CHAPTER IV

RESULTS AND DISCUSSION

Theophylline Therapeutic level Monitoring

1. Therapeutic Monitoring of Theophylline

Sixty one admitted patients who met the criteria in this study were monitored. Table 2 showed the characteristics, ie., age, height, body weight, history of smoking along with the disease or disorder of the patients studied, their mean age was 62.44 ± 12.61 (mean ± SD). Table 3 showed that majority of the patients treated with theophylline were COPD patients (59.02%) and Asthmatic patients (26.23%).

Theophylline serum level and clinical responses were determined for all patients. Clinical responses to theophylline therapy were observed for both beneficial effects and adverse reaction occuring. The patient was indicated as showing clinical improvement to theophylline therapy if respiratory disorder was decreased and no adverse reaction occuring. If adverse reaction was already occured, a new dosage regimen was determined and the patient was further monitored for the decreasing in adverse reaction.

Table 4 illustrated theophylline dosage regimen, measured theophylline serum concentrations and the clinical responses along with some factors which might affect the elimination of theophylline (e.g., concurrent drug and diet, concomitant disease and/or disorder, smoking history, etc.). The eighteen pateints (29.51%) were treated with theophylline alone,and the forty-three pateints (70.49%) were treated with theophylline together with other drugs (beta-adrenergic agonists, corticosteroids and anticholinergic drugs) as shown in Table 4. Appendix III showed clinical responses of individual patient in detail including respiratory disorder symptoms, peak expiratory flow rate, and adverse reactions of theophylline and/or other drugs.

Physicians at Ratchaburi Hospital usually started theophylline therapy with oral sustained release preparations and the normal dosage regimen was 200 - 500 mg/day taken once or twice daily (dosing interval was 12 or 24 hours) as shown in Table 5. Different dosage regimens were given depending on the severity of respiratory disorder symptoms of the patients.

Table 2 Characteristics of Patients Studied

Patient Number[a]	Gender	Age (yr)	Height (cm)	BW[b] (kg)	Smoking History[c]	Respiratory Disorder[d]	Concomitant Disease or Disorder
1	M	59	164	61	Never Smoking	Asthma	-
2	F	46	150	52	Never Smoking	Asthma	-
3	M	70	161	59	Stop Smoking	COPD	Left Heart Failure
4	M	64	165	51	Stop Smoking	COPD	-
5	M	70	161	54	Stop Smoking	COPD	Ingerinal Hermia
6	M	85	*155	*58	Stop Smoking	COPD	Upper GI Bleeding
7	M	57	166	61	Stop Smoking	Asthma	Ischemic Heart Disease, Premature Ventricular Contraction
8	M	76	172	51	Stop Smoking	COPD	Urinary Tract Infection, Liver Dysfunction
9	M	56	170	76	Never Smoking	Asthma	-
10	M	57	173	51	Never Smoking	COPD	-
11	M	75	146	30	Smoking	COPD	Pneumonia
12	F	57	148	58.5	Never Smoking	Asthma	-
13	M	56	164	56	Stop Smoking	Asthma	-
14	M	77	*165	*70	Stop Smoking	COPD	Renal Failure, Pneumonia

Continued

Patient Number[a]	Gender	Age (yr)	Height (cm)	BW[b] (kg)	Smoking History[c]	Respiratory Disorder[d]	Concomitant Disease or Disorder
15	M	54	163	41	Stop Smoking	Asthma	-
16	M	61	173	45	Smoking	COPD	-
17	M	73	181	49	Smoking	COPD	Liver Dysfunction
18	M	59	161	48	Stop Smoking	Asthma	-
19	M	59	165	54	Never Smoking	Asthma	-
20	M	62	163	46	Stop Smoking	Asthma	-
21	M	55	153	47	Stop Smoking	COPD	-
22	M	74	155	37	Stop Smoking	COPD	-
23	M	27	178	70	Nerve Smoking	Asthma	-
24	M	69	173	49	Stop Smoking	COPD	Hypertension
25	M	65	165	41	Never Smoking	COPD, Bronchiolectasis	-
26	M	65	171	56	Smoking	COPD	-
27	M	72	159	44	Stop Smoking	COPD	-
28	M	49	161	54	Smoking	COPD	Pneumonia, Melioidosis
29	M	65	168	61	Stop Smoking	COPD	-

Continued

Patient Number[a]	Gender	Age (yr)	Height (cm)	BW[b] (kg)	Smoking History[c]	Respiratory Disorder[d]	Concomitant Disease or Disorder
30	F	86	140	28	Never Smoking	Asthma, Allergic Rhinitis, Bronchiolectasis	-
31	M	61	*170	*46	Stop Smoking	COPD	-
32	M	32	160	39	Smoking	Silicosis Lung	-
33	M	45	170	56	Stop Smoking	Asthma	Ischemic Heart Disease, Liver Dysfunction, Urinary Tract Infection
34	M	55	174	46	Stop Smoking	Asthma, COPD	-
35	M	62	173	52	Stop Smoking	COPD	-
36	M	78	170	63	Stop Smoking	COPD, Asthma	Diabetes Mellitus, Heart Failure
37	M	73	143	30	Smoking		-
38	F	68	145	40	Never Smoking	Asthma	-
39	M	73	160	46	Stop Smoking	COPD	-
40	M	67	155	42	Stop Smoking	COPD	Gout
41	M	68	155	41	Smoking, Stop Smoking[f]	COPD	Gout

Continued

Patient Number[a]	Gender	Age (yr)	Height (cm)	BW[b] (kg)	Smoking History[c]	Respiratory Disorder[d]	Concomitant Disease or Disorder
42	F	67	155	44	Stop Smoking	Asthma	Anemia
43	M	64	150	40	Stop Smoking	COPD	Stokes Adams Syndrom
44	M	65	165	52	Smoking	COPD, Atelectasis	-
45	M	59	160	54	Stop Smoking	COPD	Diabetes Mellitus, Ischemic Heart Disease
46	M	45	162	57	Never Smoking	COPD	Fever sustained for > 24 hrs.
47	M	67	*160	*40	Stop Smoking	Carcinoma Lung	-
48	M	39	172	54	Smoking	Bronchiectasis	-
49	M	46	152	41	Smoking	COPD	Chronic Renal Failure,Urinary Tract Infection
50	M	51	154	51	Smoking	Asthma	-
51	M	31	165	76	Smoking	Asthma	-
52	M	72	164	50	Stop Smoking	COPD	GI Bleeding
53	M	71	160	48	Never Smoking	COPD	Diabetes Mellitus
54	M	71	155	49	Stop Smoking	COPD	Urinary Tract Infection

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Patient Number[a]	Gender	Age (yr)	Height (cm)	BW[b] (kg)	Smoking History[c]	Respiratory Disorder[d]	Concomitant Disease or Disorder
55	M	75	160	*30	Stop Smoking	COPD	Acute Renal Failure, Cardiac Decompensation, Malnutrition
56	M	64	164	*56	Stop Smoking	COPD	Hypertension, Cerebral Infarction, Gastritis
57	M	75	152	33	Stop Smoking	COPD	Hypertension, Cardiac Decompensation
58	M	83	164	61	Stop Smoking	COPD	-
59	M	67	*160	*35	Stop Smoking	COPD	Multiple Myeloma
60	M	44	174	58	Smoking	COPD	Chronic Renal Failure, Hypertension
61	M	63	162	52	Stop Smoking	Infectious Bronchiolectasis	Liver Dysfunction
X ± SD	M = 56 F = 5	62.44 ± 12.61	161.92±8.74	49.84 ± 10.51			
(Range)		(27-86)	(140-181)	(28-76)			

(a) Patient Number

Number 1-43 : Patients were treated with theophylline together with other drugs (beta - adrenergic agonists, corticosteroids, and anticholinergic drugs).

Number 44-61 : Patients were treated with theophylline alone.

(b) BW = Body Weight

(c) Smoking History

- Never Smoking : Patients have never smoked cigarette and/or tobacco.
- Stop Smoking : Patients used to smoking about tweenty cigarettes/day and/or fifteen tobaccos/day but later, they have stopped smoking for ≥ one month before their blood samples were obtained.
- Smoking : Patients used to smoking about ten cigarettes/day and/or ten tobaccos/day but later, they have stopped smoking for ≤ ten days before their blood samples were obtained.

* Measurement with questionaire or estimation.

(d) Respiratory Disorder was treated with theophylline by physician's diagnosis.

(e) Their liver dysfunctions were observed from high theophylline serum level and adverse reaction occuring, later their liver functions were examined by clinical laboratory.

(f) Patient stopped smoking about ten cigarettes/day for one month before his blood sample was obtained for theophylline serum concentration measurement.

Table 3 : Percentage of Patients with Different Types of Respiratory Disorder.

Respiratory Disorder	Number of Patients	Percentage of Patients
1. COPD	36	59.02
2. Asthma	16	26.23
3. Bronchiolectasis	2	3.28
4. Silicosis Lung	1	1.64
5. Carcinoma Lung	1	1.64
6. COPD + Asthma	2	3.28
7. COPD + Bronchiolectasis	1	1.64
8. COPD + Atelectasis	1	1.64
9. Asthma + Allergic Rhinitis + Bronchiolectasis	1	1.64
	61	100

+ = together with

Table 4 : Dosage Regimen, Measured Theophylline Serum Concentration Clinical Responses, and Factors Affecting Theophylline Elimination.

Patient Number [a]		Dosage of Theophylline (mg)	Interval (hr)	Route	Serum concentrations [b]		Factor Affecting Theophylline Elimination	Clinical Responses [c]	
					Trough (mcg/ml)	Peak (mcg/ml)		Respiratory Disorder	Adverse Reaction
1		200	12	oral	4.62	5.98	-	↓	-
2		200	12	oral	7.11	10.94	-	↓	-
3		200	12	oral	8.55	11.44	Left heart failure, Fresh milk (UHT) 6 boxs/day	↓	-
4		200	12	oral	7.56	9.64	-	↓	-
*5	B	200	12	oral	11.60	14.70	Cimetidine 800mg/day	↓	+
	A	300	24	oral	-	11.06	Cimetidine 800mg/day	↓	↓
6		200	12	oral	11.87	13.38	Cimetidine 800mg/day	↓	-
*7	B	200	12	oral	12.78	13.66	Ischemic heart disease, Premature ventricular contraction	↓	+
	A	300	24	oral	-	- [d]	Ischemic heart disease, Premature ventricular contraction	↓	↓
*8	B	300	24	oral	12.15	14.20	Liver dysfunction	↓	+, ⊕ [e]
	A	200	24	oral	-	10.52	Liver dysfunction	↓	↓, ⓓ

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Patient Number[a]	Dosage of Theophylline (mg)	Interval (hr)	Route	Serum concentrations[b]		Factor Affecting Theophylline Elimination	Clinical Responses[c]	
				Trough (mcg/ml)	Peak (mcg/ml)		Respiratory Disorder	Adverse Reaction
*9 B	200	12	oral	8.72	10.64	Erythromycin 1000 mg/day	↓	-
A	300	12	oral	-	9.08	-	↓	-
10	200	12	oral	2.58	4.95	-	↓	-
*11 B	200	12	oral	15.91	22.62	Pneumonia, Smoking	↓	+ or -
A	300	24	oral	-	5.93	Smoking	↓	-
12	200	12	oral	6.32	9.97	-	↓	+
13	200	12	oral	7.44	10.71	-	↓	+
14	200	12	oral	16.79	16.86	Pneumonia	↔[f]	-
15	200	12	oral	4.26	6.64	-	↓	-
16	200	12	oral	5.27	6.42	Smoking	↓	-
*17	200	12	oral	18.39	22.01	Liver dysfunction, Smoking	↑[g]	+
C+h	-	-	-	-	-	Liver dysfunction, Smoking	↓	↓
*18 B	200	12	oral	4.31	5.55	Erythromycin 1000 mg/day, Fresh milk (UHT) 3 boxs/day	↔	-
A	300	12	oral	-	9.60	-	↓	-

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Patient Number [a]	Dosage of Theophylline (mg)	Interval (hr)	Route	Serum concentrations [b]		Factor Affecting Theophylline Elimination	Clinical Responses [c]	
				Trough (mcg/ml)	Peak (mcg/ml)		Respiratory Disorder	Adverse Reaction
19	200	12	oral	5.57	8.43	-	↓	-
20	250	12	oral	11.40	16.55	-	↓	-
21	300	24	oral	7.58	11.20	-	↓	-
22	200	12	oral	13.66	13.79	-	↓	-
23	400	24	oral	3.74	5.89	-	↓	-
24	300	24	oral	4.87	8.67	-	↓	-
25	200	12	oral	5.69	7.49	-	↓	-
26	300	24	oral	4.61	5.26	Smoking	↓	-
27	200	12	oral	6.15	7.40	-	↓	-
28	200	12	oral	3.96	6.41	Pneumonia, Smoking, Fresh milk (UHT) 3 boxs/day	↓	-
29	200	12	oral	7.82	11.17	-	↓	+, ⊕
30	100	12	oral	9.77	13.00	-	↓	+, ⊕
	100	12	oral	-	7.47	Moripront® F 200 ml/day, Geriatric Pharmaton® 1 Cap/day, and Moriamine® 3 Caps/day	↓	↓, ⊕

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Patient Number [a]	Dosage of Theophylline (mg)	Interval (hr)	Route	Serum concentrations [b]		Factor Affecting Theophylline Elimination	Clinical Responses [c]	
				Trough (mcg/ml)	Peak (mcg/ml)		Respiratory Disorder	Adverse Reaction
31	200	12	oral	9.01	12.28	-	↑ [d]	-
32	200	12	oral	5.31	10.22	Rifampicin 450 mg/day, Smoking	↓	-
	200	12	oral	-	6.92	Smoking	↓	-
*33 B	300	24	oral	30.60	31.4	Ischemic heart disease, Liver dysfunction, Lexinor® 800 mg/day	↓	+
C	-	-	-	-	-	Ischemic heart disease, Liver dysfunction, Lexinor® 800 mg/day	↓	↓
*34 B	Aminophylline 250 mg	6	IV infusion for 15 mins	15.47	21.58	-	↓	↓, ⊕
A	200	12	oral	-	10.83	-	↓	-, ⊕
*35 B	Aminophylline 250 mg	6	IV infusion for 15 mins	19.04	26.73	Cimetidine 800 mg/day	↓	-
A	300	12	oral	-	14.97	Cimetidine 800 mg/day	↓	-
A	200	12	oral	-	10.93	Cimetidine 800 mg/day	↑ [d]	-

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Patient Number [a]		Dosage of Theophylline (mg)	Interval (hr)	Route	Serum concentrations [b]		Factor Affecting Theophylline Elimination	Clinical Responses [c]	
					Trough (mcg/ml)	Peak (mcg/ml)		Respiratory Disorder	Adverse Reaction
*36	B	Aminophylline 250 mg	6	IV infusion for 15 mins	23.8	28.15	Heart Failure	↓	+
	A	200	12	oral	-	16.15	Heart failure	↓	↓
37		125	12	oral	4.53	6.3	Smoking	↓	+
*38	B	300	24	oral	7.93	7.98	-	↔	-
	A	400	24	oral	-	9.52	-	↓	-
39		300	24	oral	5.21	8.88	-	↓	-
40		200	12	oral	11.37	16.83	Allopurinol 300 mg/day	↓	+, ⊕
*41	B	250	12	oral	9.20	10.48	Allopurinol 300 mg/day Smoking	↔	-
	A	200	12	oral	-	14.64	Allopurinol 300 mg/day	↓	-
42	[k]	100	12	oral	3.41	4.09	-	↓	-
*43	B	Theo Dur® 400 mg/day and Tedral® 4 tabs/day		oral	28.11	32.30	Phenobarbital (in Tedral®) 32 mg/day	↓	+ (Toxicity)
	A	Tedral® 4 tabs/day		oral	-	-	Phenobarbital (in Tedral®) 32 mg/day	↓	↓
44		200	12	oral	5.34	7.42	Erythromycin 2000 mg/day,Smoking	↓	-

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Patient Number [a]	Dosage of Theophylline (mg)	Interval (hr)	Route	Serum concentrations [b]		Factor Affecting Theophylline Elimination	Clinical Responses [c]	
				Trough (mcg/ml)	Peak (mcg/ml)		Respiratory Disorder	Adverse Reaction
45	200	12	oral	11.21	11.70	Smoking, Ischemic heart disease	↓	-
46	200	12	oral	11.15	13.67	Fever sustained for > 24 hrs	↓	-
47	200	12	oral	6.26	7.47	Rifampicin 450 mg/day	↓	-
48	200	12	oral	2.54	3.90	Smoking	↓	-
49	200	12	oral	6.25	7.54	Lexinor® 800 mg/day, Smoking	↓	-
50	250	12	oral	4.29	8.26	Smoking	↓	-
51	200	12	oral	3.57	5.27	Smoking	↓	-
52	300	24	oral	8.41	8.87	Cimetidine 800 mg/day	↓	-
53	200	12	oral	8.50	10.97	Rifampicin 450 mg/day	↓	-
	200	12	oral	-	8.06	-	↓	-
*54 B	200	12	oral	14.41	16.65	Fever sustained for > 24 hrs, Smoking	↓	+
A	300	24	oral	-	8.70	Smoking	↓	↓
55* B	200	12	oral	31.24	34.07	Cardiac decompensation	↓	+
A	100	12	oral	-	- [f]	Cardiac decompensation	↓	↓
56	250	12	oral	11.58	18.21	Cimetidine 800 mg/day	↓	+
	250	12	oral	8.27	12.67	-	↓	↓

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Patient Number [a]	Dosage of Theophylline (mg)	Interval (hr)	Route	Serum concentrations [b]		Factor Affecting Theophylline Elimination	Clinical Responses [c]	
				Trough (mcg/ml)	Peak (mcg/ml)		Respiratory Disorder	Adverse Reaction
*57 B	250	12	oral	-	31.09	Cardiac decompensation	↓	+
A	200	24	oral	-	7.43	-	↓	↓
58	200	24	oral	3.08	4.63	-	↓	-
59	200	12	oral	12.31	14.00	-	↓	+
60	200	12	oral	7.23	8.72	Cardiac decompensation, Smoking	↓	-
*61 B	200	12	oral	-	-	-	↓	+
A	300	24	oral	7.43	8.12	Erythromycin 2000 mg/day	↓	↓
A	300	24	oral	-	15.61	Liver dysfunction [m]	↓	+
A	200	24	oral	-	10.44	Liver dysfunction	↓	+
C	-	-	oral	-	-	Liver dysfunction	↓	↓

(a) Patient Number 1-43 : Patients were treated with theophylline together with other drugs (beta-adrenergic agonists, corticosteroids, and anticholinergic drugs).

Patient Number 44-61 : Patients were treated with thophylline alone.

* Dosage regimen had been adjusted.

B : Before dosage regimen adjustment

A : After dosage regimen adjustment

C : Theophylline was discontinued and changed to other drugs (beta-adrenergic agonists, corticosteroids, and anticholinergic drugs).

(b) Serum Concentrations

- Trough serum concentration : Blood sample was obtained immediately before the next dose.
- Peak serum concentration of sustained release dosage form was obtained at midpoint of dosing interval.
- Peak serum concentration of intermittant IV infusion was obtained at one hour after finished IV infusion.

(c) Clinical Responses

- Respiratory Disorder

  ↓ : Improved

  ⟷ : Not Improved

  ↑ : Worsen

  These symbols were comparison of respiratory disorders between before treatment with theophylline and when patients were discharged from hospital.

- Adverse Reactions

  - : No Adverse reaction was observed.

  + : Adverse reaction of theophylline was observed.

  ↓ : Adverse reaction of theophylline was decreased or disappeared.

  + or - : Patient with high risk for adverse reaction.

  ⊕ : Adverse reaction of other drugs was observed.

  ⊕↓ : Adverse reaction of drugs was decreased or disappeared.

(d) Patient losed follow up.

(e) Berotec R was discontinued because of muscle tremor occuring in paitent.

(f) Patient was refered to private hospital.

(g) Patient had respiratory failure status and was treated in CCU.

(h) Patient was treated respiratory failure status by Brid's respiration.

(i) Patient had respiratory failure status, Later, patient died in CCU.

(k) Tedral® consists theophylline hydrous 130 mg, ephedrine HCL 24 mg, and phenobarbital 8 mg in one table. These peak and trough serum concentration were obtained when patient received Theo Dur® for six hours after the dose and immediately before the next dose of Theo Dur®.

(l) The patient rested at home and could not follow up.

(m) Liver dysfunction was first suspected since measured theophylline serum concentration was high and was later comfirmed by clinical laboratory test.

Table 5 : Percentage of Pateints Receiving Different Dosing Patterns.

Theophylline Dosage Regimens	Number of Patients (n=60)	Percentage of Patients (n=60)
1. Theophylline + Other Drugs* (n=42)		
1.1 Aminophylline : 250 mg by IV infusion for 15 mins every 6 hrs	3	5
1.2 Oral Sustained Release Preparations : 200 - 500 mg/day, dosing interval was 12 or 24 hrs	39	65
2. Theophylline alone (n=18)		
2.1 Oral Sustained Release Preparations : 200 - 500 mg/day, dosing interval was 12 or 24 hrs	18	30

+ = together with

Other Drugs* = Beta - Adrenergic Agonists, Corticosteroids and Anticholinergic Drugs.

(a) One of the sixty-one patients was excluded from this table because of receiving both Theo Dur^{R} and Tedral^{R}.

Theophylline was given according to the physician traditional dosage regimen,the majority of patients had peak theophylline serum concentration within subtherapeutic range (45.76%) , and therapeutic range (40.68%) while their trough theophylline serum concentration were mostly within subtherapeutic range (64.41%) as shown in Table 6 and 7. The six patients (10.17%) showed no clinical beneficial effect from theophylline therapy and the fifteen patients (25.42%) showed theophylline adverse reactions were illustrated in Table 8. These patients should be closely monitored for improvement in their respiratory disorders and for decreasing in theophylline adverse reactions.

From Table 9 indicated that higher number of patients showed beneficial effects when their peak theophylline serum concentrations were higher than 5 mcg/ml and their trough theophylline serum concentrations were higher than 5 mg/ml. The result also showed that the beneficial effect on respiratory disorder could be observed even when trough theophylline serum concentration was as low as 3.85 ± 0.78 mcg/ml (mean ± SD) which was not too surprising since foreign literature reported that beneficial effect on lung function could be observed over the theophylline serum range 3 to 25 mcg/ml (Neville and McDevitt, 1991).

Table 10 illustrated that the beneficial effects on respiratory disorder were observed at trough theophylline serum concentrations less than 5 mcg/ml (mean ± SD =3.85±0.78 mcg/ml) in the patients with mild respiratory disorder who treated with theophylline alone (30.77%) , and in the patients treated with theophylline together with beta- adrenergic agonists and corticosteroids (30.77%).

Figure 4 showed that when the patients were treated with theophylline, the percentage of patients showed beneficial effects was nearly the same whether their peak theophylline serum concentrations were subtherapeutic, therapeutic or overtherapeutic ranges. Furthermore, the correlation between the percentage of patients showed beneficial effects and their trough theophylline serum concentrations was also not able to observed. From Figure 5, when the patients were treated with theophylline , the percentage of patients showed adverse reactions when their peak serum theophylline concentrations were within subtherapeutic, therapeutic and overtherapeutic peak theophylline levels as 0, 37.50 and 75, respectively, while trough concentrations within subtherapeutic, therapeutic and overtherapeutic ranges showed the incidence of adverse reactions to be 5.26%, 52.94% and 100%, respectively. The results from Figure 4-5 indicated that there were no correlation between beneficial effect and theophylline serum concentration. However ,higher incidence of theophylline adverse reactions could be observed when trough levels rather than peak levels were classified. It should be concluded that theophylline dosage regimen adjustment for individual patient should be determined from the patient peak theophylline serum

concentration. In addition, these results were corresponded to those reported in foreign literature which suggested that the usually accepted therapeutic range of 10 to 20 mcg/ml is not an absolute but a statistical concept (Kelly and Hill, 1993) and theophylline has a good correlation between theophylline serum level and adverse reaction or toxicity.

The Figure 6,7 indicated that there were no difference in the incidence of theophylline adverse reactions between the group of patients treated with theophylline together with other drugs and the group of patients treated with theophylline alone (24% and 29.41%,respectively). However, the incidence of adverse reactions from other drugs were observed significantly (19%) in the former group.

Table 6 : Percentage of Patients with Peak Theophylline Serum Concentrations within Therapeutic, Subtherapeutic and Overtherapeutic Ranges after Treatment with Traditional Dosage Regimen.

Peak Level[a]	Number of Patients	Percentage n = 59[b]	Number of Patients with No Beneficial Effect (%)	Number of Patients with Adverse Reactions (%)
S	27	45.76	2 (7.41)	0 (0)
T	24	40.68	3 (12.50)	9 (37.50)
O	8[C]	13.56	1 (12.50)	6 (75.00)

(a) S = Subtherapeutic range (< 10 mcg/ml)
T = Therapeutic range (10 -20 mcg/ml)
O = Overtherapeutic range (> 20 mcg/ml)

(b) n = 59 because two of the sixty - one patients were excluded from this table. One patient received Theo Dur^{R} together with Tedral^{R} and theophylline serum concentration of other one patient could not be obtained.

(c) Three of the eight patients initially received theophylline by IV infusion of aminophylline for fifteen minutes every six hours.

Table 7 : Percentage of Patients with Trough Theophylline Serum Concentrations within Therapeutic, Subtherapeutic and Overtherapeutic Ranges after Treatment with Traditional Dosage Regimen.

Trough Level[a]	Number of Patients	Percentage n = 59[b]	Number of Patients with No Beneficial Effect (%)	Number of Patients with Adverse Reactions (%)
S	38	64.41	4 (10.53)	2 (5.26)
T	17	28.81	2 (11.76)	9 (52.54)
O	4	6.78	0 (0)	4 (100)

a) S = Subtherapeutic range (<10 mcg/ml)
T = Therapeutic range (10 -20 mcg/ml)
O = Overtherapeutic range (> 20 mcg/ml)

(b) n = 59 because two of the sixty - one patients were excluded from this table. One patient received Theo Dur^{R} together with Tedral^{R} and theophylline serum concentration of other one patient could not be obtained.

Table 8 : Incidence of No Beneficial Effect and Adverse Reactions of Theophylline in Pateints after Treatment with Traditional Dosage Regimen.

Clinical Responses	Number of Patients	Percentage of Patients n = 59 [(a)]
No Beneficial Effect	6	10.17
Adverse Reaction Occuring	15	25.42

(a) n = 59 because two of the sixty - one patients were excluded from this table. One patient received Theo Dur[R] together with Tedral[R] and theophylline serum concentration of other one patient could not be obtained.

Table 9 : Percentage of Patients Showed Beneficial Effects while Theophylline Serum Concentrations within Subtherapeutic Range.

Theophylline Seum Level	Theophylline Measured Serum Concentration (mcg/ml) (mean ± SD)	Number of Patients Showed Beneficial Effects (%)
Trough Level (n = 34)		
< 5 mcg/ml	3.85 ± 0.78	12 (38.24)
> 5 mcg/ml	6.96 ± 1.35	21 (61.76)
Peak Level (n = 25)		
< 5 mcg/ml	4.39 ± 0.48	4 (16.00)
> 5 mcg/ml	7.47 ± 1.38	21 (84.00)

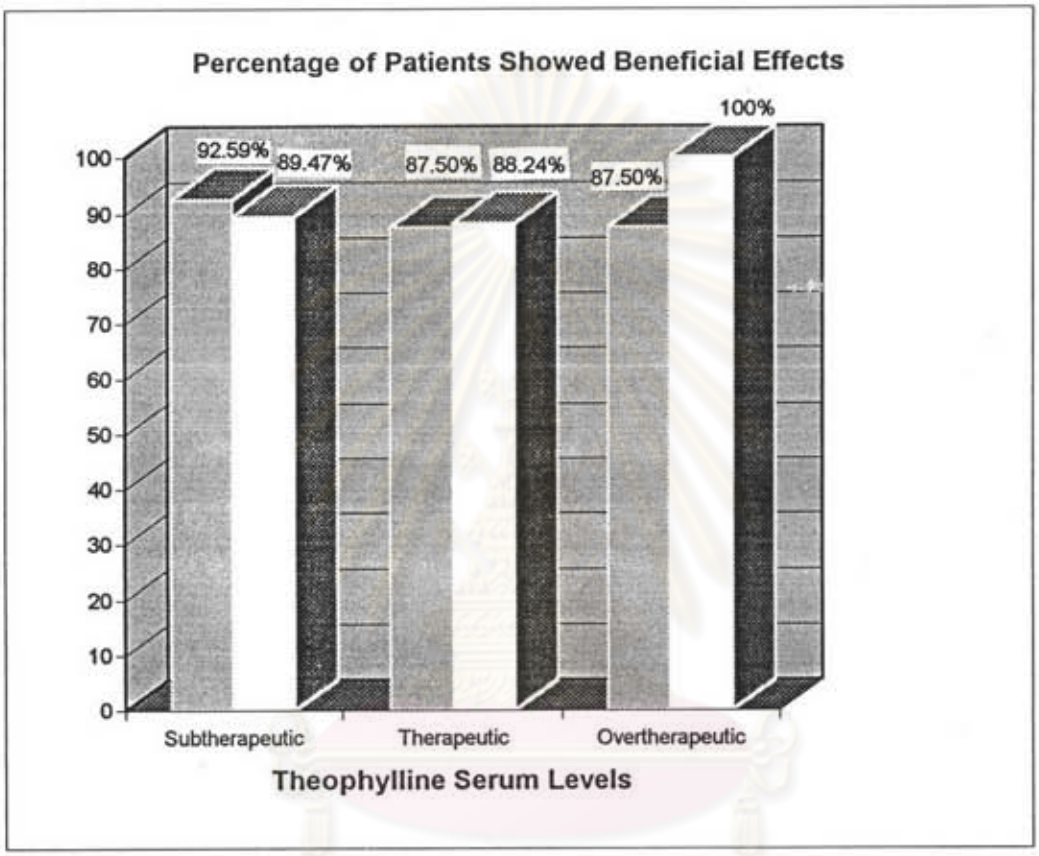
Table 10 : Percentage of Patients Showed Beneficial Effects while Trough Theophylline Serum Concentrations less than 5 mcg/ml.

Theophylline Dosage Regimens	Number of Patients	Percentage of Patients (n = 13)
1. Theophylline alone	4	30.77
2. Theophylline + Other Drugs	9	69.23
2.1 T[(a)] + Beta[(b)]	2	15.38
2.2 T + Beta + Corticosteroids	4	30.77
2.3 T + Beta + Corticosteroids + Berodual[R]	2	15.38
2.4 T + Beta + Berodual[R]	1	7.69

(a) T = Theophylline

(b) Beta = Beta - Adrenergic Agonists

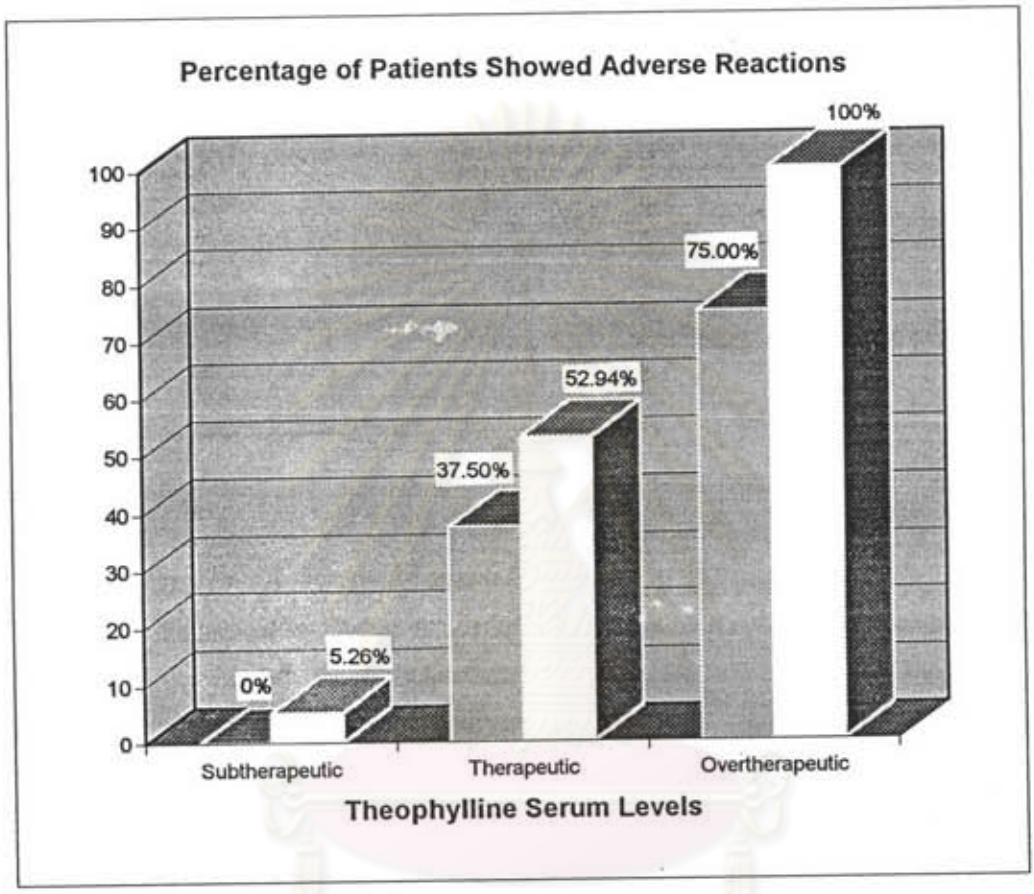
Figure 4 : Correlation between Percentage of Patients Showed Beneficial Effects Versus Peak and Trough Theophylline Serum Concentrations Classified as Subtherapeutic, Therapeutic and Overtherapeutic Ranges in Patients Treated with Theophylline Given Traditional Dosage Regimen.



: Peak Theophylline Serum Concentrations

: Trough Theophylline Serum Concentrations

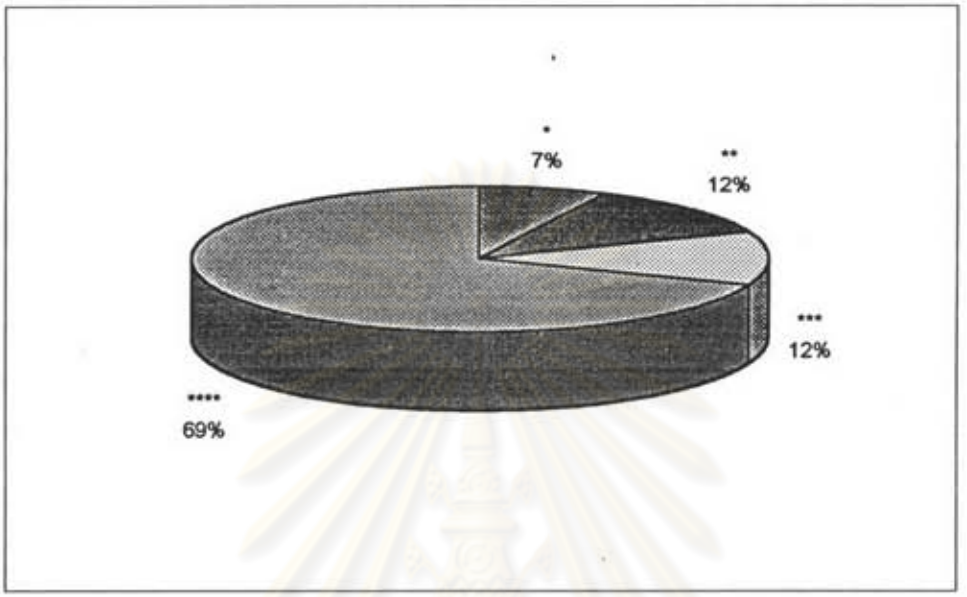
Figure 5 : Correlation of Peak and Trough Theophylline Serum Concentrations with Incidence of Adverse Reactions in Patients Treated with Theophylline Given Traditional Dosage Regimen.



: Peak Theophylline Serum Concentrations

: Trough Theophylline Serum Concentrations

Figure 6 : Percentage of Patients Showed Sign of Adverse Reactions after Patients Treated with Theophylline together with Other Drugs (beta - adrenergic agonists, corticosteroids, and anticholinergic drugs) Given Traditional Dosage Regimen.



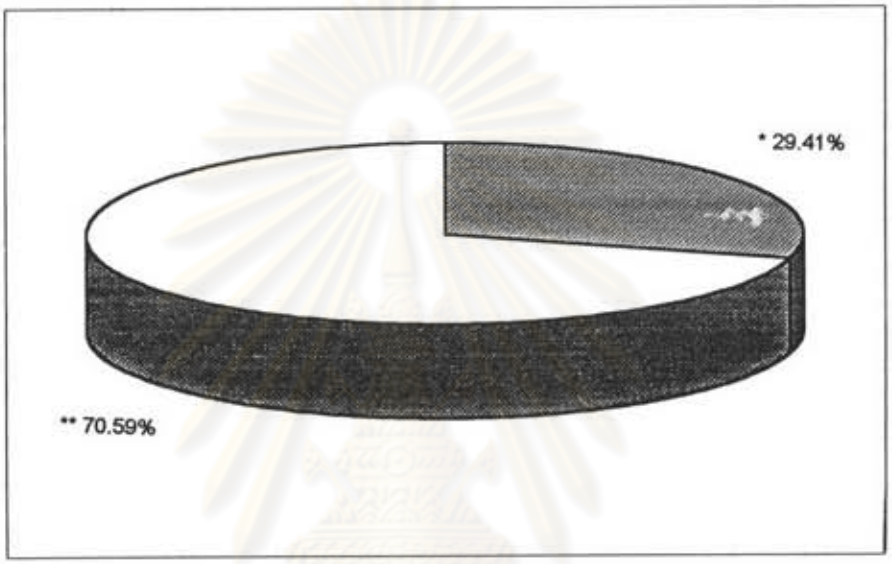
* Adverse Reactions of Other drugs

** Adverse Reactions of both Theophylline and Other Drugs

*** Adverse Reactions of Theophylline

*** No Adverse Reaction was Observed

Figure 7 : Percentage of Patients Showed Sign of Adverse Reactions after Patients Treated with Theophylline alone Given Traditional Dosage Regimen.



* Adverse Reactions of Theophylline

** No Adverse Reactions was Observed

Table 11 indicated that all types of theophylline adverse reactions were able to occurred while the theophylline serum concentrations were within the therapeutic range except for nervousness which occurred in only one patient with the peak theophylline serum concentration equal to 22.01 mcg/ml. The most frequent incidence of theophylline adverse reactions were pulse rate ≥ 100/min and palpitation (18.33%). Palpitation was usually mild and transient. Anorexia (11.67%), nausea (8.33%) and vomiting (6.67%) were the most common adverse gastrointestinal effects of theophylline. Nausea occured at the lowest theophylline serum level comparing to other adverse reactions. This result was corresponding to those reported in foreign literature. Frew and Holgate (1993) reported that some patients may experience nausea even though their theophylline serum concentrations were at the lower end of the therapeutic range. Therefore, adverse reactions of theophylline which might occured while serum concentrations were within therapeutic range were pulse rate ≥ 100/min, palpitation, anorexia, nausea, dizziness, vomiting, insomnia, sinus tachycardia, muscle tremor and hypotension.

Table 12 showed the percentage of theophylline adverse reactions in the patients with factors affecting theophylline elimination. All patients with cardiac disorder status or liver dysfunction showed some types of theophylline adverse reaction. Therefore, theophylline therapeutic monitoring would be required when theophylline was used for treatment of respiratory disorder in these patients.

Table 13,14 indicated that when theophylline was given according to the physician traditional dosage regimen, 43 of 61 patients (70.49%) did not require thophylline dosage regimen adjustment , however , 18 of 61 patients (29.51%) required. The patients requiring theophylline dosage regimen adjustments were the patients who had the peak theophylline serum concentrations within overtherapeutic range (9 of 18) , therapeutic range (6 of 18) , or subtherapeutic range (2 of 18) , and one patient could not be obtained his blood sample for theophylline level measurement. Additionally , 16 of the 18 patients (88.89%) requiring theophylline dosage regimen adjustments had some factors which affected theophylline elimination. Therefore , clinical responses should be closely monitored in the patients with factors affecting theophylline elimination.

Table 15 showed that the percentage of patients whose clinical responses were improved after theophylline dosage regimen adjustments were 94.44 (17of 18). Only one patient who did not show his clinical improvement died from respiratory failure status. The majority of patients (61.11%) showed clinical response improvement through adverse reaction decreasing, while 22.22% of the patients showed improvement in their respiratory disorder. Therefore, application of pharmacokinetic theories to adjust for the appropriate theophylline dosage regimen to optimize therapy for individual patient, could improve clinical response in patients.

Table 11 : Incidence of Different Adverse Reactions, and Minimal Peak Theophylline Serum Concentration which Adverse Reaction Occured.

Adverse Reactions of Theophylline	Number of Patients with Adverse Reactions	Incidence of Adverse Reactions	Minimal Peak Theophylline Serum Concentration Which Adverse Reaction Occured (mcg/ml)**
1. Pulse Rate ≥ 100/min	11	18.33	11.17
2. Palpitation	11	18.33	11.17
3. Anorexia	7	11.67	13.00
4. Nausea	5	8.33	10.44
5. Dizziness	4	6.67	13.00
6. Vomiting	4	6.67	14.20
7. Insomnia	4	6.67	15.61
8. Sinus Tachycardia	4	6.67	18.21
9. Muscle Tremor	2	3.33	13.00
10. Hypotension	1	1.67	14.70
11. Nervousness	1	1.67	22.01

Total number of patients = 60

** Range of peak theophylline serum concentration = 10.44 -34.07 mcg/ml.

Table 12 : Incidence of Adverse Reactions in Patients with Different Factors Affecting Theophylline Elimination.

Factors Affecting Theophylline Elimination	Peak Theophylline Serum Concentration (Number of Patients)				Number of Patients with Adverse Reactions	Percentage of Patients with Adverse Reactions
	S*	T**	O***	Total		
1. Cardiac Disorder	0	1	3 [(a)]	4	4	100
2. Liver Dysfunction	0	2	0	2	2	100
3. Cardiac Disorder combined with Smoking	1	1	0	2	0	0
4. Liver Dysfunction combined with Smoking	0	0	1	1	1	100
5. Age ≥ 60 yrs combined with Cimetidine 800 mg/day	1	3	1	5	2	40
6. Age ≥ 60 yrs	7	5	0	12	3	25

S* , T** , 0***

S* = Subtherapeutic range

T** = Therapeutic range

0*** = Overtherapeutic range

(a) One of the three patients had the peak theophylline serum concentrations within overtherapeutic range from aminophylline by IV infusion for fifteen minutes every six hours.

Table 13 : Theophylline Dosage Regimen Adjustment and Its Corresponding Clinical Responses

Patient Number [a]	Theophylline Dosage Regimen [b]	Peak [c] (mcg/ml)	Factor Affecting Theophylline Elimination	Clinical Responses [d]	
				Respiratory Disorder	Adverse Reaction
5	B: Theophylline 400 mg/day (oral)	14.70	Cimetidine 800 mg/day	↓	+
	A: Decrease dose to 300 mg/day (oral)	11.06	Cimetidine 800 mg/day	↓	↓
7	B: Theophylline 400 mg/day (oral)	13.66	Ischemic heart disease, Premature ventricular contraction	↓	+
	A: Decrease dose to 300 mg/day (oral)	- [e]	Ischemic heart disease, Premature ventricular contraction	↓	↓
8	B: Theophylline 300 mg/day (oral)	14.20	Liver dysfunction	↓	+
	A: Decrease dose to 200 mg/day (oral)	10.52	Liver dysfunction Lexinor® 800 mg/day	↓	↓
9	B: Theophylline 400 mg/day (oral)	10.64	Erythromycin 1000 mg/day	↓	-
	A: Increase dose to 600 mg/day (oral)	9.08	-	↓	-
11	B: Theophylline 400 mg/day (oral)	22.62	Pneumonia, Smoking	↓	+ or -
	A: Decrease dose to 300 mg/day (oral)	5.93	Smoking	↓	-

Patient Number [a]	Theophylline Dosage Regimen [b]	Peak [c] (mcg/ml)	Factor Affecting Theophylline Elimination	Clinical Responses [d]	
				Respiratory Disorder	Adverse Reaction
17	B: Theophylline 400 mg/day (oral)	22.01	Liver dysfunction, Smoking	↑	+
	A: Theophylline was discontinued and changed to other drug*. Patient was also treated with Brid's respiration	-	Liver dysfunction, Smoking	↓	↓
18	B: Theophylline 400 mg/day (oral)	5.55	Erythromycin 1000 mg/day Fresh milk (UHT) 3 boxs/day	⟷	-
	A: Increase dose to 600 mg/day (oral)	9.60	-	↓	-
33	B: Theophylline 300 mg/day (oral)	34.41	Ischemic heart discase, Liver dysfunction, Lexinor 800 mg/day	↓	+
	A: Theophylline was discontinued and changed to other drugs*.	-	Ischemic heart discase, Liver dysfunction, Lexinor 800 mg/day	↓	↓
34	B: Aminophylline 250 mg by IV infusion for 15 minutes every 6 hours	21.58	-	↓	+
	A: Adjust to theophylline 400 mg/day in oral form	10.83	-	↓	↓

Continued.....

Patient Number [a]	Theophylline Dosage Regimen [b]	Peak [c] (mcg/ml)	Factor Affecting Theophylline Elimination	Clinical Responses [d]	
				Respiratory Disorder	Adverse Reaction
35	B: Aminophylline 250 mg by IV infusion for 15 minutes every 6 hours	26.73	Cimetidine 800 mg/day	↓	-
	A: Adjust to theophylline 600 mg/day in oral form	14.93	Cimetidine 800 mg/day	↓	-
	A: Decrease dose to 400 mg/day (oral)	10.93	Cimetidine 800 mg/day	↑ [f]	-
36	B: Aminophylline 250 mg by IV infusion for 15 minutes every 6 hours	28.15	Heart failure	↓	+
	A: Adjust to theophylline 400 mg/day in oral form	16.15	Heart failure	↓	↓
38	B: Theophylline 300 mg/day (oral)	7.98	-	⟷	-
	A: Increase dose to 400 mg/day (oral)	9.52	-	↓	-
41	B: Theophylline 500 mg/day (oral)	10.48	Allopurinol 300 mg/day, Smoking	↓	-
	A: Decrease dose to 400 mg/day (oral)	14.64	Allopurinol 300 mg/day	↓	-
43 [h]	B: Theo Dur® 400 mg/day and Tedral® 4 tabs/day	32.3	Phenobarbital (in Tedral®) 32 mg/day	↓	+ (Toxicity)
	A: Theo Dur® was discontinued but Tedral® was continued.	-	Phenobarbital (in Tedral®) 32 mg/day	↓	↓

Continued.....

Patient Number[a]	Theophylline Dosage Regimen[b]	Peak[c] (mcg/ml)	Factor Affecting Theophylline Elimination	Clinical Responses[d]	
				Respiratory Disorder	Adverse Reaction
54	B: Theophylline 400 mg/day (oral)	16.65	Fever sustained for > 24 hrs, Smoking	↓	+
	A: Decrease dose to 300 mg/day (oral)	8.70	Smoking	↓	↓
55	B: Theophylline 400 mg/day (oral)	34.07	Cardiac decompensation	↓	+
	A: Decrease dose to 200 mg/day (oral)	-[(f)]	Cardiac decompensation	↓	↓
57	B: Theophylline 500 mg/day (oral)	31.09	Cardiac decompensation	↓	+
	A: Decrease dose to 200 mg/day (oral)	7.43	-	↓	↓
61	B: Theophylline 400 mg/day (oral)	-	-	↓	+
	A: Decrease dose to 300 mg/day (oral)	8.12	Erythromycin 2000 mg/day	↓	↓
	A: Maintenance dose to 300 mg/day (oral)	15.61	Liver dysfunction[(f)]	↓	+
	A: Decrease dose to 200 mg/day (oral)	10.44	Liver dysfunction	↓	+
	A: Theophylline was discontinued and changed to other drugs*.	-	Liver dysfunction	↓	↓

(a) Patient Number 5-43 : Patients were treated with theophylline together with other drugs* (beta-adrenergic agonists, corticosteroids and anticholinergic drugs).

Patient Number 54-61 : Patients were treated with theophylline alone.

(b) B = Before Theophylline Dosage Regimen Adjustment

A = After Theophylline Dosage Regimen Adjustment

(c) Peak serum concentration of sustained release dosage form was obtained at midpoint of dosing interval. Peak serum concentration of IV infustion for fifteen minutes every six hours was obtained at one hour after finished IV infusion.

(d) Clinical responses.

- Respiratory Disorder
  - ↓ : Improved
  - ⟷ : Not Improved
  - ↑ : Worsen
- Adverse Reactions
  - \- : No adverse reaction was observed
  - \+ : Adverse reactions was observed
  - ↓ : Adverse reactions was decreased or disappeared

+ or - :Patient with high risk for adverse reaction.

(f) Patient had respiratory failure status, later patient died in CCU.

(h) Peak serum concentration was obtained after patient received Theo Dur® for six hours.

(i) The follow up was losed because the patient was rested at home.

(j) Liver dysfunction of the patient was first observed through high serum theophylline concentration, later his liver function was examined by clinical laboratory test.

Table 14 : Percentage of Patients Receiving Theophylline Serum Level Monitoring and Dosage Regimen Adjustment.

Theophylling Serum Level Monitoring	Number of Patients n = 61	Percentage of Patients n = 61
(1) No adjust dosage regimen because of appropriate clinical responses	43	70.49
(2) Adjust dosage regimen because of inappropriate clinical responses	18	29.51
2.1 Decrease dose of theophylline	8	13.11
2.2 Increase dose of theophylline	3	4.92
2.3 Adjust from aminophylline (IV) to theophylline (oral)	3	4.92
2.4 Theophylline was discontinued and changed to other drugs*.	3	4.92
2.5 Adjustment for overdose theophylline	1 [a]	1.64

other drugs* = beta-adrenergic agonists, corticosteroids, and anticholinergic drugs.

(a) Patient received both Theo Dur® and Tedral®.

Table 15 : Percentage of Patients with Improvement in Clinical Responses.

Clinical Response Improvement	Number of Patients n = 18	Percentage of Patients n = 18
(1) Respiratory Disorder Improvement	4	22.22
(2) Adverse Reaction Decreasing	11	61.11
(3) Decreasing of Risk from Adverse Reactions	1 [(a)]	5.56
(4) Toxicity Decreasing	1	5.56
	17 [(b)]	94.45

(a) Patient had peak serum concentration after administration of oral sustained release dosage form equal to 22.62 mcg/ml, then recommend physician to decrease dose of theophylline.

(b) One patient died from respiratory failure status.

2. Comparison between the measured and the predicted theophylline sreum concentrations

One of the purpose in this study was to compare between the measured theophylline serum concentrations and predicted serum concentrations by applying pharmacokinetic parameters and equations from literatures. Table 16 showed comparison between measured and predicted theophylline serum concentrations in the patients receiving theophylline sustained release dosage form. The mean measure and predicted average theophylline serum concentrations were 11.25 ± 5.79 mcg/ml and 10.99 ± 6.62 mcg/ml (mean ± SD), respectively, and the mean difference between measured and predicted values was 2.06 ± 1.93 (mean ± SD), the mean percentage of difference between measured and predicted values was 19.40 ± 15.21 (mean ± SD).

Table 17, 18 showed that the mean measured peak and trough theophylline serum concentrations after intravenous administration (intravenous infusion for 15 minutes every 6 hours) were 25.49 ± 3.46 mg/ml and 19.44 ± 4.18 mcg/ml (mean ± SD), respectively. The mean percentage of difference between measured and predicted peak serum concentration was 11.05 ± 9.78 (mean ± SD) while the mean percentage of difference between measured and predicted trough serum concentration was 17.00 ± 7.56 (mean ± SD).

Table 19 showed percent coefficient of variation (%cv) in comparison between measured and predicted theophylline serum concentrations. Coefficent of variation of measured and predicted average serum concentrations after administration of oral sustained release dosage form was 24.96% while coefficient of variation of measured and predicted peak serum concentrations, coefficient of variation of measured and predicted trough serum concentration for aminophylline by intravenous infusion for fifteen minutes every six hours were 10.97% and 15.35%, respectively.

Most of the time, the difference between masured and predicted value after administration of theophylline sustained release dosage form were less than 30% as shown in table 20. Table 21 showed the frequency in which the measured average theophylline serum concentration was in the various range of theophylline concentrations and the percentage of difference between the measured and the predicted values. Most often, the average serum theophylline concentrations were measured to be in the range of 5.01 to 10.00 mcg/ml (44.74%) and 10.01 - 15.00 mcg/ml (35.53%). The percentage of difference between measured and predicted values in these two range were 21.57 ± 17.52 and 17.92 ± 12.61, respectively.

When theophylline was given by intravenous infusion for fifteen minutes every 6 hours, most often, the difference between measured and predicted peak theophylline serum concentration less than 10% as shown in table 22. While most often the difference between measured and predicted trough theophylline serum concentration was in the range of 20% to 30% as shown in Table 23. However, the number of theophylline serum concentrations obtained after intravenous infusion in this study was too few to make any confident conclusion.

In this study, predicted theophylline serum concentrations were calculated from pharmacokinetic parameters and equations from literatures. (Peck 1991; Winter 1992; 1993). Some patients had several factors which might affect their theophylline elimination, such as concurrent drug factors, smoking history and concurrent diet factors (e.g., fresh milk which is high protein), etc. Predicted clearance in these patients might be erratic from true clearance of the patients which was achieved from measured serum concentration. These might result the difference between the measured and the predicted serum concentrations.

Table 16 : Comparison between Measured and Predicted Theophylline Serum Concentrations in Patients Receiving Theophylline Oral Sustained Release Dosage Form.

Patient Number [a]		Cpss ave [b] (measured) (mcg/ml)	Cpss ave (perdicted) (mcg/ml)	Difference (mcg/ml)	Percentage of Difference
1		5.98	6.86	0.88	14.72
2		10.94	9.63	1.31	11.97
3		11.44	14.49	3.05	26.67
4		9.64	8.17	1.47	15.25
*5	B	14.70	12.82	1.88	12.79
	A	11.06	9.61	1.44	13.02
6		13.38	13.66	0.28	2.09
*7	B	13.66	17.01	3.35	24.52
	A	Not measured	-	-	-
*8	B	14.20	15.24	1.04	7.32
	A	10.52	11.42	0.90	8.56
*9	B	10.64	8.29	2.35	22.09
	A	9.08	9.33	0.25	2.75
10		4.95	8.17	3.22	65.05
*11	B	22.62	21.70	0.92	4.07
	A	5.93	6.51	0.58	9.78
12		9.97	10.04	0.07	0.07

Continued

Patient Number [a]		Cpss ave [b] (measured) (mcg/ml)	Cpss ave (perdicted) (mcg/ml)	Difference (mcg/ml)	Percentage of Difference
13		10.71	7.44	3.27	30.53
14		16.86	16.84	0.02	0.12
15		6.64	10.16	3.52	53.01
16		6.42	5.79	0.63	9.81
17*	B	22.01	13.33	8.68	39.44
	A	Not measured	-	-	-
18*	B	5.55	9.26	3.71	66.85
	A	9.60	13.02	3.42	35.63
19		8.43	7.72	0.71	8.42
20		16.55	11.32	5.23	31.60
21		11.20	6.65	4.55	40.63
22		13.79	11.26	2.53	18.35
23		5.89	5.95	0.06	1.02
24		8.67	6.38	2.29	26.41
25		7.49	10.16	2.67	35.65
26		5.26	3.49	1.77	33.65
27		7.40	9.47	2.07	27.97
28		6.41	9.63	3.22	50.23
29		11.17	6.83	4.34	38.85
30		13.00	7.44	5.56	42.77

Continued

Patient Number [a]	Cpss ave [b] (measured) (mcg/ml)	Cpss ave (perdicted) (mcg/ml)	Difference (mcg/ml)	Percentage of Difference
Recieved Moripront^{R} - F, Moriamine^{R}, and Geriatric Pharmaton^{R}	7.47	5.95	1.52	20.35
31	12.28	9.06	3.22	26.22
32	10.22	9.21	1.01	9.88
Discontinued Rifampicin	6.92	6.67[c]	0.25	3.61
*33 B	34.41	39.06	7.65	24.36
C	Not measured	-	-	-
*34 A	10.83	9.06	1.77	16.34
*35 B	10.93	13.89	2.96	27.08
A	14.97	20.83	5.86	39.14
36* A	16.15	16.50	0.36	2.17
37	6.30	5.43	0.87	13.81
38 B	7.98	8.06	0.08	1.00
A	9.52	10.75	1.23	12.92
39	8.88	6.79	2.09	23.54
40	16.83	13.22	3.61	21.45

Continued

Patient Number [a]	Cpss ave [b] (measured) (mcg/ml)	Cpss ave (perdicted) (mcg/ml)	Difference (mcg/ml)	Percentage of Difference
41* B	10.48	10.58	0.10	0.95
A	14.64	12.92	1.72	11.75
42	4.09	4.73	0.64	15.65
43* B	-	-	-	-
A	-	-	-	-
44	7.42	6.67	0.75	10.11
45	11.70	12.08	0.38	3.25
46	13.64	14.62	0.95	6.95
47	7.47	5.83 [d]	1.64	21.95
48	3.90	4.82	0.92	23.59
49	7.54	7.06	0.48	6.37
50	8.26	6.53	1.73	20.94
52	8.87	10.42	1.55	17.47
53	10.97	11.97	1.00	9.12
Discontinued Rifampicin	8.06	9.26 [c]	1.2	14.89
*54 B	16.65	10.62	6.03	36.22
A	8.70	4.87	3.83	44.02
*55 B	34.07	34.72	0.65	1.94
A	Not measured [e]	-	-	-
56	18.21	17.36	0.85	4.67

Continued

Patient Number [a]	Cpss ave [b] (measured) (mcg/ml)	Cpss ave (perdicted) (mcg/ml)	Difference (mcg/ml)	Percentage of Difference
Discontinued Cimetidine	12.67	10.41	2.25	17.76
* 57 B	31.09	39.31	8.22	26.44
A	7.43	6.31	1.12	15.07
58	4.63	3.43	1.20	25.93
59	14.00	11.90	2.10	15.00
60	8.72	11.26	2.54	29.14
61 B	Not measured	-	-	-
A	8.12	8.01	0.11	1.35
A	15.61	15.63	0.02	0.13
A	10.44	10.45	0.02	0.19
Mean ± SD	11.25 ± 5.79	10.99 ± 6.62	2.06 ± 1.93	19.40 ± 15.21
(Range)	(3.90 - 34.07)	(3.43 - 39.06)	(0.02 - 8.86)	(0.13 - 66.85)
n	76	76	76	76

n = Number of Cpss ave measurements after administration of theophylline sustained release dosage form.

(a) Patient Number 1 - 43 : Patient were treated with theophylline together with other drugs (beta - adrenergic agonists, corticosteroids, and anticholinergic drugs).

Patient Number 44 - 61 : Patients were treated with theophylline alone.

* Dosage regimen had been adjusted.

B : Befor dosage regimen adjustment

A : After dosage regimen adjustment

C : Theophylline was discontinued and changed to other drugs

(b) Cpss ave (measured) : Average theophylline serum concentration at steady state which was obtained at midpoint of dosing interval for oral sustained release dosage form.

(c) Predicted Cpss ave was determined from Rifampicin decreased clearance of theophylline about 25 - 30% after 7 days of concurrent therapy.

(d) Predicted Cpss ave was determined from Rifampicin increased clearance of theophylline average of 79% after 2 days of concurrent therapy .

(e) The follow up was losed because the patient was rested at home.

Table 17 : Comparison between Measured and Predicted Peak Theophylline Serum Concentrations in Patients who initially Received Theophylline by Intravenous Administration (IV infusion 15 minutes every 6 hours).

Patient Number	Peak[a] (measured) (mcg/ml)	Peak (predicted) (mcg/ml)	Difference (mcg/ml)	Percentage of Difference
34	21.58	21.05	0.48	2.23
35	26.73	29.23	2.50	9.35
36	28.15	34.22	6.07	21.56
Mean ± SD	25.49 ± 3.46	28.17 ± 6.65	3.02 ± 2.83	11.05 ± 9.78
(Range)	(21.58 - 28.15)	(21.05 - 34.22)	(0.48 - 6.07)	(2.23 - 21.56)

(a) Peak serum concentrations were obtained at one hour after finished IV infusion .

Table 18 : Comparison between Measured and Predicted Trough Theophylline Serum Concentrations in Patients who initially Received Theophylline by Intravenous Administration (IV infusion 15 minutes every 6 hours).

Patient Number	Trough[a] (measured) (mcg/ml)	Trough (predicted) (mcg/ml)	Difference (mcg/ml)	Percentage of Difference
34	15.47	14.19	1.28	8.27
35	19.04	23.07	4.03	21.17
36	23.80	28.93	5.13	21.55
Mean ± SD	19.44 ± 4.18	22.06 ± 7.42	3.48 ± 1.98	17.00 ± 7.56
(Range)	(15.47 - 23.80)	(14.19 - 28.93)	(1.28 - 5.13)	(8.27 - 21.55)

(a) Trough serum concentrations were obtained immediately before the next dose.

Table 19 : Percent Coefficient of Variation between Measured and Predicted Theophylline Serum Concentrations.

Serum Concentration Comparison	Percent Coefficient of Variation (%CV)
(1) Cpss ave * Cpss ave (measured) VS Cpss ave (predicted)	24.96
(2) Peak Serum Concentration ** Peak (measured) VS Peak (predicted)	10.97
(3) Trough Serum Concentration *** Trough (measured) VS Trough (predicted)	15.35

Cpss ave * = Average Serum Concentration of theophylline substained release dosage form was obtained at midpoint of dosing interval

Peak Serum Concentration ** = Peak Serum Concentration of Aminophylline by IV infusion for fifteen minutes every six hours was obtained at one hour after finished IV infusion.

Trough Serum Concentration *** = Trough Serum Concentration of Aminophylline by IV infusion for fifteen every six hours was obtained immediately before the next dose.

Table 20 : Number of Serum Concentrations in Various Range of Difference between Measured and Predicted Values after Administration of Theophylline Sustained Release Dosage Form.

Range of Difference between Measured and Predicted Values (Cpss ave)	Number of Serum Concentrations in the Range n (%)
< 10%	25 (32.90)
10% to < 20%	18 (23.68)
20% to < 30%	17 (22.37)
30% to < 40%	9 (11.84)
40% to < 50%	3 (3.95)
50% to < 60%	2 (2.63)
60% to < 70%	2 (2.63)
Total	76 (100)

Table 21 : Percentage of Difference between Measured and Predicted Values in Various Range of Theophylline Serum Concentrations after Administration of Sustained Release Dosage Form.

Measured Average Theophylline Serum Level (mcg/ml)	Percentage of Difference between Measured and Predicted Values (Mean ± SD)	Number of Serum Concentrations in the Level n (%)
0 - 5.00	32.56 ± 22.11	4 (5.26)
5.01 - 10.00	21.57 ± 17.52	34 (44.74)
10.01 - 15.00	17.92 ± 12.61	27 (35.53)
15.01 - 20.00	13.77 ± 15.66	7 (9.21)
20.01 - 25.00	21.76 ± 25.01	2 (2.63)
25.01 - 30.00	0	0 (0)
30.01 - 35.00	14.18 ± 17.35	2 (2.63)
Total		76 (100)

Table 22 : Number of Serum Concentrations in Various Range of Difference between Measured and Predicted Peak Theophylline Serum Concentrations after Intravenous Administration.

Range of Difference between Measured and Predicted Peak Serum Concentrations	Number of Serum Concentrations in the Range n (%)
< 10%	2 (66.67)
10% to < 20%	0 (0)
20% to < 30%	1 (33.33)
Total	3 (100)

Table 23 : Number of Serum Concentrations in Various Range Difference between Measured and Predicted Trough Theophylline Serum Concentrations after Intravenous Administration.

Range of Difference between Measured and Predicted Trough Serum Concentrations	Number of Serum Concentrations in the Range n (%)
< 10%	1 (33.33)
10% to < 20%	0 (0)
20% to < 30%	2 (66.67)
Total	3 (100)

3. Pharmacokinetic Parameters of Theophylline in Thai Patients.

According to foreign literatures (Peck 1991; Winter 1992; 1993), theophylline clearance was calculated from its correlation to theophylline concentration and dosage regimen while the same correlation did not apply to volume of distribution, volume of distribution was set as a remained relatively unaffected and was a fixed value multiplied with patient's body weight. Theophylline half - life was calculated from its correlation with both theophylline clearance and volume of distribution. Table 24 indicated that the mean theophylline clearance and half - life in the patients not requiring theophylline dosage regimen adjustment were 39.45 ± 13.99 ml.hr/kg of Ideal Body Weight (IBW) and 9.91 ± 3.22 hours (mean ± SD), respectively. Theophylline clearances and half - lives of the two patients (Number 14 and 30) were excluded from these results since the patient number 14 was refered to the private hospital and the patient number 30 received the factors increasing the theophylline clearance, therefore, theophylline adverse reactions decreased in this patient. Table 25 illustrated that the majority of patients requiring theophylline dosage regimen adjustments had some factors which affected their theophylline elimination such as liver dysfunction, cardiac disorder status, cimetidine, and erythromycin, etc. The mean theophylline clearance and half - life in these patients were 26.45 ± 14.25 ml/hr/kg of IBW and 17.17 ± 9.99 hours (mean ± SD), respectively. Therefore, Theophylline dosage regimen should be adjusted in the patient with low theophylline clearance and long theophylline half - life by using pharmacokinetic theories. This could improve the patient's clinical response.

Table 24 : Pharmacokinetic Parameters of Patients not requiring Theophylline Dosage Regimen Adjustment.

Patient Number [a]	Factor Affecting Theophylline Elimination	Cpss ave [b] (mcg/ml)	Clearance [c] (ml/hr/kg of IBW)	Volume of [d] Distribution (L)	Half-Life [e] (hr)
1	-	5.98	46.01	30.41	7.55
2	-	10.94	35.10	23.83	10.86
3	Left heart failure, Fresh milk (UHT) 6 boxs/day	11.44	25.43	29.11	13.82
4	-	9.64	33.92	25.50	10.21
6	Cimetidine 800 mg/day	13.38	24.52	27.25	15.11
10	-	4.95	69.61	25.50	4.98
12	-	9.97	40.22	25.01	10.38
13	-	10.71	27.86	28.00	12.44
14	Pneumonia	16.86	16.04	32.93	23.05
15	-	6.64	61.22	20.50	5.66
16	Smoking	6.42	57.78	22.50	6.00
19	-	8.49	36.67	27.00	9.45
20	-	16.55	27.39	23.00	12.65
21	-	11.20	23.83	23.50	14.54
22	-	13.79	32.70	18.50	10.59
23	-	5.89	40.43	35.50	8.69
24	-	8.67	29.39	24.50	11.79
25	-	7.49	54.15	20.50	6.40
26	Smoking	5.26	42.50	28.00	8.15
27	-	7.40	51.14	22.00	6.78
28	Pneumonia, Smoking, Fresh milk (UHT) 3 boxs/day	6.41	48.10	27.00	7.20

Continued..

Patient Number [a]	Factor Affecting Theophylline Elimination	Cpss ave [b] (mcg/ml)	Clearance [c] (ml/hr/kg of IBW)	Volume of [d] Distribution (L)	Half-Life [e] (hr)
29	-	11.17	24.43	30.50	14.19
30	-	13.00	22.86	14.00	15.16
	Moripront^{R} F 200 ml/day Geriatric Pharmaton^{R} 1 Cap/day, and Moriamine^{R} 3 Caps/day	7.47	40.00	14.00	8.67
31	-	12.28	29.57	23.00	11.72
32	Rifampicin 450 mg/day (after 7 days of concurrent therapy), Smoking	10.22	41.79	19.50	8.29
	Smoking	6.92	61.76	19.50	5.61
37	Smoking	6.30	55.00	15.00	6.30
39	-	8.88	30.65	23.00	11.30
40	Allopurinol 300mg/day	16.83	23.57	21.00	14.70
42	-	4.09	46.36	22.00	7.47
44	Erythromycin 2000mg/day, Smoking	7.42	43.27	26.00	8.00
45	Smoking, Ischemic heart disease	11.70	26.30	27.00	13.18
46	Fever sustained for > 24 hrs	13.67	21.40	28.50	16.19
47	Rifampicin 450 mg/day (after 2 days of concurrent therapy)	7.47	55.75	20.00	6.22
48	Smoking	3.90	79.07	27.00	4.38
49	Lexinor^{R} 800 mg/day, Smoking	7.54	53.90	20.50	6.43
50	Smoking	8.26	50.50	25.23	6.94
51	Smoking	5.27	51.20	34.43	6.77
52	Cimetidine 800 mg/day	8.87	28.20	25.00	12.29

Continued..

Patient Number [a]	Factor Affecting Theophylline Elimination	Cpss ave [b] (mcg/ml)	Clearance [c] (ml/hr/kg of IBW)	Volume of [d] Distribution (L)	Half-Life [e] (hr)
53	Rifampicin 450 mg/day (after 7 days of concurrent therapy)	10.97	31.67	24.00	10.94
	-	8.06	46.00	22.50	7.53
56	Cimetidine 800 mg/day	18.21	20.35	25.00	15.20
		12.67	29.29	25.00	10.56
58	-	4.63	29.68	30.41	11.71
59	-	14.00	34.00	17.50	10.19
60	Cardiac decompensation Smoking	8.73	32.93	29.00	10.52

(a) Patient Number 1-43 : Patients were treated with theophylline together with other drugs (beta - adrenergic agonists, corticosteroids, and anticholinergic drugs).
Patient Number 44-61 : Patients were treated with theophylline alone.

(b) Cpss ave or peak serum concentration of sustained release dosage form : Blood sample was obtained at midpoint of dosing interval.

(c) Clearance was obtained from measured serum theophylline level (measured value).

(d) Volume of Distribution was culculated from equation in liturature

(e) Half - Life was calculated from clearance (obtained from measured theophylline level) and volume of distribution (calculated from equation in liturature).

Table 25 : Pharmacokinetic Parameters of Patients requiring Theophylline Dosage Regimen Adjustments.

Patient Number [a]		Factor Affecting Theophylline Elimination	Cpss ave [b] (mcg/ml)	Clearance [c] (ml/hr/kg of IBW)	Volume of [d] Distribution (L)	Half-Life [e] (hr)
5	B	Cimetidine 800 mg/day	14.70	20.92	27.00	16.56
	A	Cimetidine 800 mg/day	11.06	20.92	27.00	16.56
7	B	Ischemic heart disease, Premature ventricular contraction	13.66	20.00	30.50	17.33
	A	Ischemic heart disease, Premature ventricular contraction	Not measured [f]	-	-	-
8	B	Liver dysfunction	14.20	17.65	25.50	20.08
	A	Liver dysfunction, Lexinor^{R} 800 mg/day	10.52	15.49	25.50	22.37
9	B	Erythromycin 1000 mg/day	10.64	23.40	35.77	15.79
	A		9.08	41.00	35.77	9.01
11	B	Pneumonia, Smoking	22.62	24.67	15.00	14.05
	A	Smoking	5.93	70.33	15.00	4.93
17	B	Liver dysfunction, Smoking	22.01	15.51	22.34	24.50
	C	Liver dysfunction, Smoking	Not measured	-	-	-
18	B	Erythromycin 1000 mg/day, Fresh milk (UHT) 3 boxs/day	5.55	62.50	24.00	5.54
	A	-	9.60	53.06	24.50	6.53
33	B	Ischemic heart disease, Liver dysfunction, Lexinor^{R} 800 mg/day	31.41	7.14	28.00	48.51
	C	Ischemic heart disease, Liver dysfunction, Lexinor^{R} 800 mg/day	Not measured	-	-	-
34[g]	B	-	21.58 (Peak) 15.47 (Trough)	35.00	23.00	9.90
	A	-	10.83	33.48	23.00	10.35

continued...

Patient Number [a]		Factor Affecting Theophylline Elimination	Cpss ave [b] (mcg/ml)	Clearance [c] (ml/hr/kg of IBW)	Volume of [d] Distribution (L)	Half-Life [e] (hr)
35[g]	B	Cimetidine 800 mg/day	26.73 (Peak) 19.04 (Trough)	34.04	26.00	10.18
	A	Cimetidine 800 mg/day	10.93	29.23	26.00	11.85
	A	Cimetidne 800 mg/day	14.97	33.40	25.00	10.37
36[g]	B	Left heart failure	28.15 (Peak) 23.80 (Trough)	16.35	31.50	21.19
	A	Left heart failure	16.15	16.98	31.50	20.40
38	B	-	7.98	40.43	19.71	8.70
	A	-	9.52	45.07	19.71	7.81
41	B	Allopurinol 300 mg/day, Smoking	10.48	48.54	20.50	7.14
	A	Allopurinol 300 mg/day	14.64	26.51	21.50	13.07
43[h]	B	Phenobarbital (in Tedral^{R})32 mg/day	32.3	-	20.00	-
	A	Phenobarbital (in Tedral^{R})32 mg/day	-	-	20.00	-
54	B	Fever sustained for > 24 hrs, Smoking	16.65	20.41	24.50	16.98
	A	Smoking	8.70	28.25	25.74	12.39
55	B	Cardiac decompensation	34.07	16.33	15.00	21.21
	A	Cardiac decompensation	Not measured[i]	-	-	-
57	B	Cardiac decompensation	31.09	20.30	16.50	17.07
	A	-	7.43	33.94	16.50	10.21

Continued..

Patient Number [a]		Factor Affecting Theophylline Elimination	Cpss ave [b] (mcg/ml)	Clearance [c] (ml/hr/kg of IBW)	Volume of [d] Distribution (L)	Half-Life [e] (hr)
61	B	-	Not measured	-	-	-
	A	Erythromycin 2000 mg/day	8.12	29.62	26.00	11.70
	A	Liver dysfunction	15.61	15.38	26.00	22.52
	A	Liver dysfunction	10.44	15.38	26.00	22.52
	C	Liver dysfunction	Not measured	-	-	-

(a) Patient Number 1-43 : Patients were treated with theophylline together with other drugs (beta - adrenergic agonists, corticosteroids, and anticholinergic drugs).
Patient Number 44-61 : Patients were treated with theophylline alone.
B : Before dosage regimen adjustment
A : After dosage regimen adjustment
C: Theophylline was discontinued and changed to other drugs

(b) Cpss ave or peak serum concentration of oral sustained release dosage form : Blood sample was obtained at midpoint of dosing interval.

(c) Clearance was obtained from measured theophylline level (measured value).

(d) Volume of Distribution was calculated from equation in literature.

(e) Half - Life was calculated from clearance (obtained from measured theophylline level) and volume of distribution (calculated from equation in liturature).

(f) Patient losed follow up.

(g) Patient initially received theophylline by IV infusion for fifteen minutes every six hours of aminophylline. Peak serum concentration was obtained at one hour after finished IV infusion. And trough serum concentration was obtained immediately before the next dose.

(h) Patient received Theo Dur® together with Tedral®. Cpss ave of theophylline was obtained at midpoint of dosing interval of Theo Dur® and clearance could not evaluated from theophylline serum level. Patient did not received theophylline serum concentration measurement when patient was treated with Tedral® alone.

(i) The follow up was losed because the patient was rested at home.

From table 26, the mean theophylline clearance and half - life in the adult patients without factor affecting theophylline elimination (mean ± SD of age = 53.33 ± 9.00 years) were 42.44 ± 13.28 ml/hr/kg of IBW and 9.19 ± 2.77 hours (mean ± SD), respectively. From Table 27, the mean theophylline clearance and half - life in the elderdy patients without factor affecting theophylline elimination (mean ± SD of age = 70.67 ± 7.46 years) were 35.47 ± 10.50 ml/hr/kg of IBW and 10.54 ± 2.84 hours, respectively. When the mean theophylline clearance between these two groups of patients were compared, the mean theophylline clearance was 16.42% lower in the ederly patients. The difference between the mean theophylline clearance of these two groups of patients was not statistically significant ($p > 0.10$) using two - tailed unpaired Student's t - test as shown in table 33. One of the reason that the significant difference between the two groups could not be determined, might due to the majority age of the patients in the adult group was over 50 years (mean ± SD = 53.33 ± 9.00 years) which was closed to the age of the elderly (60 years or older).

Theophylline clearance and age of the patients from Table 26 and 27 could create the relationship between theophylline clearance and the age of patients using Linear Regression. The summary equation was : Clearance = 54.55 - 0.25 Age, Correlation Coefficient = -0.25 Theophylline clearance in the elderly patients were lower than theophylline clearance in the adult patients according to this relationship illustrated in Figure 8.

Table 28 showed that the mean theophylline clearance and half - life of the smoking adult patients (mean ± SD of age = 38.25 ± 9.22 years) were 60.63 ± 13.33 ml/hr/kg of IBW and 5.93 ± 1.19 hours (mean ± SD), repectively. From 29, the mean theophylline clearance and half - life of the smoking elderly patients (mean ± SD of age = 66.33 ± 6.11 years) were 51.76 ± 8.14 ml/hr/kg of IBW and 6.82 ± 1.16 years (mean ± SD), respectively. The mean theophylline clearance between these two groups of patients was not significantly different ($p < 0.10$) using two tailed unpaired Student's t - test as shown in Table 33.

From the results showed in Table 33 demonstrated that the mean theophylline clearance between nonsmoking adult patients (mean ± SD of age = 53.33 ± 9.00 years and smoking adult patients (mean ± SD of age = 38.25 ± 9.22 years) was statistically significant different ($p < 0.05$) using two tailed unpaired Student's t - test. The mean theophylline clearance between nonsmoking elderly patients (mean ± SD of age = 70.69 ± 7.46) and smoking elderly patients (mean ± SD of age = 63.33 ± 6.11) was statistically significant different ($p < 0.05$) using two - tailed unpaired Student's t - test.

Table 30 showed that the mean theophylline clearance and half - life in the elderly patients receiving cimetidine together with theophylline (mean ± SD of age = 70.60 ± 9.04 years) were 25.24 ± 5.01 ml/hr/kg of IBW and 14.00 ± 2.37 hours, respectively. The mean theophylline clearance between the elderly patients and the elderly patients receiving cimetidine together with theophylline was statistically significant different ($p < 0.01$) using two - tailed unpaired student's t - test as shown in Table 33. In patients with cardiac disorder status (mean ± SD of age = 71.25 ± 9.60 years) the mean clearance and half - life were 18.33 + 2.12 ml/hr/kg of IBW and 19.10 ± 2.21 hours, respectively as shown in Table 29. From Table 32, the mean clearance and half - life in the patients with liver dysfunction status (mean ± SD of age = 69.50 ± 9.19 years) were 16.52 ± 1.61 ml/hr/kg of IBW and 21.30 ± 1.73 hours, respectively. Comparison of theophylline clearance between group of patients as shown in table 33. Figure 9 showed the mean theophylline clearance in various clinical situations of patients. From Figure 9, the mean theophylline clearance of the patients with liver dysfunction status and cardiac disorder status were lower than those of the patients with other clinical situations since these two factors were the major causes of alteration in theophylline metabolism.

From this study, factors which may cause decreasing in theophylline elimination were as follows : (1) Concurrent drug therapy e.g., cimetidine, (2) Concomitant diseases or disorder e.g., cardiac disorder status and liver dysfunction status. The patients with these factors should be monitored closely for theophylline adverse reaction since their theophylline clearance were lower than the clearance of the patients without these factors. The smoking patients should be monitored closely for their respiratory disorder improvement since their theophylline clearance were higher than the clearance of nonsmoking patients.

Half - life of theophylline of Thai patients in various clinical situations in this study corresponded well with those reported in foreign literatures (Blackbourn and Sunderland, 1987; Ellis and Hendeles, 1986; Hendeles et al., 1986; Kelly 1992).

Table 34 showed that theophylline clearance altering effect was caused by factor affecting theophylline elimination in the patients. Percentage of alteration of theophylline clearance from some factors (e.g., Lexinor^{R} Cimetidine, Rifampicin and Pneumonia) were corresponded well with those reported in foreign literatures (Kelly and Hill, 1993; Peck et al., 1991; Winter, 1992) The number of patients studied for each factor were too few. Further study in a larger patient groups is recommended before any confident conclusion could be made.

Table 26 : Clearance and Half - Life of Theophylline in Adult Patients without Factors Affecting Theophylline Elimination

Patient Number (n=12)	Age (yr)	Clearance (ml/hr/kg of IBW)	Half - Life (hr)
1	59	46.01	7.55
2	46	35.10	10.86
9	56	41.00	9.01
10	57	69.61	4.98
12	57	40.22	10.38
13	59	27.86	12.44
15	54	61.22	5.66
18	59	53.06	6.53
19	59	36.64	9.45
21	55	23.83	14.54
23	27	40.43	8.69
34	55	34.24	10.13
Mean ± SD (Range)	53.33 ± 9.00 (27 - 59)	42.44 ± 13.28 (23.83 – 69.61)	9.19 ± 2.77 (5.66 – 14.54)

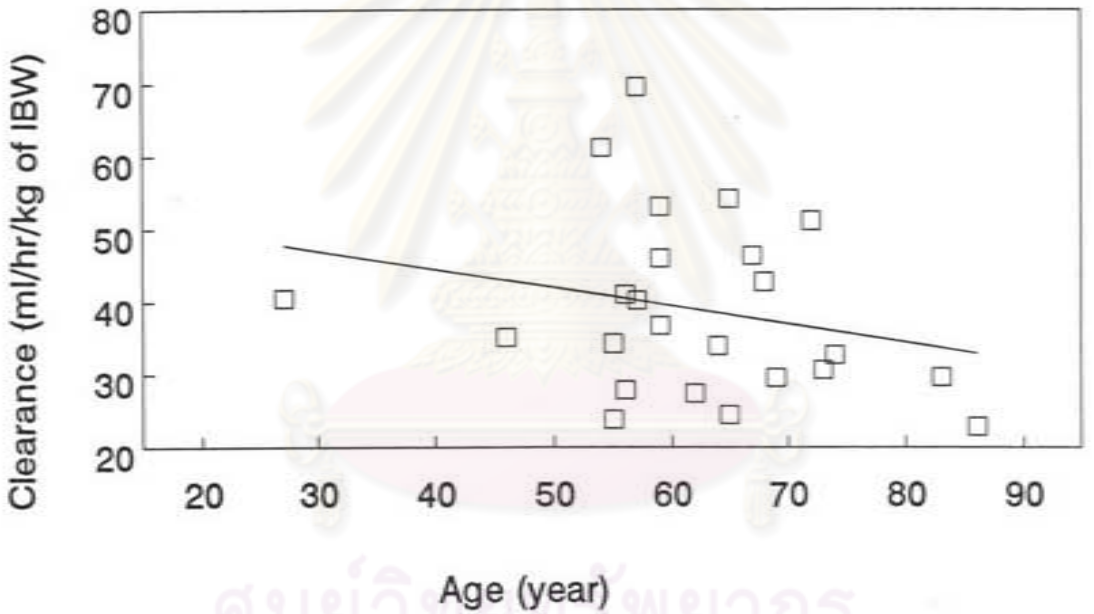
Adult Patients : Age of patients were 20 - 59 years

Table 27 : Clearance and Half - Life of Theophylline in Elderly Patients without Factors Affecting Theophylline Elimination

Patient Number (n=12)	Age (yr)	Clearance (ml/hr/kg of IBW)	Half - Life (hr)
4	64	33.92	10.21
20	62	27.39	12.62
22	74	32.70	10.59
25	65	54.15	6.40
27	72	51.14	6.78
29	65	24.43	14.19
30	86	22.86	15.16
31	69	29.57	11.72
38	68	42.75	8.26
39	73	20.65	11.30
42	67	46.36	7.47
58	83	29.68	11.71
Mean ± SD (Range)	70.67 ± 7.46 (62 - 86)	35.47 ± 10.50 (22.86 – 54.15)	10.54 ± 2.84 (6.40 –15.16)

Elderly Patients : Age of Patients were equal to or greater than 60 years

Figure 8 : Relationship between
Clearance and the Age of Patients



Clearance = 54.55 - 0.25 Age ml/hr/kg of IBW

Correlation Coefficient = 0.25

Standard Error of Y estimate = 12.13

Table 28 : Clearance and Half - Life of Theophylline in Smoking Adult Patients.

Patient Number n = 4	Age (yr)	Clearance (ml/hr/kg of IBW)	Half - Life (hr)
32	32	61.76	5.61
48	39	79.07	4.38
50	51	50.50	6.94
51	31	51.20	6.77
Mean ± SD	38.25 ± 9.22	60.63 ± 13.33	5.93 ± 1.19
(Range)	(31 - 51)	(50.50 - 79.07)	(4.38 - 6.77)

Table 29 : Clearance and Half - Life of Theophylline in Smoking Elderly Patients.

Patient Number n = 3	Age (yr)	Clearance (ml/hr/kg of IBW)	Half - Life (hr)
16	61	57.78	6.00
26	65	42.50	8.15
37	73	55.00	6.30
Mean ± SD	66.33 ± 6.11	51.76 ± 8.14	6.82 ± 1.16
(Range)	(61 - 73)	(42.50 - 57.78)	(6.00 – 8.15)

Table 30 : Clearance and Half - Life of Theophylline in Elderly Patients Receiving Cimetidine together with Theophylline

Patient Number n = 5	Age (yr)	Clearance (ml/hr/kg of IBW)	Half - Life (hr)
5	70	20.92	15.56
6	85	24.52	15.11
35	62	32.22	10.80
52	72	28.20	12.29
56	64	20.35	15.20
Mean ± SD	70.60 ± 9.04	25.24 ± 5.01	14.00 ± 2.37
(Range)	(62 - 85)	(20.35 - 32.22)	(10.80 - 16.56)

Table 31 : Clearance and Half - Life of Theophylline in Patients with Cardiac Disorder Status.

Patient Number n = 4	Age (yr)	Clearance (ml/hr/kg of IBW)	Half - Life (hr)
7	57	20.00	17.33
36	78	16.67	20.80
55	75	16.33	21.21
57	75	20.30	17.07
Mean ± SD	71.25 ± 9.60	18.33 ± 2.12	19.10 ± 2.21
(Range)	(57 - 78)	(16.33 - 20.30)	(17.07 - 21.21)

Table 32 : Clearance and Half - Life of Theophylline in Patients with Liver Dysfunction Status.

Patient Number n = 2	Age (yr)	Clearance (ml/hr/kg of IBW)	Half - Life (hr)
8	76	17.65	20.08
61	63	15.38	22.52
Mean ± SD	69.50 ± 9.19	16.52 ± 1.61	21.30 ± 1.73
(Range)	(63 - 76)	(15.38 - 17.65)	(20.08 - 22.52)

Table 33 : Comparison of Theophylline Clearance between Group of Patients.

Group of Patients		Calculated	Estimated	Result
No factor (n)	With factor (n)	t - Value	t - Value	
Age 20 - 59 yrs (12)	Age ≥ 60 yrs (12)	1.43	1.32	s ($p < 0.20$)
Age 20 - 59 yrs + Smoking (4)	Age ≥ 60 yrs + Smoking (3)	0.77	0.73	s ($p < 0.50$)
Age 20 - 59 yrs (12)	Age 20 - 59 yrs + Smoking (4)	-2.36	-2.15	s ($p < 0.05$)
Age ≥ 60 yrs (12)	Age ≥ 60 yrs + Smoking (3)	-2.48	-2.16	s ($p < 0.05$)
Age ≥ 60 yrs (12)	Age ≥ 60 yrs + Cimetidine (5)	5.07	4.07	s ($p < 0.001$)

+ = Combined with

Figure 9 : Mean Theophylline Clearance in Patients with Various Clinical Situations

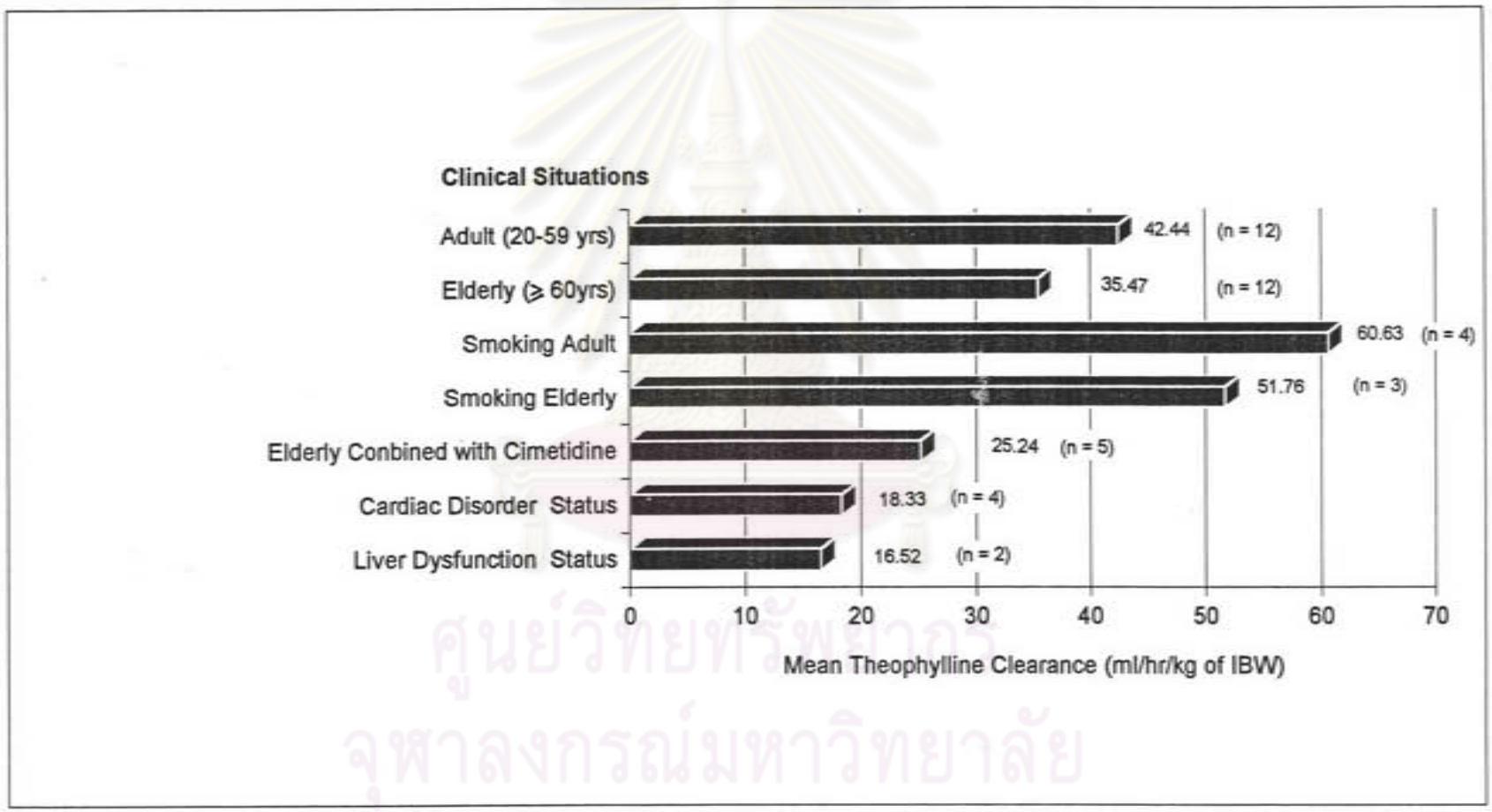


Table 34 : Theophylline Clearance Altering Effects in Patients with Factors Affecting Theophylline Elimination.

Patient Number	Factor Affecting Theophylline Elimination	Theophylline Clearance Altering Effects	
		Decrease	Increase
8	Lexinor® 800 mg/day (after 5 days of concurrent therapy)	12.24%	
9	Erythromycin 1000 mg/day (after 4 days of concurrent therapy)	42.93%	
11	Pneumonia	64.92%	
30	Moriamine® 3 caps/day, Moripront - F® 200 ml/day, and Geriatric Pharmaton® 1 Cap/day (after 7 days of concurrent therapy)		74.98%
32	Rifampicin 450 mg/day (after 7 days of concurrent therapy)	32.33%	
41	Smoking (ten cigarettes/day)		83.10%
53	Rifampicin 450 mg/day (after 7 days of concurrent therapy)	31.15%	
56	Cimetidine 800 mg/day (after 6 days of concurrent therapy)	30.52%	
57	Cardiac decompensation	40.19%	