CHAPTER 4

RESULTS AND DISCUSSION

Demographic Data of the Patients

75 hospitalized patients who met the inclusion criteria were enrolled in this study but 72 subjects completed the study. Among the 3 subjects were excluded: one was additionally administered aminophylline IV infusion before drug level monitoring, and two were dead. Table 4 summarizes the demographic data of the control group and the the study group. Among patients in each group, the majority of the patients is male (25 of the the control group and 29 of the the study group). Age of the patients as well as distribution of disease states was not statistically significant different. It is also noted that some patients possesed factors that might affect theophylline level. Number of patients who were smoking, possessing such a co-disease states as CHF and taking concurent medications are higher in the the control group as compared to those of the the study group.

Table 4 Demographic data of patients in the control group and the study group

	Control group	Study group	*p*-value
Sex - Female	11 (30.6%)	7 (19.4%)	0.280[a]
- Male	25 (69.4%)	29 (80.6%)	
Average age(mean ± SD)(ys)	61.94 ± 14.41	67.25 ± 14.48	0.558[b]
- < 60 ys	14 (38.9%)	6 (16.7%)	
- ≥ 60 ys	22 (61.1%)	30 (83.3%)	
Co-disease states			0.900[a]
- None	16 (44.4%)	16 (44.4%)	
- Congestive heart failure	3 (8.3%)	2 (5.6%)	
- Others[1]	17 (47.2%)	18 (50%)	
Blood chemistry			
- BUN	19.58± 15	17.91±9.63	0.185[b]
- Scr	1.32±0.51	1.16±0.32	0.035[b]
- SGOT	31.22±14.36	29.72±11.85	0.442[b]
- SGPT	26.08±11.87	26.28±10.12	0.524[b]
Factors affecting pharmacokinetics of theophylline			
- Smoking	5	-	0.021[a]
- Congestive heart failure	5	2	0.236[a]
- Age (≥ 60 ys)	19	30	0.006[a]
Medication concurent (factor)			
- Cimetidine	2	1	0.558[a]
- Erythromycin	1	-	0.317[a]
- Rifampicin	4	2	0.397[a]
More than 1 factor[2]	8	5	0.361[a]
Medication concurent (synergistic)			
- β_2-agonists	35	36	0.317[a]
- Anticholinergic	14	24	0.474[a]
- Steroids	15	19	0.348[a]
- Antitussis, mucolytic	28	30	0.554[a]

Table 4 (continue)

a Chi-square

b student-t-test

[1] detail of other diseases see in appendix I

[2] patients who had more than one factors which may affect pharmacokinetic of theophylline, more than one medications concurently used, or had both factor which may affect pharmacokinetics of theophylline and medication concurenly used

Other potential medicine taking factors including allopurinol, ciprofloxacin, propanolol, carbamazepine, phenobarbital, and phenytoin were not found except those who are taking combination (> 1 factors)

Comparison between the measured and the predicted theophylline serum concentrations

Before the serum concentration of theophylline was monitored, the dosage regimen was assigned using the population pharmackinetic dosage program. The predicted theophylline serum concentrations ($C_{predict}$) were calculated from pharmacokinetic parameters and equations from review literatures (Winter, 1998). Some patients had several factors which might affect their theophylline elimination, such as concurrent drugs used, smoking history and co-diseases. The calculations were then adjusted accordingly throughout this study. Table 5 compares the measured serum concentration of the drug ($C_{real(a)}$) collected between November 2000 and October 2001 with the predicted serum concentration value pre-calculated using the program. ($C_{predict(a)}$) It was found that actual serum theophylline ($C_{real(a)}$) was precisely agreed with that calculated from the program ($C_{predict(a)}$).

Table 5 Comparison between $C_{predict(a)}$ and $C_{real(a)}$ (November 2000-October 2001)

$C_{predict(a)}$ (mcg/ml) Mean ± SD	$C_{real(a)}$ (mcg/ml) Mean ± SD	*p*-value (Paired-t-test)
12.701±5.416	12.486±5.142	0.682

Note : $C_{predict(a)}$, $C_{real(a)}$ derived from overall patients (control group+study group)

The difference between theophylline average level obtained from Theophylline dosage program ($C_{predict}$) and measured theophylline level (C_{real}) was not statistically significant (at α-level of 0.05).

Comparison Theophylline Level, Adverse Drug Reactions and Clinical Response between the Control Group and the Study Group

Theophylline was dosing by two methods, the control group received the theophylline dosed according to the physician traditional practical dosage regimen, while the study group received the dose recommended by the pharmacists calculated by Theophylline dosage program. The range of theophylline therapeutic was defined as 10-15 mcg/ml (USFDA, 1996). With this defined range, serum theophylline concentrations less than 10 mcg/ml was considered to be subtherapeutic range, and serum theophylline concentrations more than 15 mcg/ml be toxic range.

Table 6 show that in the control group the majority of patients possesed either subtherapeutic (52.78%) or toxic ranges (33.34%) while few patients had theophylline level within therapeutic range (13.88%). In contrast to the control group , subjects in the study group demonstrated the opposite trend. The majority of patients in the study group had theophylline level in therapeutic range (55.56%) while few patients had theophylline level in subtherapeutic range (25%) and toxic range (19.44%). When compared with the control group, the study group had theophylline level in therapeutic range more than 50% at significant level of 0.05

Table 6 Comparison of theophylline therapeutic range between the control group and the study group

Theophylline Drug Concentrations	Control group n (%)	Study group n (%)	*p*-value (Binomial)
Therapeutic range	5 (13.88%)	20 (55.56%)	0.015
Subtherapeutic range	19 (52.78%)	9 (25%)	0.054
Toxic range	12 (33.34%)	7 (19.44%)	0.648

p-value (Chi-square) = 0.847

Table 7 Actual theophylline level (C_{real}) show in minnimum, maximum, the difference of average theophylline level (mean ± SD) between the control group and the study group

Theophylline level (mcg/ml)	Control group n = 36	Study group n = 36	Total n = 72	*p*-value (unpaired t-test)
Minimum	4.5	6.4	4.5	
Maximum	27.5	24	27.5	
C_{real}	12.089± 6.021	12.881± 3.852		0.493
$C_{predict} - C_{real}$	3.453 ± 3.719	2.831 ± 2.399	3.142 ± 3.123	0.682

Table 7 illustrates the mean actual drug level between the control group and the study group and the differences of average theophylline level ($C_{predict} - C_{real}$) calculated due to grouping as well as combination. As seen in Table 7, the data showed that at significant level of 0.05, there were no difference in theophylline level (C_{real}) and the difference of average theophylline ($C_{predict}$-C_{real}) between the control group and the study group.

Table 8 Comparison of adverse drug reactions between the control group and the study group

ADR	No of patients (n)		Total ADR(%)
	Control group	Study group	
GI tract	1	3	4 (18.18%)
Central nervous system	10	3	13 (59.09%)
Cardiovascular system	2	3	5 (22.73%)
no ADR	23	27	50
Total	36	36	72

p-value (Chi-square) = 0.170

Table 9 Number of patients showed adverse drug reactions while thephylline serum concentrations within subtherapeutic, therapeutic and toxic range

Theophylline level	ADR (n)			Total ADR	No ADR
	GI	Nervous	CVS		
Subtherapeutic range	-	1	-	1 (4.34%)	27
Therapeutic range	1	2	2	5 (21.74%)	20
Toxic range	3	11	3	17 (73.92%)	2
Total	4	14	5	23 (100%)	49

Tables 8 and 9 showed the comparisons of adverse reactions sub-categorized as groups and ranges, respectively. There were no differences in the incidence of theophylline adverse reactions between the control group and the study group. One and five patients showed signs of adverse reactions while the theophylline serum level was within subtherapeutic and therapeutic ranges, respectively. Whereas, 2 patients

did not show any sign of adverse reactions even though theophylline serum concentrations was categorized in toxic range. One patient whose theophylline serum level was 7.4 mcg/ml. and adverse reactions probability scale of Naranjo was 2 showed sign of headache. Five patients experienced adverse reactions while theophylline level were 11.4,12,12.7,14.6,15 mcg/ml respectively and mostly produce headache, nausea and vomiting, tachycardia which defined as minor adverse reactions. It is demonstrated that some patients experiened minor adverse reactions whereas theophylline level in subtherapeutic, or therapeutic range. In addition two patients whose theophylline level was in toxicity range showed no sign of toxicity (theophylline level were 15.7, 16 mcg/ml). Normally, the adverse and toxic effects of theophylline should be related to plasma drug concentrations (Skiner M.H., 1990). It was found from this study that there were no statistical correlation between theophylline level and adverse reactions, with small the Pearson correlation coefficient as 0.057 (p-value of 0.633). There was considerable interindividual variation both in the nature of the adverse reactions exhibited and the concentrations at which they occured.

Table 10 Data analysis by logistic regression between actual theophylline concentrations and adverse drug reactions

Variable	B	S.E.	Wald	df	sig	R	Exp(B)
LCREAL	0.658	0.3242	0.0412	1	0.8932	0.0000	1.0680
Constant	-1.0113	.6661	2.3048	1	0.1290		

From table 10 the probability in ADRs show nearly the same theophylline concentration due to in this study it had small sample size and each patients were monitored theophylline level to be therapeutic range, so there were few patients showed sign of adverse reactions.

Table 11 Comparison of clinical response after 3 days treatment with theophylline in the control group and the study group

Clinical response	Control group (n)	Study group (n)	Total (n)	*p*-value (Chi-square)
Grade 1	17 (47.22%)	19 (52.78%)	36 (50%)	0.758
Grade 2	13 (36.11%)	10 (27.78%)	23 (31.95%)	
Grade 3	6 (16.67%)	7 (19.44%)	13 (18.05%)	
Total	36 (100%)	36 (100%)	72 (100%)	

note ; Grade 1(complete response): no wheeze, dyspnea, rale, cough, and sputum

Grade 2(partial response): no wheeze, dyspnea, rale, but showing cough, and sputum

Grade 3(not response) : show wheeze, dyspnea, rale, cough, and sputum

Table 11 Compared clinical response between the control group and the study group after 3 days treatment with theophylline. The percentage of patients whose clinical response was improved after three days in grade1 and grade 2 were 50%, 31.95% and only 18.05% of patients had symptoms of wheeze, dyspnea, rale, cough and sputum. There were no statistically significant differences in clinical responses between groups with and without pharmacist recommendation.

Table 12 Comparison between theophylline therapeutic level and clinical response

Thephylline level	Clinical response(n)			Total
	Grade1	Grade2	Grade3	
Subtherapeutic range	12	11	5	28
Therapeutic range	13	5	7	25
Toxic range	11	7	13	18
Total	36	23	13	72

Table 12 showed clinical response after 3-days treatment with theophylline categoried as the variety of theophylline level. It is noticed that 23 patients had improved clinical responses (grade 1=12, grade 2=11) while theophylline level was within subtherapeutic range (one patient as low as 4.5 mcg/ml). Most of patients whose theophylline level in therapeutic range had appropriate clinical response, although 7 patients showed no improvement in clinical response. Subjects whose theophylline was in toxic range had nearly no improvement in clinical response whereas some showed improvement. Table 13 tabulated theophylline levels corresponded to clinical responses. It was, thus, found that there is no definitive evidence to demonstrate that the clinical outcome improvement is dependent on therapeutic level of the drug. In addition, there were no significant difference in theophylline levels between patients with co-disease, and without co-disease cases (Table 14) as well as among patients who concurently administered theophylline with enzyme inducer, enzyme inhibitor, and administered alone (Table15). The finding may indicated that theophylline therapeutic level previously categorized in Caucasian race might not be applicable to Thai patients due to the differences in genetics, the drug bioavailability, and physiological thresholds.

Table 13 Actual theophylline level (mean) by clinical response after 3 days treatment with theophylline

Clinical response	Theophylline level (mean) (mcg/ml)
Grade 1	12.186
Grade 2	13.357
Grade 3	11.777

Comparison between grade 1 and grade 2

Significant level (unpaired t-test) = 0.228

Comparison between grade 2 and grade 3

Significant level (unpaired t-test) = 0.221

Comparison between grade 1 and grade 3

Significant level (unpaired t-test) = 0.387

Table 14 Comparison of theophylline level (mean) between patients with and without co-disease

Status diseases	Theophylline level (mcg/ml)	*p*-value (unpaired t-test)
no co-disease	12.862	0.582
co-disease	12.185	

Table 15 Comparison of theophylline level between thophylline combined with enzyme inducer / inhibitor and without enzyme inducer / inhibitor

Status	Theophylline level (mcg/ml)	*p*-value (One-way ANOVA)
With enzyme inducer	11.471	0.747
With enzyme inhibitor	13.950	
Without enzyme inducer/inhibitor	12.507	