steady state theophylline serum concentration, mcg/ml

Table 8 : Percentage of the predicted steady state theophylline serum concentration corresponded to the maintenance dose recommended by different equations was within subtherpeutic, therapeutic and overtherapeutic range

Theophylline range	Number of the predicted steady state theophylline serum concentations (%)			
	FDA	Hendeles equation	Bhatt-Mehta equation	New equation
Subtherapeutic range < 6 mcg/ml	24 (63.16)	4 (10.53)	3 (7.90)	8 (21.05)
Therapeutic range 6 – 12 mcg/ml	14 (36.84)	18 (47.37)	19 (50.00)	22 (57.90)
Overtherapeutic range > 12 mcg/ml	-	16 (42.10)	16 (42.10)	8 (21.05)

Total number of drug concentrations, N = 38
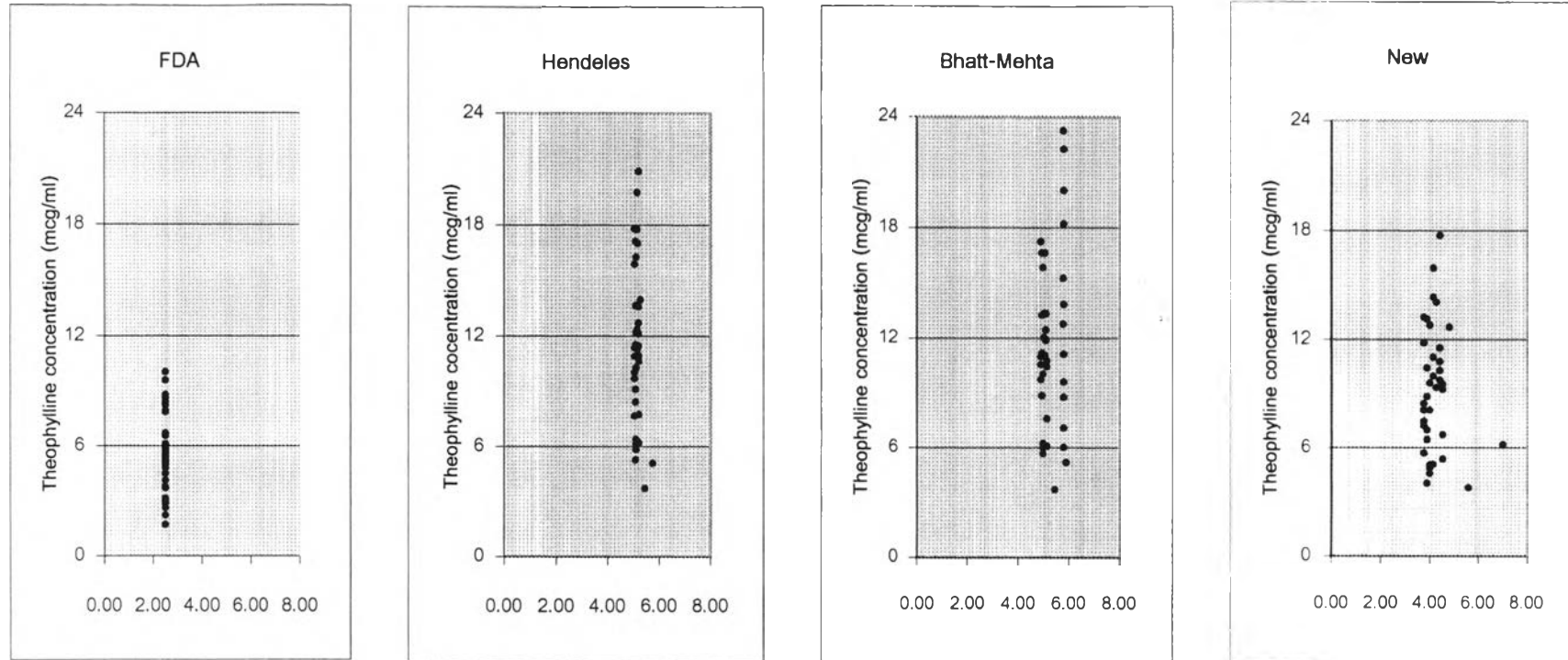
Aminophylline maintenance dose (mg/kg/day)

Figure 2 : Scatterplot of calculated theophylline serum concentration versus aminophylline recommended dose for FDA, Hendeles, Bhatt-Mehta and new equations. Horizontal lines at theophylline concentration of 6 and 12 mcg/ml represent the therapeutic range for patients used theophylline for apnea and used theophylline as an adjuvant to weaning (6-12 mcg/ml).

2. Reliability and Precision of the Predicted Theophylline Serum Concentration during Steady State by Methods based on the Serum Concentration during Non-steady state

2.1 Comparison between the Predicted and the Observed Theophylline Serum Concentrations

Various pharmacokinetic methods were used to evaluate the serum concentration during steady state and the predicted steady state theophylline serum concentrations were shown in table 9. In this study, the model of aminophylline administration in preterm infants was short infusion model, usually, the principle equation for calculation of the predicted steady state theophylline serum concentrations should be equation 5.1. However, equation 5.2 which was the principle equation of the bolus model could be used if the half life was longer than six times of the infusion time (Winter, 1994). Previous studies of theophylline pharmacokinetics in neonates found that the half life was long (nearly 30 hours) and the infusion time in this study was short (only 10 – 15 minutes), therefore, we compared the values of the theophylline concentrations calculated from the equations of the short infusion model and the bolus model (Appendix I) were compared. The results demonstrated that the values of the theophylline concentrations calculated from the equation of the bolus model were not different from the values of the theophylline concentrations calculated from the equation of the short infusion model (rmse = 0.25 , 95%CI = -0.26, 0.44). Consequently, in this study, equation 5.2 was used to predict the steady state theophylline concentration instead of equation 5.1 which was more complex. In addition, the serum concentration did not changed very largely since aminophylline was administered every eight or every twelve hours resulted from the long half life, the simplified equation such as equation 6 was used as a principle equation for prediction of the theophylline serum concentration during steady state and the result was compared with those obtained from the more complex equations.

Each principle equation could be used to calculate the predicted theophylline serum concentrations during steady state when the pharmacokinetic parameters such as elimination rate constant (Ke), volume of distribution (Vd) and clearance (Cl) were known. Elimination rate constant (Ke) could be calculated by using equation 1 based on the two point, non-steady state theophylline serum concentrations. Every methods, besides method 7, the elimination rate constant (Ke) was calculated from this equation. The volume of distribution (Vd) was either calculated as the individual value using equation 3.2 (method 1 and 4) or taken as the population Vd in neonatal period reported by Aranda et al (1992) (method 2 and 5) or Moore et al (1989) (method 3 and 6).

Driscoll et al (1989) reported that the interindividual difference in the clearance (Cl) was less than the interindividual difference in the volume of distribution (Vd) in pediatric population, with coefficients of variation were 19 and 28%, respectively. We, therefore, together examined the reliability and precision of the predicted steady state theophylline serum concentrations which were calculated by using population theophylline clearance in neonatal period reported by Aranda et al (1992) (method 7).

Table 10 showed predictive performance for the predicted theophylline serum concentrations during steady state by different methods. The results demonstrated that the correlation between the predicted and the observed theophylline serum concentrations was statistically significant for every methods. However, higher significant level was found with the methods which used the population pharmacokinetic parameters (either Vd or Cl) in calculation of the steady state serum concentrations. No statistical significance in precision was found in any methods. When the results of the predicted steady sate theophylline serum concentrations by using the method 5, 6 and 7 which used the same principle equation and used one value of the population pharmacokinetic parameters (Vd or Cl) were determined, the method 7 got poor precision. Those illustrated that the clearance of the preterm infants might be more variable among individual infants than the volume of distribution. However, among the different methods, the predicted theophylline serum concentration calculated from using the population volume of distribution or the population clearance (method 2, 3, 5, 6, and 7) was more precise than the predicted theophylline serum concentrations calculated from the individual volume of distribution obtained from the complex pharmacokinetic equations (method 1 and 4).

Table 11 demonstrated percentage of difference between the observed and the predicted steady state theophylline serum concentrations. The results from the comparison between the observed and the predicted steady state serum concentrations by difference methods indicated that the methods which the steady state serum concentrations were calculated by using the individual Vd and Cl (method 1 and 4) had more the percentage of difference between the observed and the predicted steady state serum concentration than the methods which the steady state serum concentrations were calculated by using the population values (method 2, 3, 5, 6 and 7). When the percentage of difference between the observed and the predicted steady state serum concentrations was determined especially in the methods which used the population Vd or Cl and the same principle equation (method 5, 6 and 7), the methods which used the population Cl (method 7) had more the percentage of difference between the observed and the predicted steady state serum concentrations than the methods which used the population Vd (method 5 and 6).

For the mehods which used the same value of the population Vd but different principle equations for calculation of the steady state serum concentrations (metnod 2 and 5 , method 3 and 6), the percentage of difference between the observed and the predicted steady state serum concentrations of the methods which used the principle equation of the bolus model were similar to the percentage of difference between the observed and the predicted steady state serum concentrations of the methods which used the simplified equation. In clinical practice, the simplified equation might be better than the equation of the bolus model for prediction of the steady state serum concentrations because it less complex while the percentage of difference between the observed and the predicted steady state serum concentrations obtained from the two principle equations when used the same Vd was not significantly difference.

For the methods which used the same principle equation but different Vd, in the methods which used the principle equation of the bolus model, the percentage of difference between the observed and the predicted steady state serum concentrations obtained from the method which used the population Vd (0.69 L/kg) reported by Aranda et al (1992) (method 2) was similar to the percentage of difference between the observed and the predicted values obtained from the method which used the population Vd (0.858 L/kg) reported by Moore et al (1989) (method 3). For the methods which the simplified equation was used to calculate the steady state serum concentrations, the method which used the population Vd (0.858 L/kg) reported by Moore et al (1989) (method 6) had less percentage of difference than the method which used the population Vd (0.69 L/kg) reported by Aranda et al (1992) (method 5).

Table 12 demonstrated the number of theophylline serum concentrations within various range of difference between the predicted and the observed steady state theoophylline serum concentrations. Although from table 10 statistical significant was not found in any methods, more than 50% of the predicted steady state theophylline serum concentrations calculated by method 6 was within the 20% difference with approximately 30% of the predicted steady state theophylline serum concentrations was more than the 40% difference. On the other hand, less than 40% of the predicted steady state thophylline serum concentrations calculated by the other was within the 20% difference.

As a whole, although the precision for prediction of the steady state serum concentrations was not found in any methods, the methods which calculated the steady state serum concentrations by using the population Vd had more precision than the methods which calculated the steady state serum concentrations by using the individual Vd obtained after the loading dose and the simplified equation was

preferred for used to prediction of the steady state serum concentrations because it was not complex when compared with the equations of the bolus model. Among the different methods, method 6 which calculated the steady state serum concentrations by using the individual Ke obtained after the loading dose and population Vd (0.858 L/kg) reported by Moore et al (1989) applied to the simplified equation might be the best method for prediction of the steady state theophylline serum concentrations based on the non-steady state data. However, cautious use of this method is recommended. Clinical response should be monitored and the drug level should be confirmed especially in the patients who have inadequate response or have sign of the adverse reactions.

Table 9 : Comparison between observed theophyline serum concentrations and predicted theophylline serum concentrations during steady state calculated by different methods

Pt. No.	Observed values (mcg/ml)	Predicted values (mcg/ml)						
		Method1	Method 2	Method 3	Method 4	Method 5	Method 6	Method 7
1	4.55	4.13	5.51	4.43	4.36	5.82	4.68	3.20
2	7.44	4.28	4.38	3.52	4.58	. 4.68	3.77	3.21
3	4.05	5.32	4.95	3.98	6.05	5.63	4.53	3.70
4	4.60	1.99	1.83	1.47	2.59	2.39	1.92	3.16
5	5.28	3.71	4.59	3.70	4.58	5.68	4.56	9.09
6	5.36	4.87	5.30	4.26	5.49	5.98	4.81	3.72
7/1	4.15	4.39	6.05	4.87	5.08	7.00	5.63	5.22
7/2	5.89	6.92	9.54	7.67	7.62	10.51	8.45	9.09
8	10.45	8.65	6.57	5.28	9.61	7.30	5.87	5.90
9	4.43	4.74	5.66	4.55	5.31	6.35	5.10	3.74
10/1	15.64	7.54	9.28	7.46	8.29	10.20	8.20	7.45
10/2	6.61	4.79	5.89	4.74	5.53	6.80	5.47	4.97
11	4.80	7.43	5.58	4.49	8.35	6.28	5.05	3.79
12	3.79	4.18	3.42	2.75	5.02	4.11	3.31	3.79
13	6.31	3.14	3.46	2.78	3.74	4.12	3.32	3.66

continued

Pt. No.	Observed values (mcg/ml)	Predicted values (mcg/ml)						
		Method1	Method 2	Method 3	Method 4	Method 5	Method 6	Method 7
14	8.22	8.81	10.36	8.33	9.32	10.96	8.81	3.79
15	3.57	6.18	6.02	4.85	6.42	6.26	5.03	1.35
16	2.81	3.32	3.18	2.55	3.94	3.77	3.03	3.40
17	4.26	6.97	7.17	5.76	8.07	8.30	6.67	6.22
18	1.88	3.51	3.54	2.85	4.23	4.26	3.43	4.18
19	5.08	10.27	4.02	3.23	11.73	4.60	3.70	2.91
20	8.07	8.40	9.98	8.02	8.23	9.77	7.86	3.19
21	3.55	2.57	2.57	2.07	3.31	3.31	2.66	4.55
22	6.01	10.53	6.03	4.85	11.75	6.73	5.41	3.79
23	5.97	5.37	4.41	3.54	5.95	4.88	3.93	3.79
24	5.76	13.32	7.35	5.91	14.28	7.87	6.33	2.78
25/1	16.20	4.25	6.57	5.28	4.86	7.50	6.03	7.10
25/2	3.82	3.04	4.70	3.78	3.24	5.00	4.02	4.73
26	5.33	3.66	4.91	3.95	4.08	5.46	4.39	3.46
27	5.57	1.81	2.17	1.75	2.28	2.73	2.19	3.18
28	5.67	5.71	5.26	4.23	6.35	5.85	4.70	3.79

.continued

Pt. No.	Observed values (mcg/ml)	Predicted values (mcg/ml)						
		Method 1	Method 2	Method 3	Method 4	Method 5	Method 6	Method 7
29	8.16	5.04	6.61	5.31	5.52	7.23	5.82	3.67
30	8.86	6.27	2.83	2.28	8.56	3.86	3.11	5.93
31	5.43	2.84	3.04	2.45	3.38	3.63	2.92	3.37
32/1	5.04	8.99	6.16	4.95	10.57	7.24	5.82	5.17
32/2	12.02	15.94	10.92	8.78	18.32	12.55	10.10	8.95
32/3	10.70	14.46	9.91	7.97	15.86	10.86	8.74	7.75
33	6.25	6.88	6.47	5.20	7.81	7.34	5.90	4.76
Mean ± SD	6.36 ± 3.14	6.16 ± 3.35	5.69 ± 2.36	4.57 ± 1.89	6.95 ± 3.08	6.39 ± 2.44	5.14 ± 1.96	4.62 ± 1.87

* Total number of drug concentrations, N = 38

Observed   :   Observed theophylline serum concentrations during steady state

Method 1   :   The steady state theophylline serum concentrations were predicted from equation 5.2 by using individual elimination rate constant

calculated from equation 1 and individual volume of distribution calculated from equation 2 and 3.2.

Method 2   :   The steady state theophylline serum concentrations were predicted from equation 5.2 by using individual elimination rate constant

calculated from equation 1 and the population Vd (0.69 l/kg) reported by Aranda et al (1992).

Method 3   :   The steady state theophylline serum concentrations were predicted by equation 5.2 by using individual elimination rate constant calculated from equation 1 and the population Vd (0.858 l/kg) reported by Moore et al (1989).

Method 4   :   The steady state theophylline serum concentrations were predicted by equation 6 by using the predicted clearance calculated by the use of individual elimination rate constant calculated from equation 1 and individual Vd calculated from equation 2 and 3.2.

Method 5   :   The steady state theophylline serum concentrations were predicted by equation 6 by using the predicted clearance calculated by the Use of individual elimination rate constant calculated from equation 1 and the population Vd (0.69 l/kg) reported by Aranda et al (1992).

Method 6   :   The steady state theophylline serum concentrations were predicted by equation 6 by using the predicted clearance calculated by the use of individual rate constant calculated from equation 1 and the population Vd (0.858 l/kg) reported by Moore et al (1989).

Method 7   :   The steady state theophylline serum concentrations were predicted by equation 6 by using the population clearance (22 ml/hr-kg) in neonatal period reported by Aranda et al (1992).

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Pt. No	Observed CL	CL1, 4	CL2, 5	CL3, 6	CL7
26	14.30	18.69	13.94	17.34	22.00
27	12.55	30.69	25.64	31.88	22.00
28	14.70	13.12	14.25	17.72	22.00
29	9.90	14.64	11.17	13.89	22.00
30	14.85	15.37	34.07	42.37	22.00
31	13.64	21.92	20.42	25.40	22.00
32/1	22.55	10.75	15.69	19.51	22.00
32/2	16.39	10.75	15.69	19.51	22.00
32/3	15.93	10.75	15.69	19.51	22.00
33	16.77	13.42	14.28	17.76	22.00
Mean ± SD	17.97±8.82	17.30±8.56	17.10±6.78	21.26±8.43	22.00
Range	8.69 – 48.91	4.29 – 43.68	4.73 – 35.24	5.89 –43.82	22.00

** unit of the clearance : ml/hr-kg

Total number of theophylline clearances, N = 38

Observed Cl   Observed theophylline clearance which was calculated by the use of equation 6 (displaced C_{md} with observed theophylline serum concentration during steady state).

CL 1, 4   The predicted clearance which was calculated by the use of individual elimination rate constant calculated from equation 1 and individual volume of distribution calculated from equation 2 and 3.

CL 2, 5   The predicted clearance which was calculated by the use of individual elimination rate constant calculated from equation 1 and population volume of distribution (0.69 l/kg) reported by Aranda et al (1992).

CL 3, 6   The predicted clearance which was calculated by the use of individual elimination rate constant calculated from equation 1 and population volume of distribution (0.858 l/kg) reported by Moore et al (1989).

CL 7   Population theophylline clearance in preterm infants(22 ml/hr-kg) reported by Aranda et al (1992).

Table 14 : Number of theophylline clearances in various range of difference between the predicted and the observed clearances

Range of difference between predicted and observed values	Number of theophylline clearances (%)			
	CL1, 4	CL 2, 5	CL3, 6	CL 7
≤ 10%	7 (18.42)	8 (21.05)	8 (21.05)	3 (7.90)
≤ 20%	15 (39.47)	14 (36.84)	16 (42.10)	5 (13.16)
≤30%	18 (47.37)	22 (57.90)	22 (57.90)	10 (26.32)
≤40%	22 (57.90)	24 (63.17)	26 (68.42)	15 (39.47)
≤50%	27 (71.05)	30 (78.95)	28 (73.68)	21 (55.26)
≤60%	31 (81.58)	34 (89.47)	29 (76.32)	25 (65.79)
≤70%	34 (89.47)	34 (89.47)	29 (76.32)	27 (71.05)
≤80%	35 (92.10)	34 (89.47)	30 (78.95)	30 (78.95)
≤90%	36 (94.74)	34 (89.47)	31 (81.58)	30 (78.95)
≤ 100%	36 (94.74)	35 (92.10)	34 (89.47)	30 (78.95)
> 100%	2 (5.26)	3 (7.90)	4 (10.53)	8 (21.05)
Total	38 (100)	38 (100)	38 (100)	38 (100)

Total number of theophylline clearances, N = 38

Table 15 : Correlation between the theophylline clearance and endogenous factors.

Parameter comparison	N	Correlation	P value
After loading dose			
CL vs post natal age (PNA)	33	0.537*	0.001
CL vs gestation age (GA)	33	0.264	0.137
CL vs weight	33	0.173	0.336
During steady state			
CL vs post natal age (PNA)	38	0.391*	0.015
CL vs gestation age (GA)	38	0.013	0.940
CL vs weight	38	0.028	0.868

Parameter comparison	N	Correlation	P value
Ke vs post natal age (PNA)	33	0.443*	0.010
Vd vs post natal age (PNA)	33	0.123	0.496

* statistical significant

2.3 Pharmacokinetic Parameters Obtained after the Loading dose and during Steady state of the Preterm Infants

Theophylline pharmacokinetic parameters obtained after the loading dose and during steady state of the preterm infants were shown in table 16.

The volume of distribution (Vd), the clearance (Cl) and the half life (T $\frac{1}{2}$) were the three principle pharmacokinetic parameters which have often been reported in the literatures. The mean volume of distribution obtained after the loading dose of the preterm infants was 0.697 ± 0.190 L/kg (range 0.270 – 1.066 L/Kg) which was closed to the population Vd (0.69 L/kg) reported by Aranda et al (1992) while the mean volume of distribution obtained during steady state was 0.768 ± 0.190 L/kg which was in the middle range between the population Vd (0.69 L/kg) reported by Aranda et al (1992) and the population Vd (0.858 L/kg) reported by Moore et al (1989). The volume of distribution of neonates found by some other investigators were repoerted as follow : Aranda et al (1992), 0.69 L/kg ; Jones and Baillie (1979), 0.7 L/kg ; Moore et al (1989), 0.858 L/kg and Giacoia et al (1976), 0.91 L/kg.

Aranda et al (1992) suggested the population theophylline clearance in neonatal period to be 22 ml/hr-kg. In this study, the mean theophylline clearance obtained after the loading dose was 17.30 ± 8.56 ml/hr-kg and the mean theophylline clearance obtained during steady state was 17.97 ± 8.82 ml/hr-kg. The mean clearances obtained either after the loading dose or during steady state were slightly lower than the population clearance reported by Aranda et at (1992) which might be resulted from the difference in age of the patients studied. The population Cl reported by Aranda et al (1992) was generated from the data of the patients in neonatal period which included either the preterm and the full term neonates while the mean clearance obtained from this study was generated from the data of the preterm neonates only. Theophylline clearance in neonatal period correlated to the maturity of the metabolizing drug system and the age of the patients. In full term infants, the metabolizing drug system may be more effective than that in the preterm infants resulted from more maturity. Therefore, the mean clearance obtained after the loading dose and during steady state of the preterm infants in this study was lower than the population clearance reported by Aranda et al (1992) which was obtained from the data of the preterm and the full term infants.

The mean half life obtained after loading dose of the preterm infants was 33.75 ± 17.52 hours which was slightly higher than the half life reported by Donthey et al (1989). However, the age of the infants in Donthey 's study was higher than 10 days while the age in most patients in this study (about 70%) was less than one weeks. For the elimination rate constant obtained after loading dose, the mean value was $0.02481 \pm 0.01050\ hr^{-1}$ while the mean value reported by Donthey et al (1989) was $0.0373 \pm 0.0383\ hr^{-1}$. The difference of the two mean values possible due to the difference in age in the studied group, the same as the difference in the half life when compared with the previous report.

The results from this study indicated that pharmacokinetic parameters of the preterm infants differ from the pharmacokinetic parameters of the older children. Theophylline clearance is very low and the volume of distribution is larger when compares with the older children, the treatment regimen usually consists of a loading dose follow by small maintenance dose given at short interval to avoid fluctuation in plasma concentration. Therefore, to achieve sufficient blood concentration, the appropriated dosage regimen should be recommended. However, intrapatients and interpatients variation in theophylline pharmacokinetic parameters were resulted in wide variation of the serum concentration when the standard dosage regimen was used. Consequently, individual dosage regimen should be performed for appropriate treatment in the patients.

Table 16 : Pharmacokinetic parameters obtained after loading dose and during steady state of the preterm infants

Pt. No.	pharmacokinetic parameters					
	Ke*	Vd*	Vd**	Cl*	Cl**	T1/2*
1	0.01752	0.920	0.882	16.12	15.45	39.55
2	0.02180	0.706	0.434	15.40	9.47	31.79
3	0.02095	0.643	0.960	13.47	20.11	33.08
4	0.04218	0.635	0.358	26.78	15.10	16.43
5	0.05107	0.855	0.742	43.68	37.88	13.57
6	0.01981	0.752	0.770	14.89	15.26	34.98
7(1)	0.02378	0.951	1.165	22.61	27.27	29.14
7(2)	-	-	1.231	-	29.27	-
8	0.02580	0.524	0.482	13.52	12.43	26.86
9	0.01880	0.824	0.988	15.49	18.58	36.86
10(1)	0.02329	0.849	0.450	19.78	10.48	29.76
10(2)	-	-	0.710	-	16.53	-
11	0.01924	0.518	0.902	9.97	17.36	36.02
12	0.02938	0.565	0.748	16.60	21.99	23.59
13	0.02827	0.761	0.451	21.50	12.75	24.51
14	0.01102	0.811	0.920	8.94	10.14	62.89
15	0.00686	0.673	1.210	4.61	8.30	101.02
16	0.02881	0.660	0.925	19.02	26.66	24.05
17	0.02388	0.710	1.344	16.95	32.10	29.02
18	0.03128	0.695	1.564	21.74	48.91	22.15
19	0.02021	0.270	0.624	5.46	12.62	34.29
20	0.01040	0.820	0.836	8.53	8.69	66.63
21	0.04380	0.691	0.643	30.24	28.17	15.82
22	0.01794	0.395	0.773	7.09	13.87	38.63
23	0.02473	0.566	0.564	14.00	13.96	28.02
24	0.01126	0.381	0.942	4.29	10.61	61.55

continued

Pt. No.	pharmacokinetic parameters					
	Ke*	Vd*	Vd**	Cl*	Cl**	T 1/2*
25(1)	0.03018	1.066	0.320	32.16	9.65	22.96
25(2)	-	-	0.904	-	27.27	-
26	0.02021	0.925	0.708	18.69	14.30	34.29
27	0.03716	0.826	0.338	30.69	12.55	18.65
28	0.02065	0.636·	0.712	13.12	14.70	33.56
29	0.01619	0.904	0.611	14.64	9.90	42.80
30	0.04938	0.311	0.301	15.37	14.85	14.03
31	0.02960	0.741	0.461	21.92	13.64	23.41
32(1)	0.02274	0.473	0.992	10.75	22.55	30.47
32(2)	-	-	0.721	-	16.39	-
32(3)	-	-	0.701	-	15.93	-
33	0.02070	0.648	0.810	13.42	16.77	33.48
mean	0.02481	0.697	0.768	17.30	17.97	33.75
SD	0.01050	0.190	0.293	8.56	8.82	17.52
range	.00686 - 0.0510	0.270 - 1.066	0.301 - 1.564	4.29 - 43.68	8.69 - 48.91	13.57 - 101.02
CV	42.32	27.26	38.15	49.48	49.08	51.91

unit of parameters :

Ke (Elimination rate constant) : hr-1 , Ke calculated from equation 1.

Vd (Volume of distribution) : L/Kg , Vd calculated from equation 3.2.

Cl (Clearance) : ml/hr-kg , Cl calculated from equation 4.

T 1/2 (Half life) : hr. , T 1/2 calculated from equation 8.

* The pharmacokinetic parameters obtained after the loading dose, N = 33

** The pharmacokinetic parameters obtained during steady sate, N = 38

The steady state Vd = The Vd which was calculated by using the individual Ke obtained after

the loading dose and the observed clearance during steady state

The steady state clearance = The observed clearance during steady state

3. Correlation between theophylline serum concentration and clinical response

Correlation between theophylline serum concentration and clinical response both benefit effect and adverse reaction was determined in all patients. Table 17 showed theophylline serum concentrations, clinical response both benefit effect and adverse reaction along with other treatments during theophylline therapy.

Table 18 demonstrated percentage of the patients who gained benefit effect and/or got adverse reaction when theophylline serum concentration was within subtherapeutic, therapeutic and overtherapeutic range. Set 6 -12 mcg/ml as the therapeutic range, 16 of the 22 patients (72.73%) whose theophyllline serum concentrations were at subtherapeutic level showed benefit effect from theophylline treatment. When four of these 16 patients who used other treatments along with the use of theophylline and had apnea after discontinued the co-treatments were excluded, only 54.55% of the patients could be considered as getting benefit effect from theophylline treatment. Adverse reaction was found in one patient who had thophylline serum concentration at subtherapeutic level. When theophylline serum concentration was within therapeutic range, 6 of the 9 patients (66.67%) got benefit effect while one patient (11.11%) showed adverse reaction associated with theophylline treatment. Only two patients had their theophylline serum concentrations at the overtherapeutic level, none of them showed benefit effect while adverse reaction was happened in one patient. Only one type of adverse reaction, tachycardia with the heart rate higher than 180 beats per minute, was noted in this study. For the patients whose traditional maintenance dose was adjusted before the steady state was reached, the clinical response was improved in most patients while none of them got adverse reaction from theophylline therapy. Table 19 demonstrated percentage of the patients who showed benefit effect from using theophylline alone or in combination with other treatments. When theophylline was used alone, 53.33% of the patients got benefit effect when theophylline serum concentrations were at subtherapeutic level and this percentage increased to 71.43% when theophylline serum concentrations were at therapeutic level.

Correlation between theophylline serum concentration and clinical response in the patients classified by indication for theophylline treatment, were considered. Among all patients, 18 patients used theophylline for apnea and 15 patients used theophylline as an adjuvant to weaning.

Among patients who used theophylline for apnea, 11 patients had their theophylline serum concentrations within subtherapeutic range and 10 of these patients (90.90%) got benefit effect from theophylline therapy. When the 2 patients who received other treatments along with theophylline therapy and

had apnea after discontinued the co-treatments were excluded, only 8 of these patients (72.73%) got benefit effect from theophylline therapy while none of them showed sign of adverse reaction from theophylline therapy. For the patients who had theophylline serum concentration within therapeutic range, all patients (100%) got benefit effect from theophylline therapy. Only one patient with apnea had theophylline serum concentration higher than the therapeutic range, no benefit effect was found while adverse effect, i.e., tachycardia with the heart rate higher than 180 beats per minute, did happen (Table 20).

The correlation between theophylline serum concentration and clinical response in patients with apnea demonstrated that 100% of the patients who had theophylline serum concentrations within the therapeutic range got benefit effect from theophylline therapy while adverse reaction did not happen. Only one patient had theophylline serum concentration higher than the therapeutic range, his apnea was not eliminated while adverse effect was found. For the patients who had theophylline serum concentrations at subtherapeutic level, the percentage of patients who got benefit effect was lower than the patients who had theophylline serum concentrations within the therapeutic range. However, most patients with apnea received other treatments concurrently with theophylline treatment.

Table 21 showed percentage of the patients who showed benefit effect from using theophylline alone or in combination with other treatments such as oxygen, respirator or external stimulant to manage apnea from any causes. When theophylline was used alone, 57.14% of the patients got benefit effect when their serum concentrations were at subtherapeutic level. The percentage of the patients who used theophylline alone and got benefit effect was increased to 100% when theophylline serum concentrations were at therapeutic level. When the cause of apnea brough into consideration, only 3 of the 4 patients (75%) who had apnea due to infection got benefit effect when theophylline was used alone and the serum concentration was less than the therapeutic range. Whereas, all of the patients who had their theophylline serum concentration within therapeutic range got benefit effect when theophylline was used alone. For the patients who had apnea caused by immaturity of the respiratory system, only 1 of the 3 patients (33.33%) whose serum concentration was less than the therapeutic level got benefit effect when theophylline was used alone, while benefit effect was found in all three patients whose theophylline serum concentration were within the therapeutic range even when theophylline was used alone.

For patients who used theophylline as an adjuvant to weaning , 6 of the 11 patients got benefit effect when theophylline serum concentrations were less than therapeutic range. However, 2 of these 6 patients received other treatments for apnea prevention and apnea occurred after discontinued the co-treatment. The

result indicated that theophylline when used alone at subtherapeutic serum concentration could only prevent apnea in 36.36% of the patients (Table 22). Benefit effect was not found either of the four patients whose theophylline serum concentrations were within therapeutic range and overtherapeutic range. Two patients showed adverse effect associated with theophylline therapy, the theophylline serum concentration of one patient was at subtherapeutic level while the other was within therapeutic range. The theophylline serum concentration of only one patient in this group was at the overtherapeutic level, neither benefit effect nor adverse effect was not found in this patient. Table 23 demonstrated the causes of non-benefit effect in patients who used theophylline as an adjuvant to weaning. Apnea resulted from infection was a primary cause of non-benefit effect in most patients (80%) with theophylline serum concentrations which was at subtherapeutic level. The cause of non-benefit effect in the three patients with therapeutic theophylline serum concentrations were apnea resulted from infection in one patient, failure from extubation caused by severe retraction in one patient and brain death in the other. For the patient with overtherapeutic theophylline serum concentration, apnea resulted from infection was the cause of non-benefit.

The results in patients who used theophylline as an adjuvant to weaning by using it for prevention of apnea after weaning indicated that theophylline was not an effective agent when used to prevent apnea caused by infection since 80% of these patients had apnea after weaning. However, theophylline serum concentrations of these patients were also low at subtherapeutic level. For the three patients whose theophylline serum concentrations were within therapeutic level, one patient had apnea resulted from infection after weaning, one patient had severe retraction and the other got brain death. None of them showed benefit effect from theophylline therapy. However, the amount of patients in this group was too small, further studies in a larger group of patients are required before any stronger conclusion could be made.

The correlation between theophylline serum concentration and clinical response in this study was not clear since other treatments were given along with theophylline treatment. At the same time, the cause of apnea in most patients were secondary cause. However, as a total viewpoint, the result obtained indicated that most patients got benefit effect when theophylline serum concentrations were within therapeutic range, when the serum concentration was less than therapeutic range, benefit effects were often obtained when other treatments were used concurrently with theopylline. In addition, the study found correlation between adverse reaction and theophylline serum concentration. The incidence of adverse reaction was increased when the serum concentration was increased. The higher incidence of adverse reaction was found in the patients with overtherapeutic theophylline serum concentration. The benefit effect of theophylline was obvious when the drug was used to control primary apnea which the serum concentration of theophylline was quite correlate

with the clinical result whether or not some other treatment was used along with theophylline. In contrast, the benefit effect of theophylline and its correlation with serum concentration was not found when theophylline was used to prevent secondary apnea especially the apnea that caused by infection in the patients used theophylline as an adjuvant to weaning.

Theophylline should be used in primary apnea. But it was often used in almost all types of apnea in the ward since quite often the cause of apnea could not be confirmed. Even though theophylline could not completely control apnea resulted from infection, it might help decrease the episode and led to the decrease of the CNS damage. However, the primary source of apnea is the most important to be treated. The use of theophylline should be reevaluated after the cause of apnea was known.

Table 17 : Steady state theophylline serum concentrations and the clinical response of the patients

Pt. No.	Theophylline serum conc. during steady state (mcg/ml)	Clinical response**		Cotherapy	Remark
		benefit effect	Adverse reaction		
1*	4.55	yes	-	respirator (3 days), antibiotics	-
2*	7.44	yes	-	respirator (3 days), antibiotics	-
3*	4.05	yes	-	respirator (2 days), antibiotics	-
4	4.60	no	yes (tachycardia)	antibiotics	Patient had failure extubation because of apnea (pneumonia).
5*	5.28	yes	-	antibiotics	-
6*	5.36	yes	-	respirator, antibiotics	-
7*	4.15	no	-	antibiotics	-
8*	10.45	yes	-	antibiotics	-

continued

Pt. No.	Theophylline serum conc. during steady state (mcg/ml)	Clinical response**		Cotherapy	Remark
		benefit effect	Adverse reaction	-	
9*	4.43	yes	-	external stimulant	Patient had apnea after discontinued external stimulant.
10*	15.64	no	yes (tachycardia)	antibiotics, respirator	-
11	4.80	yes	-	-	-
12*	3.79	yes	-	oxygen	had apnea after discontinued oxygen.
13	6.31	no	yes (tachycardia)	oxygen, antibiotics	Patient had successful extubation but he had apnea (pneumonia).
14*	8.22	yes	-	oxygen	no apnea after discontinued oxygen
15*	3.57	yes	-	antibiotics	-
16*	2.81	yes	-	antibiotics	-

continued

Pt. No.	Theophylline serum conc. during steady state (mcg/ml)	Clinical response**		Cotherapy	Remark
		benefit effect	Adverse reaction		
17	4.26	no	-	antibiotics, oxygen	Patients had successful extubation but he had apnea (pneumonia)
18*	1.88	yes	-	respirator (3 days)	-
19	5.08	no	-	antibiotics, oxygen	Patients had successful extubation but he had apnea (pneumonia)
20	8.07	no	-	-	Patient could not extubation because of severe retraction.
21	3.55	yes	-	oxygen	Patient had apnea (AOP) after discontinued oxygen.

continued

Pt. No.	Theophylline serum conc. during steady state (mcg/ml)	Clinical response**		Cotherapy	Remark
		benefit effect	Adverse reaction		
22	6.01	no	-	-	Patient could not extubation because of brain death.
23	5.97	no	-	-	Patient could not extubation because of pneumothorax.
24	5.76	yes	-	oxygen	patients had apnea (AOP) after discontinued oxygen.
25	16.20	no	-	antibiotics, oxygen	Patients had successful extubation but he had apnea (pneumonia).
26*	5.33	yes	-	-	-
27	5.57	yes	-	-	-

continued

Pt. No.	Theophylline serum conc. during steady state (mcg/ml)	Clinical response**		Cotherapy	Remark
		benefit effect	Adverse reaction		
28	5.67	yes	-	-	-
29*	8.16	yes	-	-	-
30*	8.86	yes	-	oxygen, external stimulant	no apnea after discontinued oxygen and external stimulant.
31	5.43	yes	-	-	-
32	5.04	no	-	antibiotics, oxygen	Patient had failure extubation because of apnea (pneumonia).
33*	6.25	yes	-	antibiotics	-

* Patients used theophylline for apnea.

** Clinical response :

Benefit effect :

Patients used theophylline for apnea

Yes = Absent of apnea within 5 day after theophylline treatment or dose adjustment.

No = Apnea still presented 5 days after theophylline treatment or dose adjustment.

In patients used theophylline as an adjuvant to weaning

Yes = Patient had successful extubation and no apnea occurred.

No = Patient had reintubation within 72 hours after extubation and/or had apnea.

Table 18 : Percentage of the patients who gained benefit effect and/or got adverse reaction when
theophylline serum concentration was within subtherapeutic, therapeutic and overtherpeutic range

Theophylline serum concentration	N	Number of the patients (%)	
	(%)	Benefit effect	Adverse reaction
Subtherapeutic range < 6 mcg/ml	22 (66.67)	16 (72.73) or 12 (54.55)**	1 (4.35)
Therapeutic range 6 – 12 mcg/ml	9 (27.27)	6 (66.67)	1 (11.11)
Overtherapeutic range > 12 mcg/ml	2 (6.06)	-	1 (50.00)

** Excluded the 4 patients (2 cases used theophylline for apnea and 2 cases used theophylline as an adjuvant
to weaning) who used other treatments along with the use of theophylline and had apnea after discontinued
co-treatments.

Table 19 : Percentage of the patients who showed benefit effect from using theophylline alone or in
combination with other treatments

Theophylline serum concentration	Benefit effect	Number of the patients (%)					
		n	T	n	T + other	n	Total
Subtherapeutic range < 6 mcg/ml (n = 22)	Yes	11 or 15*	8 (72.73) or 8 (53.33)	11 or 7**	8 (72.73) or 4 (57.14)**	22	16 (72.73) or 12 (54.55)**
	No		3 (27.27) or 7 (46.67)*		3 (27.27) 3 (42.86)		6 (27.27) or 10 (45.46)*
Therapeutic range 6 – 12 mcg/ml (n = 9)	Yes	7	5 (71.43)***	2	1 (50)	9	6 (66.67)
	No		2 (28.57)		1 (50)		3 (33.33)
Overtherapeutic range > 12 mcg/ml (n = 2)	Yes	0	-	2	-	2	-
	No		-		2 (100)		2 (100)

Benefit effect : Yes = The patients got benefit effect from theophylline treatment.

No = The patients did not gain benefit effect from theophylline treatment.

T   :   Theophylline alone

T+other :   Theophylline combined with other treatments (oxygen, respirator or external stimulant)

*   Included the 4 patients who had apnea after discontinued the co-treatments.

** Excluded the 4 patients (2 patients used theophylline for apnea and 2 patients used theophylline as an adjuvant to weaning) who used other treatments along with theophylline treatments and had apnea after discontinued the co-treatments.

***Included the 2 patients who did not have apnea after discontinued the co-treatments.

Table 20 : Percentage of the patients used theophylline for apnea who had benefit effect and adverse
reaction when theophylline serum concentration was within subtherpeutic, therapeutic and
overtherapeutic range

Theophylline serum concentration	N	Number of the patients (%)	
	(%)	Benefit effect	Adverse reaction
Subtherapeutic range < 6 mcg/ml	11 (61.11)	10 (90.90) or 8 (72.73)**	-
Therapeutic range 6 – 10 mcg/ml	6 (33.33)	6 (100)	-
Overtherapeutic range > 12 mcg/ml	1 (5.56)	-	1 (100)

** Excluded the 2 patients who received other treatments along with theophylline therapy and had apnea after
discontinued the co-treatments.

Table 21 : Percentage of the patients who showed benefit effect from using theophylline alone or in combination with other treatments to manage apnea

Theophylline serum Concentration	Benefit effect	Number of the patients (%)											
		AOP (N = 7)				Infection (N = 11)				Total (N = 18)			
		n	T	n	T + other	n	T	n	T + other	n	T	n	T + other
Subtherapeutic range < 6 mcg/ml	Yes	1 or 3*	1 (100) or 1 (33.33)	2 or 0**	2 (100) or 0**	4	3 (75)	4	4·(100)	5 or 7*	4 (80) or 4 (57.14)	6 or 4**	6 (100) or 4 (100)**
	No		0 or 2 (66.67)*		-		1 (25)		-		1 (20) or 3 (42.86)*		-
Therpeutic range 6 – 12 mcg/ml	Yes	3***	3 (100)***	0	-	2	2 (100)	1	1 (100)	5***	5 (100)	1	1 (100)
	No		-		-		-		-		-		-
Overtherpeutic range > 12 mcg/ml	Yes	0	-	1	-	0	-	0	-	0	-	1	-
	No		-		1 (100)		-		-		-		1 (100)

Benefit effect :   Yes = The patients got benefit effect from theophylline treatment.

No = The patients did not gain benefit effect from theophylline treatment.

T   :   Theophylline alone

T+other   :   Theophylline combined with other treatments (oxygen, respirator or external stimulant)

*   Included the 2 patients who had apnea after discontinued the co-treatments.

**   Excluded the 2 patients who had apnea after discontinued the co-treatments.

*** Included the 2 patients who did not have apnea after discontinued the co-treatments.

Table 22 : Percentage of the patients used theophylline as an adjuvant to weaning who got benefit effect and/or got adverse reaction in correspondent with theophylline concentration

Theophylline serum concentration	N	Number of the patients (%)	
		Benefit effect	Adverse reaction
Subtherapeutic range < 6 mcg/ml	11	6 (54.54) or 4 (36.36)**	1 (9.09)
Therapeutic range 6 – 12 mcg/ml	3	-	1 (33.33)
Overtherapeutic range > 12 mcg/ml	1	-	-

**Excluded the two patients who had AOP after discontinued the co-treatments.

Table 23 : The causes for not gaining benefit effect in the patients used theophylline as an adjuvant to weaning

Theophylline serum concentration	N*	Number of the patients : cases			
		Apnea	Severe retraction	Brain death	Pneumothorax
Subtherapeutic range < 6 mcg/ml	5	4**	-	-	1
Therapeutic range 6 – 12 mcg/ml	3	1**	1	1	-
Overtherapeutic range > 12 mcg/ml	1	1**	-	-	-

* Number of patients who did not gain benefit effect from theophylline therapy.

** Apnea resulted from infection.