CHAPTER IV

RESULTS AND DISCUSSION

Fifty four epileptic patients were included in this study. They were 23 females and 31 males. Their mean age was 30.12 ± 12.26 (mean ± SD). Table 1 showed the characteristics, i.e., age, sex, body weight, height, dosage regimens, dosage of phenytoin and others antiepileptic used together with phenytoin.

1. Dermographic data

Table 2 showed educational backgroud of the epileptic patients participating in this study. Most of patients finished primary school (40.74%) and high school (24.07%).

Table 3 showed the occupation of epileptic patients. Most of the patients are employee (27.78%), commercial (16.67%), officer (12.96%) and student (12.96%), respectively. However , some of them are unemployed (14.81%).

Income of the patients participating in this study was shown in Table 4. Majority of the the patients have low income (37.04%) , either don't have any income at all (37.04%) or have income which is less than 5,000 baht (37.04%).

Table 5 showed the history of seizure of the other members in their family. Four out of fifty-four patients have history of seizure in their family.

Cause of first seizure of these epileptic patients was showed in table 6. The causes was usually unknown (55.56%) while fever was the most common known cause of first seizure (24.07%).

Most of the epileptic patients joined in this study do not have any concomitant disease (97.30%) as shown in table 7.

Table 8 showed that 83.33 percent of the patients were not smoking while table 9 showed that 83.33 percent of the patients were not drinking.

Table 1 : Characteristics of The Patients Studied

Pt. No.	Sex	Age (yr.)	BW.(kg.)	Height(cm.)	Dose/d (mg.)	Dose/BW/d (mg/kg/d)	Dosage Regimens	Antiepileptics drug used togther (mg/d)
1	F	36	50	148	300	6.00	P(100)3 caps x hs.	
2	F	47	44	148	300	6.38	P(100)3 caps x hs.	
3	M	20	58	176	350	6.03	P(100)3 caps x hs.	Phenobarbital 60 mg.
							P(50)1 tab. x hs.	
4	F	26	50.5	158	400	7.92	P(100)2 caps x 2pc	Phenobarbital 60 mg.
					300	5.94	P(100)3 caps x hs.	Phenobarbital 30 mg.
								Carbamazepine 200 mg.
5	M	44	68	160	300	4.41	P(100)3 caps x hs.	Valproic acid 600 mg
6	F	32	67.5	160	350	5.19	P(100)3 caps x hs.	Phenobarbital 60 mg.
							P(50)1 tab. x hs.	
7	M	31	51	160	300	5.88	P(100)3 caps x hs.	Phenobarbital 60 mg.
8	M	32	71	170	300	4.23	P(100)3 caps x hs.	Phenobarbital180 mg.
								Rivotril 1 mg.
					350	4.93	P(100)3 caps x hs.	Phenobarbital180 mg.
							P(50)1 tab. x hs.	Rivotril 1 mg.
9	M	44	75.5	165	300	3.97	P(100)1 caps x 3pc	Cabamazepine 600 mg

Continue....

Pt. No.	Sex	Age (yr.)	BW.(kg.)	Height(cm.)	Dose/d (mg.)	Dose/BW/d (mg/kg/d)	Dosage Regimens	Antiepileptics drug used togther (mg/d)
10	M	32	73	172	400	5.48	P(100)2 caps x 2pc	Phenobarbital180 mg.
11	M	30	47.5	165	300	6.32	P(100) 1 pc & 2 pc	Rivotril 3 mg.
12	M	28	53.5	165	300	5.61	P(100)3 caps x hs.	Phenobarbital120 mg.
					350	6.54	P(100)3 caps x hs.	
							P(50)1 tab. x hs.	
13	F	36	75.5	170	250	3.31	P(100) 1 x 2 pc.	Phenobarbital180 mg.
							P(50)1 tab. x hs.	
14	F	29	57	160	300	5.26	P(100)3 caps x hs.	
15	F	25	65	165	300	4.62	P(100)3 caps x hs.	
16	M	34	62.5	162	300	4.80	P(100)3 caps x hs.	Phenobarbital 60 mg.
								Carbamazepine 600 mg.
17	F	26	50	160	300	6.00	P(100)3 caps x hs.	Phenobarbital120 mg.
18	F	53	63	170	300	4.76	P(100)3 caps x hs.	Phenobarbital120 mg.
19	F	30	79	160	300	3.80	P(100)3 caps x hs.	
20	M	25	58	177	300	5.17	P(100)3 caps x pc.	Phenobarbital120 mg.
21	F	42	56	158	300	5.36	P(100)3 caps x hs.	

Continue....

Pt. No.	Sex	Age (yr.)	BW.(kg.)	Height(cm.)	Dose/d (mg.)	Dose/BW/d (mg/kg/d)	Dosage Regimens	Antiepileptics drug used togther (mg/d)
22	F	29	52.5	153	300	5.71	P(100)3 caps x hs.	Phenobarbital 60 mg.
								Carbamazepine CR. 600 mg.
								Valproic acid 400 mg
23	F	23	49	157	200	4.08	P(100) 1 x 2 pc.	Phenobarbital120 mg.
								Valproic acid 800 mg
					300	6.12	P(100) 1 x 3 pc.	Phenobarbital120 mg.
								Valproic acid 600 mg
24	F	32	39.5	150	200	5.06	P(100) 2 x 1 pc.	Phenobarbital 60 mg.
					250	6.33	P(100) 2 x 1 pc.	
							P(50) 1 x pc.	
					300	7.59	P(100)3 caps x hs.	
25	M	15	85	180	350	4.12	P(100)3 caps x hs.	Phenobarbital120 mg.
							P(50)1 tab. x hs.	Rivotril 1 mg.

Continue....

Pt. No.	Sex	Age (yr.)	BW.(kg.)	Height(cm.)	Dose/d (mg.)	Dose/BW/d (mg/kg/d)	Dosage Regimens	Antiepileptics drug used togther (mg/d)
26	M	42	77	160	300	3.90	P(100)3 caps x hs.	
					350	4.55	P(100)3 caps x hs.	
							P(50)1 tab. x hs.	
					400	5.19	P(100)2 caps x 2pc	
27	F	21	65	165	400	6.15	P(100)2 caps x 2pc	Rivotril 2 mg.
28	M	30	74	160	350	4.73	P(100)3 caps x hs.	Phenobarbital120 mg.
							P(50)1 tab. x hs.	Carbamazepine 200 mg.
29	M	42	77.5	164	300	3.87	P(100)3 caps x pc.	Phenobarbital120 mg.
30	M	42	58	165	300	5.17	P(100) 1 x 3 pc.	Phenobarbital120 mg.
								Rivotril 6 mg.
31	F	28	39	150	300	7.69	P(100) 1 pc & 2 pc	Phenobarbital120 mg.
32	M	24	64	171	300	4.69	P(100) 1 x 3 pc.	Phenobarbital 90 mg.
								Carbamzepine 600 mg.
33	M	7	24	130	175	7.29	P(50) 2xpc&1.5xpc	
34	M	42	64	160	300	4.69	P(100) 1 x 3 pc.	Phenobarbital120 mg.
								Carbamzepine 800 mg.

Continue...

Pt. No.	Sex	Age (yr.)	BW.(kg.)	Height(cm.)	Dose/d (mg.)	Dose/BW/d (mg/kg/d)	Dosage Regimens	Antiepileptics drug used togther (mg/d)
35	M	24	58	165	300	5.17	P(100)3 caps x hs.	Phenobarbital120 mg.
36	F	36	57	165	350	6.14	P(100)3 caps x hs.	
							P(50)1 tab. x hs.	
37	F	37	60	160	250	4.17	P(100) 1xpc.&1xhs.	
							P(50) 1xhs.	
38	M	25	52	171	300	5.77	P(100) 1 x 3 pc.	
39	F	43	50	165	300	6.00	P(100)3 caps x hs.	
40	M	20	63	173	300	4.76	P(100)3 caps x pc.	Phenobarbital120 mg.
					400	6.35	P(100) 2x2 pc.	Phenobarbital120 mg.
41	M	28	58	165	300	5.17	P(100)3 caps x hs.	Phenobarbital180 mg.
42	M	27	55.5	170	300	5.41	P(100) 1 x 3 pc.	Phenobarbital180 mg.
43	M	39	73	170	300	4.11	P(100)1xpc&2xpc.	Phenobarbital 60 mg.
								Carbamazepine 200 mg.
44	M	20	52	165	300	5.77	P(100)3 caps x hs.	Phenobarbital120 mg.
45	M	32	50	160	300	6.00	P(100)3 caps x hs.	
					200	4.00	P(100) 1 x 2 pc.	

Continue....

Pt. No.	Sex	Age (yr.)	BW.(kg.)	Height(cm.)	Dose/d (mg.)	Dose/BW/d (mg/kg/d)	Dosage Regimens	Antiepileptics drug used togther (mg/d)
46	M	60	75	170	200	2.67	P(100) 1 x 2 pc.	Phenobarbital120 mg.
47	M	54	72	170	300	4.17	P(100)3 caps x hs.	Phenobarbital180 mg.
48	F	23	80	160	300	3.75	P(100)3 caps x hs.	Phenobarbital120 mg.
								Rivotril 1 mg.
49	F	41	74	160	325	4.39	P(100)3 caps x hs.	Phenobarbital 30 mg.
							P(50) 1.5 x hs.	
50	M	12	24	130	300	12.50	P(100) 1 x 2 pc.	Phenobarbital 60 mg.
							P(50) 1 x 2 pc.	
					250	10.42	P(100) 1 x 2 pc.	Phenobarbital 60 mg.
							P(50)1.5 x 2 pc.	
51	M	3	13	65	100	7.69	P(50) 1.5x 4 pc&hs	Phenobarbital 60 mg.
								Rivotril 2 mg.
52	F	13	32	140	300	9.38	P(100) 1x2 pc&hs.	
					200	6.25	P(100) 1 x 2 pc.	
53	M	0.2	4	35.5	50	12.50	P(50) 1xpc&1xhs.	Phenobarbital 45 mg.
54	F	14	44	151	200	4.55	P(100) 1 x 2 pc.	

Patient Number 41-43 : Outpatients

Patient Number 44-54 : Inpatients

Table 2 : Educational Background of The Patients Participating in The Study.

Education	Number of patients	Percent (%)
University graduate	7	12.96
High school	13	24.07
Primary school	22	40.74
Diploma	9	16.67
No education	1	1.85
Infant	2	3.70
Total	54	100.00

Table 3 : Occupational Background of The Patients Participating in The Study.

Occupation	Number of patients	Percent (%)
Officer	7	12.96
Employee	15	27.78
Commerce	9	16.67
Student	7	12.96
Priest	2	3.70
Agriculturist	4	7.41
Unemployed	8	14.81
Infant	2	3.70
Total	54	100.00

Table 4 : Income of The Patients Participating in The Study.

Income	Number of patients	Percent (%)
No income	20	37.04
<= 5,000	20	37.04
5,001-10,000	7	12.96
10,001-20,000	5	9.26
20,001-30,000	1	1.85
>30,000	1	1.85
Total	54	100.00

Table 5 : History of Seizure of The Other Members in The Patient's Family.

History of seizure in the family	Number of patients	Percent (%)
Have seizure	4	7.41
No seizure	50	92.59
Total	54	100.00

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Table 6 : Cause of First Seizure of The Epileptic Patients.

Cause of first seizure	Number of patients	Percent (%)
unknown	30	55.56
Trauma	4	7.41
Fever	13	24.07
Psychotic	3	5.56
Hypoxia	3	5.56
Alcohol	1	1.85
Total	54	100.00

Table 7 : Concomitant Diseases of The Epileptic Patients.

Others diseases	Number of patients	Percent (%)
No disease	52	97.30
Hypertension	1	1.85
Diabetes Mellitus.	1	1.85
Total	54	100.00

Table 8 : Smoking Habit of The Epileptic Patients.

Smoking	Number of patients	Percent (%)
Smoking (always)	9	16.67
Not smoking	45	83.33
Total	54	100.00

Table 9 : Alcohol Drinking Habit of The Epileptic Patients.

Alcohol drinking	Number of patients	Percent (%)
Not drinking	45	83.33
Stop drinking for more than 1 month	5	9.26
Drinking (ocasionally)	2	3.70
Drinking (always)	2	3.70
Total	54	100.00

2. Therapeutic monitoring of phenytoin

Phenytoin serum level and clinical responses were determined in all patients. Clinical responses to phenytoin therapy were observed for both beneficial effects and adverse reaction. The patient was considered to have clinical improvement to phenytoin therapy if seizures was decreased in frequency, severity and duration and no adverse reaction was observed. If adverse reaction has been observed, a new dosage regimen was determined and the patient was further monitored for the decreasing in adverse drug reaction.

Table 10 illustrated phenytoin dosage regimen, measured phenytoin serum concentrations, predicted phenytoin concentrations (by population pharmacokinetic parameters), other antiepileptic drug concurently used and the clinical responses both beneficial and adverse effects.

Table 11 showed that 15 patients (27.78%) were treated with phenytoin alone, and 39 patients (72.22%) were treated with phenytoin along with other antiepileptic drugs (phenobarbital, carbamazepine, valproic acid, clonazepam). The antiepileptic drug most oftenly used along with phenytoin was phenobarbital (42.59%).

Table 12 and Figure 1 indicated that percentage of patients showed no beneficial effect was higher when their phenytoin serum concentrations were in the subtherapeutic range (25.93%) as compare to the patients whose phenytoin serum concentrations were within the therapeutic range(20.83%) and in the overtherapeutic range(26.67%) respectively while the percentage of patients showed central nervous system adverse drug reaction when their phenytoin serum concentrations were in overtherapeutic range (73.33%) was higher than the patients whose phenytoin serum concentrations were within the therapeutic range (37.50%) and in the subtherapeutic range (22.22%) respectively. These results agree with the foreign literatures which indicated that phenytoin serum concentration correlate well with seizure control and central nervous system adverse drug reaction (Winter, Katcher and Kimble, 1980 ; Lund, 1974).

In table 13, Figure 2 and Figure 3 showed that when the patients were treated with phenytoin, percentage of patients showed beneficial effects (absolutely control seizure and Partially control seizure) when their phenytoin serum concentrations were within subtherapeutic, therapeutic and overtherapeutic levels were 74.07%, 79.16% and 73.34%, respectively. Higher percentage of patients showed beneficial effect which absolutely seizure control when their phenytoin serum concentrations were in overtherapeutic range , therapeutic range and subtherapeutic range, respectively. However, higher percentage of patients showed beneficial effect which partially seizure control when their phenytoin serum concentrations were in subtherapeutic range and in therapeutic range. Patients were not controled seizure 24.24% and patients showed central nervous system adverse drug reaction were 39.39%.

Figure 4 showed that the incidence of phenytoin adverse reactions (general and central nervous system side effects) of the group of patients treated with phenytoin together with other antiepileptic drugs (46.00%) occured more often than the group of patients treated with phenytoin alone (20.00%).

Table 14 indicated that the general adverse drug reactions observed most often was gum hypertrophy (31.82%). Gum hypertropy was met in every range of phenytoin concentrations. However, central nervous system adverse drug reactions (Nystagmus, ataxia, drowsiness, dizziness, diplopia and headache) (52.31%) were met more than other adverse reactions (39.40%). Nystagmus occured in patients with phenytoin serum concentrations higher than 20 μg/mL and ataxia occured in patients wtih phenytoin serum concentrations higher than 30μg/mL. This supported that central nervous system side effects do correlate with serum concentration (Winter, Katcher and Kimble, 1980).

This study was found that the frequency of occurrence of gum hypertrophy tends to related to the duration of phenytoin used (As shown in Table 15). This finding is consistent with a previous study by Perlik, Kolinova, Zvarova and Patzelova (1995).

Table 16 showed that when phenytoin was given according to the physician traditional dosage regimen, 43 out of 54 (79.63%) patients did not require phenytoin dosage regimen adjustment while 11 out of 54 patients (20.37%) did require. These results were drawn from the data in table 10, since patient number 4,8,12,23,24,26,40,45,48,50 and 52 required dosage adjustment while the rest did not. Mostly patients required phenytoin dosage regimen adjustment were patients recieving inappropriate phenytoin dose (70.00%). So that appropriate phenytoin dose for patients may not require dosage adjustment.

Four patients (patient number 4,45,50 and 52) showed central nervous system side effects, their phenytoin doses were recommended to be decreased. After the new doses were administered, the central nervous system side effects of 4 patients were decreased. With the traditional dosage regimen, the seizure of 6 patients could not be controlled, their doses were therefore recommended to be increased. Five out of 6 patients showed better beneficial effect with the the new doses. The results were shown in table 17.

The saliva samples of randomly selected twelve subjects were collected at the same time when the serum samples was drawn in order to study for their correlation. Good correlation between phenytoin serum concentration and phenytoin saliva concentration (R^2 = 0.94) was found as shown in table 18, figure 5 and figure 6. This result corresponded well with that reported by Cai et al. (1993). Additionally, the mean of ratio of phenytoin serum concentration to phenytoin saliva concentration was calculated to be 13.43 which is closed to the reported value as 9.01.

Table 10 : Clinical Responses of Patients Receiving Phenytoin.

Pt. No.	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimens	Phenytoin level (Measured)	Phenytoin level (Pop.Calculated)	Antiepileptics drug used together(mg/d)	Clinical response			
								Absolutely	Partially	Not control	Adverse Reactions
1	F	36	300	P(100)3 caps x hs.	20.37	14.92		/			horizontal nystagmus, gum hypertrophy,drowsiness
2	F	47	300	P(100)3 caps x hs.	15.85	34.50			/		gum hypertrophy
3[(c)]	M	20	350	P(100)3 caps x hs. P(50)1 tab. x hs.	7.72	16.30	Phenobarbital 60 mg.		/		
4*	F	26	400	P(100)2 caps x 2pc	38.86	Not cal.	Phenobarbital 60 mg.			/	Ataxia, Diplopia, Dizziness
			300	P(100)3 caps x hs.	12.47	14.25	Phenobarbital 30 mg. Carbamazepine 200 mg.			/	
5[(a)]	M	44	300	P(100)3 caps x hs.	4.53	5.52	Valproic acid 600 mg		/		
6[(a)]	F	32	350	P(100)3 caps x hs. P(50)1 tab. x hs.	9.14	5.62	Phenobarbital 60 mg.			/	mild horizontal nystagmus
7[(a)]	M	31	300	P(100)3 caps x hs.	4.27	13.63	Phenobarbital 60 mg.		/		mild gaze horizontal nystagmus

Continue....

Pt. No.	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimens	Phenytoin level (Measured)	Phenytoin level (Pop.Calculated)	Antiepileptics drug used together(mg/d)	Clinical response			
								Absolutely	Partially	Not control	Adverse Reactions
8	M	32	300	P(100)3 caps x hs.	4.18	5.00	Phenobarbital180 mg. Rivotril 1 mg.		/		gum hypertrophy
			350	P(100)3 caps x hs. P(50)1 tab. x hs.	17.00	7.63	Phenobarbital180 mg. Rivotril 1 mg.		/		gum hypertrophy
9[a]	M	44	300	P(100)1 caps x 3pc	10.37	4.37	Cabamazepine 600 mg			/	
10	M	32	400	P(100)2 caps x 2pc	11.59	10.29	Phenobarbital180 mg.		/		
11	M	30	300	P(100) 1 pc & 2 pc	22.88	19.54	Rivotril 3 mg.	/			horizontal nystagmus
12	M	28	300	P(100)3 caps x hs.	11.72	11.21	Phenobarbital120 mg.		/		
			350	P(100)3 caps x hs. P(50)1 tab. x hs.	16.86	26.89		/			
13[a]	F	36	250	P(100) 1 x 2 pc. P(50)1 tab. x hs.	4.79	3.18	Phenobarbital180 mg.		/		gum hypertrophy
14	F	29	300	P(100)3 caps x hs.	12.92	8.98				/	gum hypertrophy, headache
15	F	25	300	P(100)3 caps x hs.	12.42	6.17			/		gum hypertrophy,drowsiness
16	M	34	300	P(100)3 caps x hs.	14.55	6.84	Phenobarbital 60 mg. Carbamazepine 600 mg.		/		gaze horizontal nystagmus

Continue....

Pt. No.	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimens	Phenytoin level (Measured)	Phenytoin level (Pop.Calculated)	Antiepileptics drug used together(mg/d)	Clinical response			
								Absolutely	Partially	Not control	Adverse Reactions
17	F	26	300	P(100)3 caps x hs.	20.24	14.92	Phenobarbital120 mg.	/			nystagmus
18[a]	F	53	300	P(100)3 caps x hs.	3.05	6.69	Phenobarbital120 mg.		/		
19[a]	F	30	300	P(100)3 caps x hs.	6.70	3.99			/		
20	M	25	300	P(100)3 caps x pc.	18.11	8.49	Phenobarbital120 mg.	/			nystagmus,gum hypertrophy
21	F	42	300	P(100)3 caps x hs.	5.77	9.52		/			gum hypertrophy
22	F	29	300	P(100)3 caps x hs.	13.97	12.07	Phenobarbital 60 mg. Carbamazepine CR. 600 mg. Valproic acid 400 mg		/		mild nystagmus
23	F	23	200	P(100) 1 x 2 pc.	4.67	4.63	Phenobarbital120 mg. Valproic acid 800 mg		/		gum hypertrophy
			300	P(100) 1 x 3 pc.	12.46	16.48	Phenobarbital120 mg. Valproic acid 600 mg	/			gum hypertrophy,acne drowsiness
24	F	32	200	P(100) 2 x 1 pc.	3.50	7.67	Phenobarbital 60 mg.		/		
			250	P(100) 2 x 1 pc. P(50) 1 x pc.	6.98	20.35		/			drowsiness
			300	P(100)3 caps x hs.	15.94	61.33		/			drowsiness

Continue....

Pt. No.	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimens	Phenytoin level (Measured)	Phenytoin level (Pop.Calculated)	Antiepileptics drug used together(mg/d)	Clinical response			
								Absolutely	Partially	Not control	Adverse Reactions
25[a]	M	15	350	P(100)3 caps x hs. P(50)1 tab. x hs.	0.24	4.85	Phenobarbital120 mg. Rivotril 1 mg.			/	
26	M	42	300	P(100)3 caps x hs.	7.97	4.20			/		
			350	P(100)3 caps x hs. P(50)1 tab. x hs.	11.60	6.12			/		
			400	P(100)2 caps x 2pc	18.42	8.61		/			
27	F	21	400	P(100)2 caps x 2pc	8.63	16.92	Rivotril 2 mg.			/	
28	M	30	350	P(100)3 caps x hs. P(50)1 tab. x hs.	9.53	6.79	Phenobarbital120 mg. Carbamazepine 200 mg.		/		drowsiness
29	M	42	300	P(100)3 caps x pc.	11.12	4.14	Phenobarbital120 mg.		/		drowsiness
30	M	42	300	P(100) 1 x 3 pc.	30.88	8.49	Phenobarbital120 mg. Rivotril 6 mg.			/	nystagmus
31	F	28	300	P(100) 1 pc & 2 pc	25.45	Not cal.	Phenobarbital120 mg.		/		gum hypertrophy
32[c]	M	24	300	P(100) 1 x 3 pc.	7.74	6.42	Phenobarbital 90 mg. Carbamzepine 600 mg.			/	gum hypertrophy

Continue....

Pt. No.	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimens	Phenytoin level (Measured)	Phenytoin level (Pop.Calculated)	Antiepileptics drug used together(mg/d)	Clinical response			
								Absolutely	Partially	Not control	Adverse Reactions
33	M	7	175	P(50) 2xpc&1.5xpc	12.81	13.07		/			dizziness
34[(c)]	M	42	300	P(100) 1 x 3 pc.	5.12	6.42	Phenobarbital120 mg. Carbamzepine 800 mg.		/		horizontal nystagmus, gum hypertrophy
35	M	24	300	P(100)3 caps x hs.	32.39	8.49	Phenobarbital120 mg.		/		nystagmus, ataxia, diziness
36	F	36	350	P(100)3 caps x hs. P(50)1 tab. x hs.	34.74	17.86			/		gum hypertrophy,drowsiness
37[(a)]	F	37	250	P(100) 1xpc.&1xhs. P(50) 1xhs.	5.19	5.03				/	gum hypertrophy
38	M	25	300	P(100) 1 x 3 pc.	19.53	12.55				/	
39[(a)]	F	43	300	P(100)3 caps x hs.	3.97	14.92			/		gum hypertrophy
40	M	20	300	P(100)3 caps x pc.	3.56	6.69	Phenobarbital120 mg.		/		gum hypertrophy
			400	P(100) 2x2 pc.	18.66	20.16	Phenobarbital120 mg.		/		gum hypertrophy,dizziness
41	M	28	300	P(100)3 caps x hs.	16.22	8.49	Phenobarbital180 mg.	/			gum hypertrophy
42	M	27	300	P(100) 1 x 3 pc.	14.94	9.81	Phenobarbital180 mg.		/		gum hypertrophy

Continue....

Pt. No.	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimens	Phenytoin level (Measured)	Phenytoin level (Pop.Calculated)	Antiepileptics drug used together(mg/d)	Clinical response			
								Absolutely	Partially	Not control	Adverse Reactions
43	M	39	300	P(100)1xpc&2xpc.	11.50	4.84	Phenobarbital 60 mg. Carbamazepine 200 mg.			/	gum hypertrophy
44	M	20	300	P(100)3 caps x hs.	1.92	12.55	Phenobarbital120 mg.		/		
45	M	32	300	P(100)3 caps x hs.	54.55	14.92		/			nystagmus, ataxia, nausea, vomitting, headache
			200	P(100) 1 x 2 pc.	23.07	4.43		/			
46	M	60	200	P(100) 1 x 2 pc.	2.66	2.16	Phenobarbital120 mg.	/			
47	M	54	300	P(100)3 caps x hs.	1.00	4.84	Phenobarbital180 mg.		/		
48[(b)]	F	23	300	P(100)3 caps x hs.	29.99	4.56	Phenobarbital120 mg. Rivotril 1 mg.			/	cerebellar atrophy
49	F	41	325	P(100)3 caps x hs. P(50) 1.5 x hs.	17.18	5.55	Phenobarbital 30 mg.	/			
50[(d)]	M	12	300	P(100) 1 x 2 pc. P(50) 1 x 2 pc.	44.23	Not cal.	Phenobarbital 60 mg.	/			nystagmus, ataxia, nausea, vomitting
			250	P(100) 1 x 2 pc. P(50)1.5 x 2 pc.	43.01	Not cal.	Phenobarbital 60 mg.	/			

Continue....

Pt. No.	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimens	Phenytoin level (Measured)	Phenytoin level (Pop.Calculated)	Antiepileptics drug used together(mg/d)	Clinical response			
								Absolutely	Partially	Not control	Adverse Reactions
51[c]	M	3	100	P(50) 1.5x 4 pc&hs	2.20	12.53	Phenobarbital 60 mg. Rivotril 2 mg.			/	
52	F	13	300	P(100) 1x2 pc&hs.	50.00	Not cal.				/	horizontal nystagmus, ataxia
			200	P(100) 1 x 2 pc.	21.23	13.09			/		
53[b]	M	0.2	50	P(50) 1xpc&1xhs.	2.53	32.62	Phenobarbital 45 mg.			/	
54	F	14	200	P(100) 1 x 2 pc.	4.59	5.85		/			

* Try to tail off phenobarbital

(a) Patients were not followed up.

(b) Changed to other antiepileptic drug.

(c) Adjustment dosage regimen of other antiepileptic drug.

(d) Can not calculate pharmacokinetic parameters(K_m and V_{max})

Table 11 : Percentage of Patients Receiving Phenytoin Alone and Phenytoin with Other Antiepileptic Drugs.

Antiepileptic drug	Number	Percent(%)
Phenytoin	15	27.78
Phenytoin + Phenobarbital *	23	42.59
Phenytoin + Carbamazepine	1	1.85
Phenytoin + Valproic acid	1	1.85
Phenytoin + Rivotril	2	3.70
Phenytoin + Phenobarbital + Carbamazepine	5	9.26
Phenytoin + Phenobarbital + Rivotril	5	9.26
Phenytoin + Phenobarbital + Carbamazepine + Valproic acid	1	1.85
Phenytoin + Phenobarbital + Valproic acid	1	1.85
Total	54	100.00

* One patient used carbamazepine together and two patients stoped phenobarbital when adjusted dosage regimen.

Table 12 : Percentage of Patients Showed No Beneficial Effect and Showed Central Nervous System Adverse Drug Reaction.

Phenytoin Serum Concentrations (n)	Number of Patients with No Beneficial Effect (%)	Number of Patients with CNS. Adverse Drug Reaction (%)
Subtherapeutic Range (27)	7 (25.93)	5 (18.52)
Therapeutic Range (24)	5 (20.83)	10 (41.67)
Overtherapeutic Range (15)	4 (26.67)	11 (73.33)
Total (66)	16 (24.24)	26 (39.39)

Subtherapeutic Range (< 10 μg/mL)

Therapeutic Range (10-20 μg/mL)

Overtherapeeutic Range (> 20 μg/mL)

Figure 1 : Incidence of No Beneficial Effect and Adverse Drug Reaction of Patients Receiving Phenytoin.

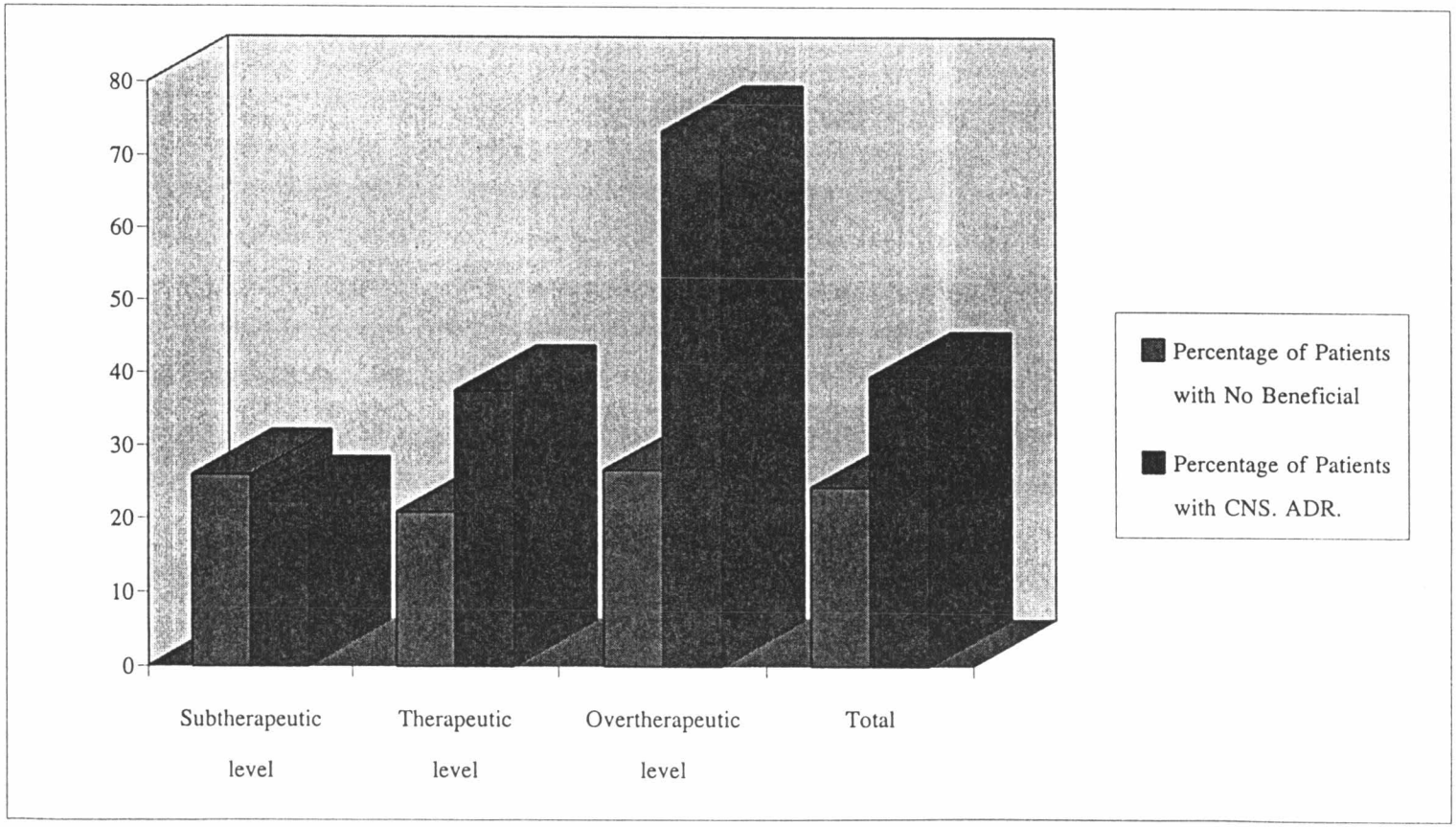


Table 13 : Percentage of Patients with Absolute Seizure Control, Partial Seizure Control or Not Control and Adverse Drug Reaction with Different Range of Phenytoin Serum Concentrations.

Phenytoin concentration (μg/mL) (n)	Number of Patients with Absolute Seizure Control(%)	Number of Patients with Partial Seizure Control(%)	Number of Patients with Seizure Not Control(%)	Number of Patients with CNS. Adverse Drug Reaction(%)
< 10 (27)	4 (14.81)	16 (59.26)	7 (25.93)	5 (18.52)
10 - 20 (24)	8 (33.33)	11 (45.83)	5 (20.83)	10 (41.67)
> 20 (15)	7 (46.67)	4 (26.67)	4 (26.67)	11 (73.33)
Total (66)	19 (28.79)	31 (46.97)	16 (24.24)	26 (39.39)

Figure 2 : Seizure Control of Patients Receiving Phenytoin.

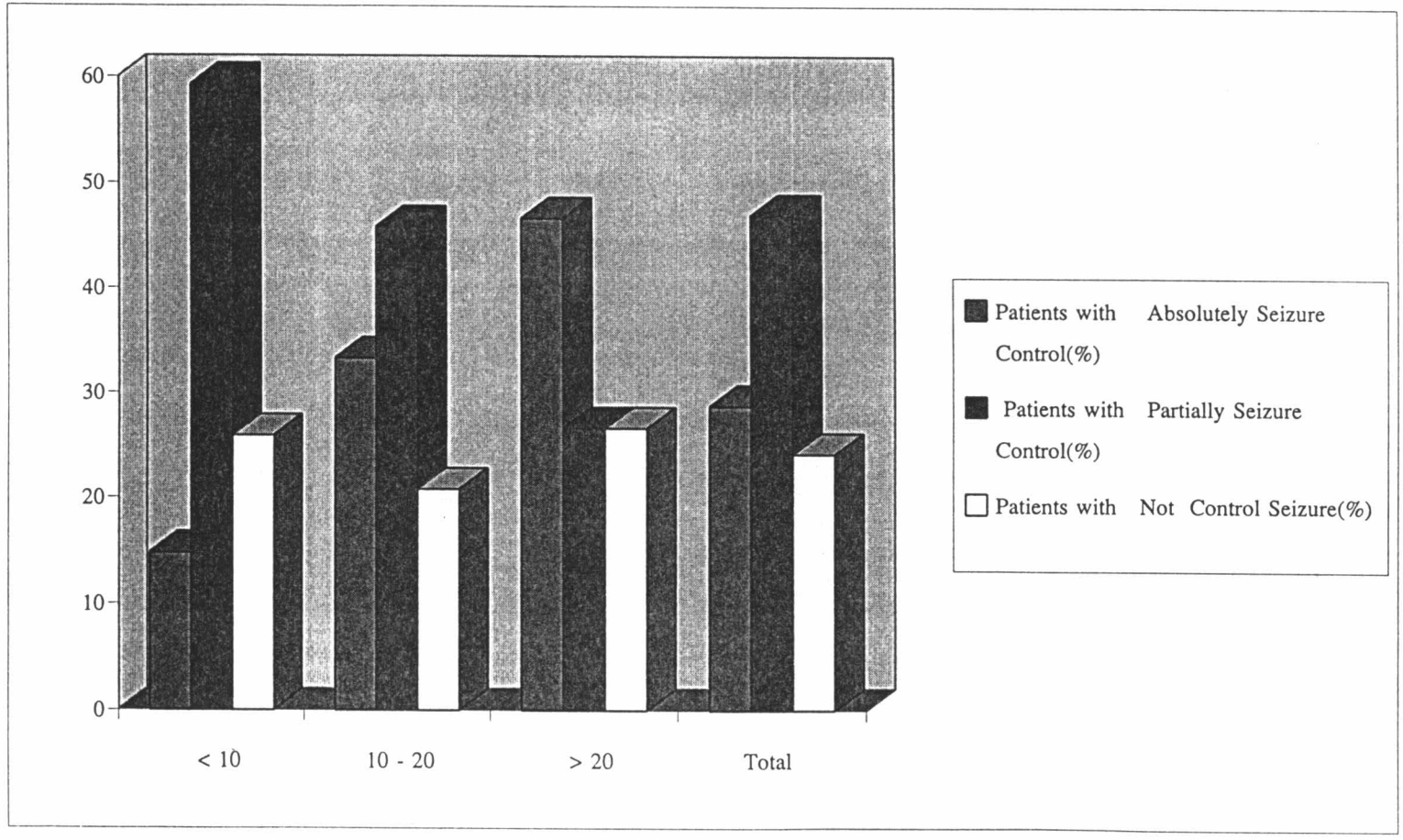


Figure 3 : Central Nervous System Adverse Drug Reactions of Patients Receiving Phenytoin.

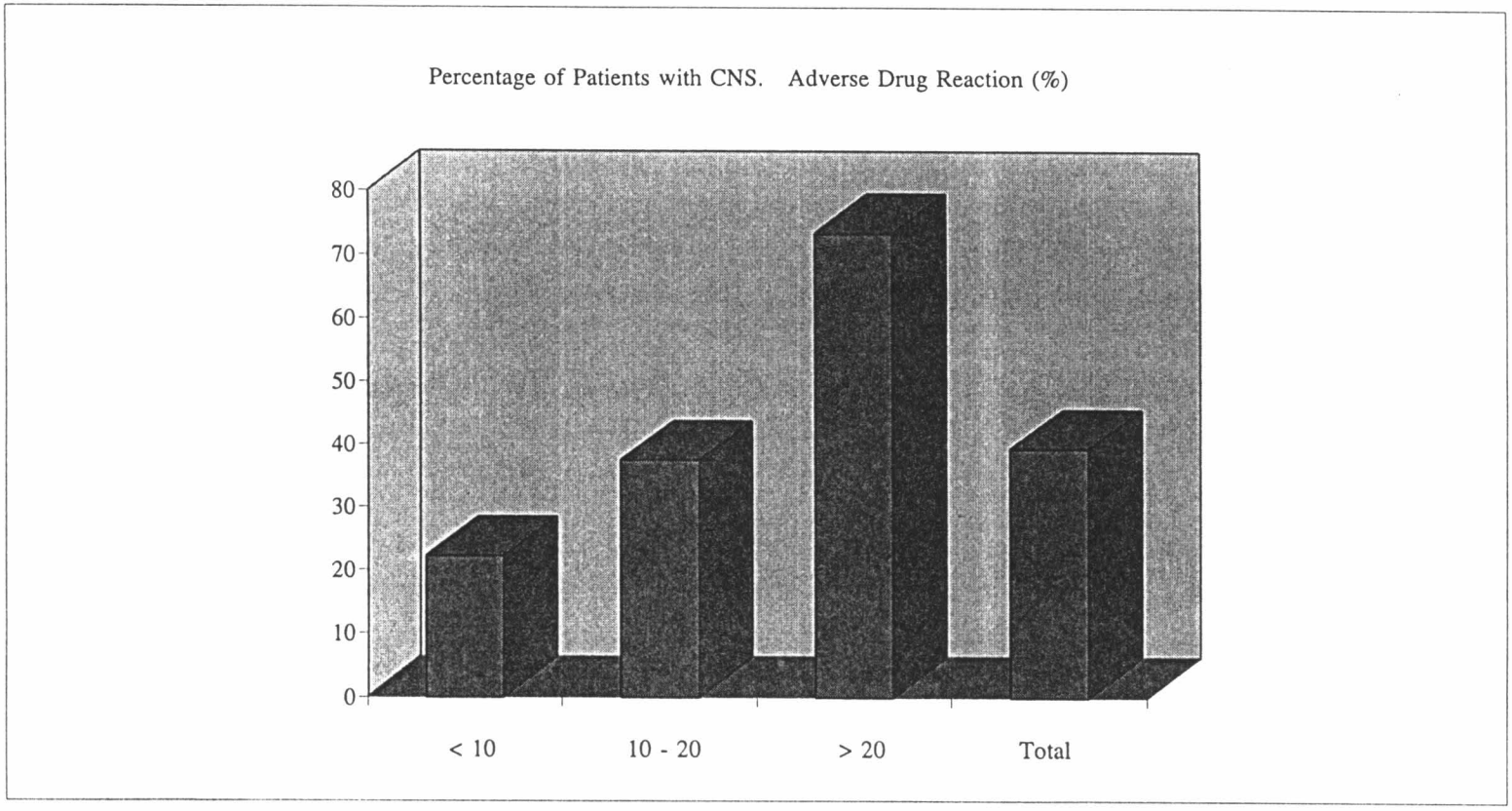


Figure 4 : Percentage of Patients Showed Sign of Phenytoin Adverse Drug Reaction after Patients were Treated with Phenytoin Alone or Phenytoin along with Other Antiepileptic Drugs. (n=54)

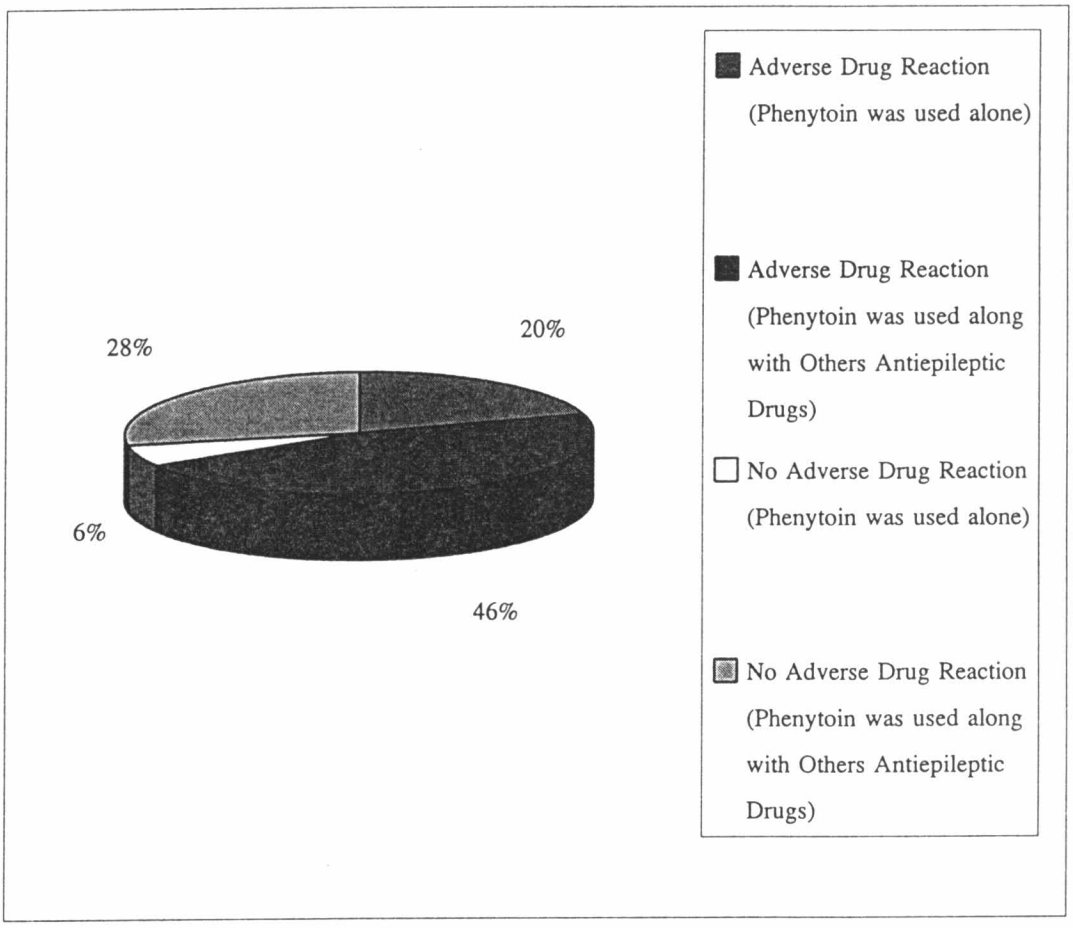


Table 14 : Incidence of Adverse Drug Reactions at Different Phenytoin Serum Level.

Adverse Drug Reaction	Phenytoin Concentration < 10 μg/mL (%) (n=27)	Phenytoin Concentration 10 - 20 μg/mL (%) (n=24)	Phenytoin Concentration 21 - 30 μg/mL (%) (n=7)	Phenytoin Concentration > 30 μg/mL (%) (n=8)	Total (%) (n=66)
Gum hypertrophy	9 (33.33)	9 (37.50)	2 (39.29)	1 (12.50)	21 (31.82)
Ataxia	0 (0.00)	0 (0.00)	0 (0.00)	5 (64.06)	5 (8.06)
Nystagmus	3 (12.35)	3 (14.06)	3 (48.47)	5 (64.06)	14 (21.33)
Cerebellar atrophy	0 (0.00)	0 (0.00)	1 (21.21)	0 (0.00)	1 (1.52)
Drowsiness	2 (7.40)	3 (12.50)	1 (21.21)	1 (12.50)	7 (10.63)
Dizziness	0 (0.00)	2 (8.33)	0 (0.00)	2 (25.00)	4 (6.22)
Diplopia	0 (0.00)	0 (0.00)	0 (0.00)	1 (12.50)	1 (1.52)
Headache	0 (0.00)	1 (4.17)	0 (0.00)	1 (12.50)	2 (3.03)
Acne	0 (0.00)	1 (4.17)	0 (0.00)	0 (0.00)	1 (1.52)
Nausea	0 (0.00)	0 (0.00)	0 (0.00)	2 (25.00)	2 (3.03)
Vomiting	0 (0.00)	0 (0.00)	0 (0.00)	2 (25.00)	2 (3.03)
Total	15 (55.56)	18 (75.00)	7 (100.00)	20 (258.01)	60 (90.91)

Table 15 : Incidence of Gum Hypertrophy depend on Phenytoin Used Duration.

Phenytoin Used Duration (yr.) (n)	Number of Patients Observed Gum Hypertrophy (%)	Number of Patients Not Observed Gum Hypertrophy (%)
< 1 (2)	0 (0.00)	2 (100.00)
1 (3)	0 (0.00)	3 (100.00)
2 (2)	1 (50.00)	1 (50.00)
3 (2)	0 (0.00)	2 (100.00)
4 (6)	2 (33.33)	4 (66.67)
5 (6)	2 (33.33)	4 (66.67)
> 5 (33)	13 (39.39)	20 (60.61)
Total (54)	18 (33.33)	36 (66.67)

Chi Square Test ($\alpha = 0.05$) ,df = 6 , $\chi^2 = 4.30$

Table 16 : Percentage of Patients Receiving Phenytoin Serum Level Monitoring and Dosage Regimen Adjustment

Phenytoin Serum Level Monitoring	Number of Patients(%) n = 54	Number of patients with inappropriate dose n (%)
(1) No adjust dosage regimen because of appropriate clinical response	42 (77.78)	23 (54.76)
(2) Adjust dosage regimen because of inappropriate clinical responses	10 (18.56)	7 (70.00)
Decrease dose of phenytoin (for overdose phenytoin)	4 (7.41)	3 (75.00)
Increase dose of phenytoin	6 (11.11)	4 (66.67)
(3) Change to other antiepileptic drugs	2 (3.70)	2 (100.00)

Normal appropriate dose for adults : 5-7 mg/kg/d

Normal appropriate dose for newborns and infants < 3 mo. : 3-5 mg/kg/d

Table 17 : Percentage of Patients with Improvement in Clinical Responses after Dosage Adjustment.

Dosage Adjustment	Number of Patients	Improve in Clinical Response	
	n=11	Increased seizure control (%)	Decreased adverse drug reaction (%)
Increased dose	6	5 (83.33)	0 (0.00)
Decreased dose	4	–	4 (100.00)

Table 18 : Correlation between Phenytoin Serum Concentrations and Phenytoin Saliva Concentrations.

Pt. No.	Sex	Age (yr.)	Dose (mg./d)	Phenytoin serum concentration (μg./mL)	Phenytoin saliva concentration (μg./mL)	Ratio
4	F	26	300	12.47	0.97	12.86
12	M	28	350	16.86	1.53	11.02
23	F	23	300	12.46	1.51	8.25
24	F	32	300	15.94	1.11	14.36
26	M	42	400	18.48	1.54	12.00
33	M	7	175	12.81	1.00	12.81
36	F	36	350	34.74	3.57	9.73
37	F	37	250	5.19	0.17	30.53
38	M	25	300	19.53	1.63	11.98
39	F	43	300	3.97	0.37	10.73
					Average =	13.43
					R =	0.97
					R^2 =	0.94

Figure 5 : Correlation between Phenytoin Serum Concentration and Phenytoin Saliva Concentration.

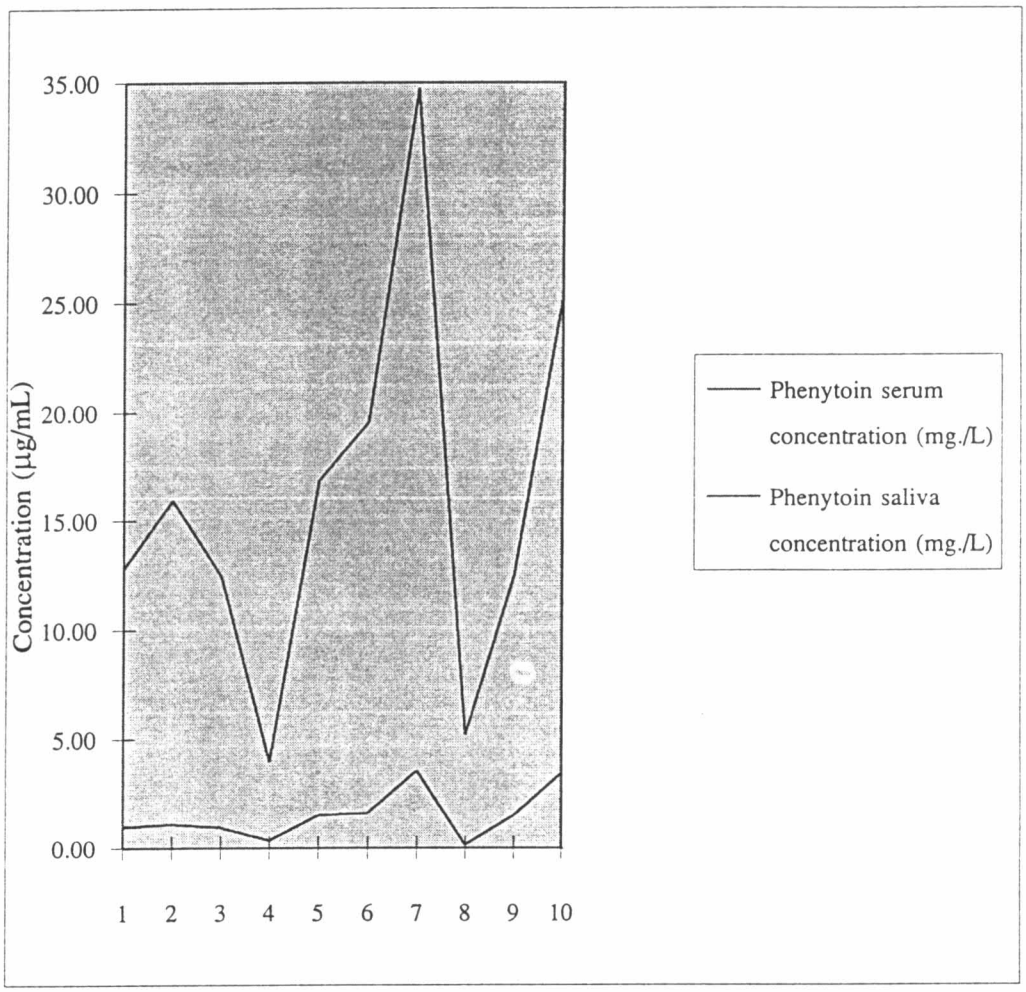
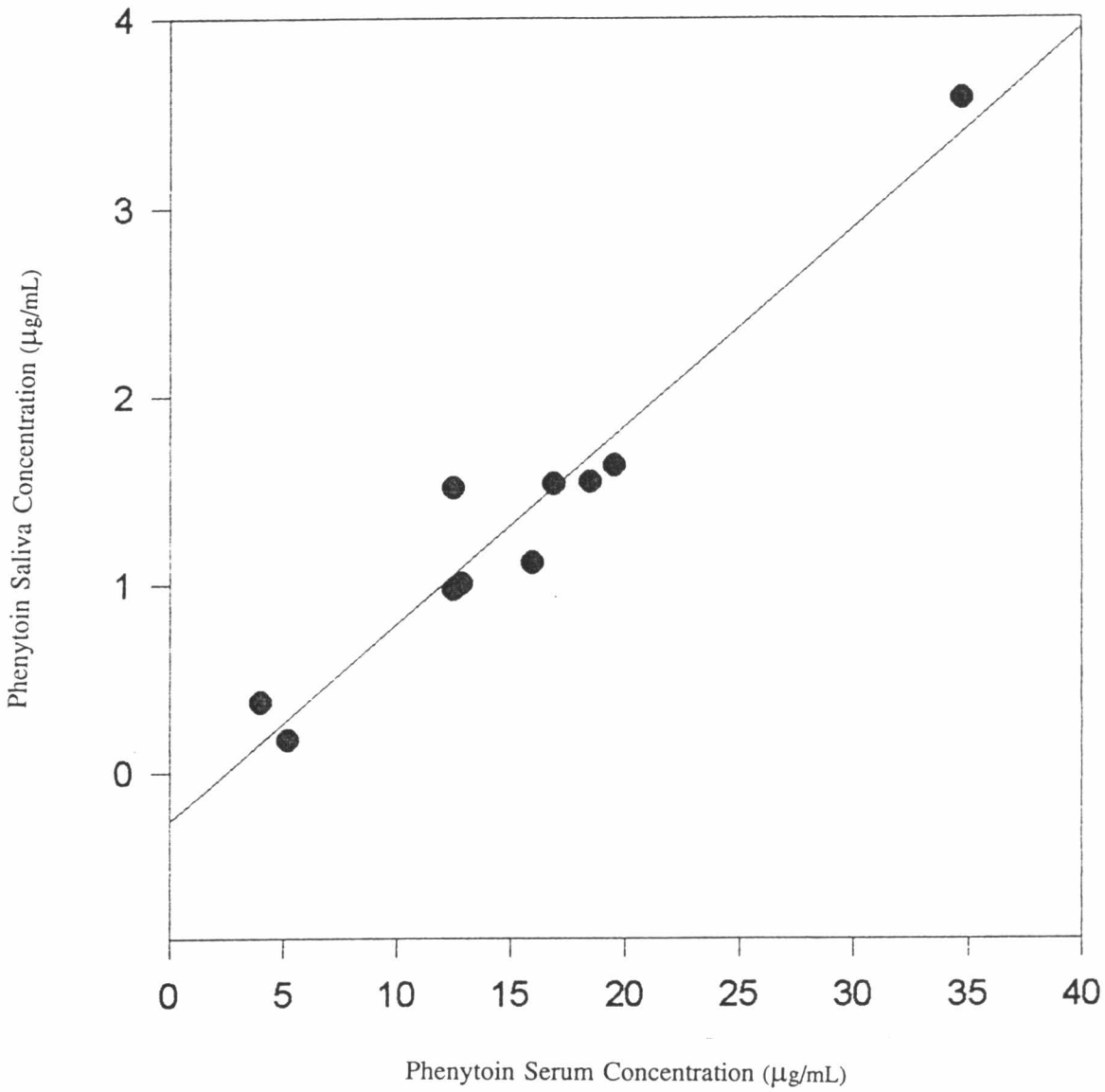


Figure 6 : Correlation between Serum Phenytoin Serum Concentration and Saliva Phenytoin Concentration.



3. Comparison between the measured and the predicted phenytoin serum concentrations

One of the purpose in this study was to compare between the measured phenytoin serum concentrations and the predicted serum concentrations by applying pharmacokinetic parameters and equations from literatures. The mean measured and predicted phenytoin serum concentrations were 14.73 ± 12.15 and 11.29 ± 9.36 μg/mL, respectively, as shown in table 19. The mean difference between measured and predicted values was 8.25 ± 9.18 while the mean percentage of difference between measured and predicted values was 129.81 ± 293.15 (mean ± SD). The percent coefficient of variation was 225.83. The percentage of difference and the coefficient of variation were great since the population parameters measured in the process of calculation. As mentioned in several text books and journals, pharmacokinetic parameters of phenytoin vary greatly among individual patient.

Table 20 showed percent concentration of phenytoin serum concentration in different range of phenytoin serum concentrations. The percent coeffecient of variation of percent concentration of phenytoin serum concentrations in the range of 10.01–15, 20.01–25 and 30.01 –35 μg/mL were 43.26%, 41.03% and 40.50% , respectively that were less variable than other range. Predicted phenytoin serum in these range may be more accurate than other range of phenytoin serum concentrations. The percent coeffecient of variation of percent concentration of phenytoin serum concentrations in the range of phenytoin serum concentrations less than 5 μg/mL was 121.02 indicated that predicted phenytoin serum concentration in this range were not accurately.

Table 21 showed comparison between measured and predicted phenytoin serum concentrations in the patients receiving phenytoin alone. The mean measured and predicted phenytoin serum concentrations were 17.34 ± 13.54 μg/mL and 14.63 ± 13.25 μg/mL respectively, and the mean difference between measured and predicted values was 11.02 ± 11.88 , the mean percentage of difference between measured and predicted values was 84.48 ± 98.56. The percent coefficient of variation was 116.67. Again, the difference between the

measured and the predicted values were quite great which may be due to the same reason as mentioned above.

Table 22 showed comparison between measured and predicted phenytoin serum concentrations in the patients receiving phenytoin along with others antiepileptic drugs. The mean measured and predicted phenytoin serum concentrations were 13.43 ± 11.33 μg/mL , 9.56 ± 5.94 μg/mL respectively. When the factors caused by other drugs were also considered while calcalated the predicted phenytoin concentration, the mean predicted phenytoin serum concentrations was calculated to be 10.16 ± 7.86 μg/mL.

The mean difference between measured and predicted values calculated by population pharmacokinetic parameter was 6.78 ± 7.15 and the mean difference between measured and predicted values calculated by population pharmacokinetic parameter plus adjusting for drug interaction factors was 7.60 ± 7.39 which were not much difference indicated that the adjustment for factors might not be necessary.

From table 21 and table 22 showed that the percent coefficient of variation of predicted phenytoin serum concentrations when patients recieving phenytoin alone was 116.67 and the percent coefficient of variation of predicted phenytoin serum concentrations when patients receiving phenytoin along with other antiepileptic drugs were 225.79 (no factors adjusting) and 272.31 (used factors adjusting). This indicated that when patients receiving phenytoin along with other antiepileptic drugs the phenytoin serum concentrations may be less predictable. However, the validation of predicted phenytoin serum concentrations in both groups of patients are questionable since the coefficient of variation in either group was too high.

The percent coefficient of variation of comparison between measured and predicted phenytoin serum concentrations when patients receiving phenytoin with phenobarbital were 171.46 (no factor adjusting) and 166.01 (used factor adjusting). This indicated that phenobarbital may affect the accuracy of prediction of phenytoin serum concentrations (as shown in table 21 and 23).

The percent coefficient of variation of comparison between measured and predicted phenytoin serum concentrations when patients receiving phenytoin with phenobarbital and carbamazepine were 56.34 (no factor adjusting) and 76.09 (used factor adjusting). This indicated that when patients receiving phenytoin along with phenobarbital and carbamazepine their phenytoin serum concentrations more accurately predicted than those patients who received phenytoin alone (as shown in table 21 and 24). However, since only six patients were categorized in this group, further studies are required before any conclusion could be confirmed.

Table 25 showed comparison between the measured values to the predicted value calculated by difference methods (calculated by using population pharmacokinetic parameters, wagner method, calculated by fixing $K_m = 4$, and calculated by fixing $V_{max} = 7$). The percent coefficient of variation of method that calculated by fixing $K_m = 4$ was lowest (63.59). Therefore, this method was suggested to be the method of choice for calculating the dosage regimen and/or predicting phenytoin serum concentration when only one pair of data, i.e. dose and the corresponding serum concentration, was known.

Table 26 showed that comparison between measured and predicted phenytoin serum conentrations which calculated from individual pharmacokinetic parameters (K_m and V_{max}). Only four patients who had been given two different dosage and their corresponding serum concentrations were known their individual pharmacokinetics parameters could then be calculated and were used to calculate the predicted serum concentrations. Their percentage of differences between measured and predicted serum concentrations were 0.50 and 10.42. This method had tendency to predict phenytoin serum concentration most accurately.

Table 19 : Comparison between Measured and Predicted Phenytoin Serum Concentrations.

Patients Number	Measured Concentrations (μg./mL)	Predicted Concentrations (μg./mL)	Differences (μg./mL)	Percent differences (%)
1	20.37	14.92	5.45	26.76
2	15.85	34.50	18.65	117.67
3	7.72	16.30	8.58	111.14
4	38.86	Not cal.	Not cal.	Not cal.
	12.47	14.25	1.78	14.27
5	4.53	5.52	0.99	21.85
6	9.14	5.62	3.52	38.51
7	4.27	13.63	9.36	219.20
8	4.18	5.00	0.82	19.62
	17.00	7.63	9.37	55.12
9	10.37	4.37	6.00	57.86
10	11.59	10.29	1.30	11.22
11	22.88	19.54	3.34	14.60

Continue....

Patients Number	Measured Concentrations (μg./mL)	Predicted Concentrations (μg./mL)	Differences (μg./mL)	Percent differences (%)
12	11.72	11.21	0.51	4.35
	16.86	26.89	10.03	59.49
13	4.79	3.18	1.61	33.61
14	12.92	8.98	3.94	30.50
15	12.42	6.17	6.25	50.32
16	14.55	6.84	7.71	52.99
17	20.24	14.92	5.32	26.28
18	3.05	6.69	3.64	119.34
19	6.70	3.99	2.71	40.45
20	18.11	8.49	9.62	53.12
21	5.77	9.52	3.75	64.99
22	13.97	12.07	1.90	13.60
23	4.67	4.63	0.04	0.86
	12.46	16.48	4.02	32.26

Continue....

Patients Number	Measured Concentrations (μg./mL)	Predicted Concentrations (μg./mL)	Differences (μg./mL)	Percent differences (%)
24	3.50	7.67	4.17	119.14
	6.98	20.35	13.37	191.55
	15.94	61.33	45.39	284.76
25	0.24	4.85	4.61	1920.83
26	7.97	4.20	3.77	47.30
	11.60	6.12	5.48	47.24
	18.42	8.61	9.81	53.26
27	8.63	16.92	8.29	96.06
28	9.53	6.79	2.74	28.75
29	11.12	4.14	6.98	62.77
30	30.88	8.49	22.39	72.51
31	25.45	Not cal.	Not cal.	Not cal.
32	7.74	6.42	1.32	17.05
33	12.81	13.07	0.26	2.03
34	5.12	6.42	1.30	25.39

Continue....

Patients Number	Measured Concentrations (μg./mL)	Predicted Concentrations (μg./mL)	Differences (μg./mL)	Percent differences (%)
35	32.39	8.49	23.90	73.79
36	34.74	17.86	16.88	48.59
37	5.19	5.03	0.16	3.08
38	19.53	12.55	6.98	35.74
39	3.97	14.92	10.95	275.82
40	3.56	6.69	3.13	87.92
	18.66	20.16	1.50	8.04
41	16.22	8.49	7.73	47.66
42	14.94	9.81	5.13	34.34
43	11.50	4.84	6.66	57.91
44	1.92	12.55	10.63	553.65
45	54.55	14.92	39.63	72.65
	23.07	4.43	18.64	80.80
46	2.66	2.16	0.50	18.80
47	1.00	4.84	3.84	384.00

Continue....

Patients Number	Measured Concentrations (μg./mL)	Predicted Concentrations (μg./mL)	Differences (μg./mL)	Percent differences (%)
48	29.99	4.56	25.43	84.80
49	17.18	5.55	11.63	67.70
50	44.23	Not cal.	Not cal.	Not cal.
	43.01	Not cal.	Not cal.	Not cal.
51	2.20	12.53	10.33	469.55
52	50.00	Not cal.	Not cal.	Not cal.
	21.23	13.09	8.14	38.34
53	2.53	32.62	30.09	1189.33
54	4.59	5.85	1.26	27.45
N	66	61	61	61
X±SD.	14.73±12.15	11.29±9.36	8.25±9.18	129.81±293.15
C.V				225.83

Table 20 : Percent Concentration of Phenytoin Serum Concentrations in Different Ranges.

Number	Phenytoin serum concentrtion range (μg/mL)							
	<5	5–10	10.01–15	15.01–20	20.01–25	25.01–30	30.01–35	>35
1	121.85	211.14	130.59	217.67	73.24	Not cal.	27.49	Not cal.
2	319.20	61.49	42.14	44.88	85.40	15.21	26.21	Not cal.
3	119.62	59.55	88.78	159.49	73.72		51.41	Not cal.
4	66.39	164.99	95.65	46.88	19.20			Not cal.
5	219.34	291.55	69.50	384.76	61.66			27.35
6	99.14	52.70	49.68	46.74				
7	219.14	196.06	47.01	64.26				
8	2,020.83	71.25	86.40	108.04				
9	375.82	82.95	132.26	52.34				
10	187.92	125.39	52.76					
11	653.65	96.92	37.23					
12	81.20		102.03					
13	484.00		65.66					
14	569.55		42.09					
15	1,289.33							
16	127.45							
X ± SD	434.65±526.00	128.54±77.88	74.41±32.19	125.01±114.65	62.64±25.70	–	35.04±14.19	–
CV.	121.02	60.59	43.26	91.71	41.03	–	40.50	–

Table 21 : Comparison between Measured and Predicted Phenytoin Serum Concentrations in Patients Receiving Phenytoin Alone.

Patient No.	Phenytoin Measured concentration (μg/mL)	Calculated concentration (Population data)	Difference	Percent difference (%)
1	20.37	14.92	5.45	26.76
2	15.85	34.50	18.65	117.67
12	16.86	26.89	10.03	59.49
14	12.92	8.98	3.94	30.50
15	12.42	6.17	6.25	50.32
19	6.70	3.99	2.71	40.45
21	5.77	9.52	3.75	64.99
24	6.98	20.35	13.37	366.90
	15.94	61.33	45.39	284.76
26	7.97	4.20	3.77	47.30
	11.60	6.12	5.48	47.24
	18.42	8.61	9.81	53.26
33	12.81	13.07	0.26	2.03
36	34.74	17.86	16.88	48.59

Continue....

Patient No.	Phenytoin Measured concentration (μg/mL)	Calculation concentration (Population data)	Diferrence	Percent difference (%)
37	5.19	5.03	0.16	3.08
38	19.53	12.55	6.98	35.74
39	3.97	14.92	10.95	275.82
45	54.55	14.92	39.63	72.65
	23.07	4.43	18.64	80.80
52	50.00	Not cal.	Not cal.	Not cal.
	21.23	13.09	8.14	38.34
54	4.59	5.85	1.26	27.45
N	22	21	21	21
X ± SD	17.34 ± 13.54	14.63 ± 13.25	11.02 ± 11.88	84.48 ± 98.56
CV.				116.67

Table 22 : Comparison between Measured and Predicted Phenytoin Serum Concentrations in Patients Receiving Phenytoin along with Other Antiepileptic Drugs.

Pt. No.	Others antiepileptics drug	Measured Phenytoin Concentration (1)	Calculated Phenytoin Concentration (2)	Calculated Phenytoin Concentration (3) (adjusting for factors)	Difference between (1) and (2)	Percent Difference (1) and (2)	Difference between (1) and (3)	Percent Difference (1) and (3)
3	Phenobarbital	7.72	16.30	15.32	8.58	111.14	7.60	98.45
4	Phenobarbital	38.86	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.
	Phenobarbital	12.47	14.25	11.40	1.78	14.27	1.07	8.58
	Carbamazepine							
5	Valproic acid	4.53	5.52	4.14	0.99	21.85	0.39	8.61
6	Phenobarbital	9.14	5.62	5.28	3.52	38.51	3.86	42.23
7	Phenobarbital	4.27	13.63	12.81	9.36	219.20	8.54	200.00
8	Phenobarbital	4.18	5.00	8.65	0.82	19.62	4.47	106.94
	Rivotril							
	Phenobarbital	17.00	7.63	13.19	9.37	55.12	3.81	22.41
	Rivotril							
9	Carbamazepine	10.37	4.37	3.80	6.00	57.86	6.57	63.36
10	Phenobarbital	11.59	10.29	9.67	1.30	11.22	1.92	16.57
11	Rivotril	22.88	19.54	35.95	3.34	14.00	13.07	57.12

Continue....

Pt. No.	Others antiepileptics drug	Measured Phenytoin Concentration (1)	Calculated Phenytoin Concentration (2)	Calculated Phenytoin Concentration (3) (adjusting for factors)	Difference between (1) and (2)	Percent Difference (1) and (2)	Difference between (1) and (3)	Percent Difference (1) and (3)
12	Phenobarbital	11.72	11.21	10.54	0.51	4.35	1.18	10.07
13	Phenobarbital	4.79	3.80	2.99	0.99	20.67	1.80	37.58
16	Phenobarbital Carbamazepine	14.55	6.84	5.47	7.71	52.99	9.08	62.41
17	Phenobarbital	20.24	14.92	14.02	5.32	26.28	6.22	30.73
18	Phenobarbital	3.05	6.69	6.29	3.64	119.34	3.24	106.23
20	Phenobarbital	18.11	8.49	7.98	9.62	53.12	10.13	55.94
22	Phenobarbital Carbamazepine Valproic acid	13.97	12.07	9.66	1.90	13.60	4.31	30.85
23	Phenobarbital Valproic acid	4.67	4.63	2.95	0.04	0.86	1.72	36.83
	Phenobarbital Valproic acid	12.46	16.48	10.52	4.02	32.26	1.94	15.57
24	Phenobarbital	3.50	7.67	7.21	4.17	119.14	3.71	106.00

Continue....

Pt. No.	Others antiepileptics drug	Measured Phenytoin Concentration (1)	Calculated Phenytoin Concentration (2)	Calculated Phenytoin Concentration (3) (adjusting for factors)	Difference between (1) and (2)	Percent Difference (1) and (2)	Difference between (1) and (3)	Percent Difference (1) and (3)
25	Phenobarbital Rivotril	0.24	4.85	8.46	4.61	1920.83	8.22	3425
27	Rivotril	8.63	16.92	31.13	8.29	96.06	22.50	260.72
28	Phenobarbital Carbamazepine	9.53	6.79	5.43	2.74	28.75	4.10	43.02
29	Phenobarbital	11.12	4.14	3.89	6.98	62.77	7.23	65.02
30	Phenobarbital Rivotril	30.88	8.49	14.68	22.39	72.51	16.20	52.46
31	Phenobarbital	25.45	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.
32	Phenobarbital Carbamazepine	7.74	6.42	5.14	1.32	17.05	2.60	33.59
34	Phenobarbital Carbamazepine	5.12	6.42	5.14	1.30	25.39	0.02	0.39
35	Phenobarbital	32.39	8.49	7.98	23.90	73.79	24.41	77.64
40	Phenobarbital	3.56	6.69	6.29	3.13	87.92	2.73	76.69
	Phenobarbital	18.66	20.16	18.95	1.50	8.04	0.29	1.55

Continue....

Pt. No.	Others antiepileptics drug	Measured Phenytoin Concentration (1)	Calculated Phenytoin Concentration (2)	Calculated Phenytoin Concentration (3) (adjusting for factors)	Difference between (1) and (2)	Percent Difference (1) and (2)	Difference between (1) and (3)	Percent Difference (1) and (3)
41	Phenobarbital	16.22	8.49	7.98	7.73	47.66	8.24	50.80
42	Phenobarbital	14.94	9.81	9.22	5.13	34.34	5.72	38.29
43	Phenobarbital Carbamazepine	11.50	4.84	3.87	6.66	57.91	7.63	66.35
44	Phenobarbital	1.92	12.55	11.80	10.63	553.65	9.88	514.58
46	Phenobarbital	2.66	2.16	2.03	0.50	18.80	0.63	23.68
47	Phenobarbital	1.00	4.84	4.55	3.84	384.00	3.55	355.00
48	Phenobarbital	29.99	4.56	4.29	25.43	84.79	25.70	85.70
49	Phenobarbital	17.18	5.55	5.22	11.63	67.69	11.96	69.62
50	Phenobarbital	44.23	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.
	Phenobarbital	43.01	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.
51	Phenobarbital Rivotril	2.20	12.53	21.68	10.33	469.55	19.48	885.45
53	Phenobarbital	2.53	32.62	30.66	30.09	1189.33	28.13	1111.86
N		44	40	40	40	40	40	40
X± SD		13.43 ± 11.33	9.56 ± 5.94	10.16 ± 7.86	6.78 ± 7.15	157.67± 356.00	7.60 ± 7.39	208.85±568.71
C.V						225.79		272.31

Table 23 : Comparison between Measured and Predicted Phenytoin Serum Concentrations in Patients Receiving Phenytoin along with Phenobarbital.

Pt. No.	Others antiepileptics drug	Measured Phenytoin Concentration (1)	Calculated Phenytoin Concentration (2)	Calculated Phenytoin Concentration (3) (adjusting for factors)	Difference between (1) and (2)	Percent Difference (1) and (2)	Difference between (1) and (3)	Percent Difference (1) and (3)
3	Phenobarbital	7.72	16.30	15.32	8.58	111.14	7.60	98.45
4	Phenobarbital	38.86	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.
6	Phenobarbital	9.14	5.62	5.28	3.52	38.51	3.86	42.23
7	Phenobarbital	4.27	13.63	12.81	9.36	219.20	8.54	200.00
10	Phenobarbital	11.59	10.29	9.67	1.30	11.22	1.92	16.57
12	Phenobarbital	11.72	11.21	10.54	0.51	4.35	1.18	10.07
13	Phenobarbital	4.79	3.80	2.99	0.99	20.67	1.80	37.58
17	Phenobarbital	20.24	14.92	14.02	5.32	26.28	6.22	30.73
18	Phenobarbital	3.05	6.69	6.29	3.64	119.34	3.24	106.23
20	Phenobarbital	18.11	8.49	7.98	9.62	53.12	10.13	55.94
24	Phenobarbital	3.50	7.67	7.21	4.17	119.14	3.71	106.00

Continue....

Pt. No.	Others antiepileptics drug	Measured Phenytoin Concentration (1)	Calculated Phenytoin Concentration (2)	Calculated Phenytoin Concentration (3) (adjusting for factors)	Difference between (1) and (2)	Percent Difference (1) and (2)	Difference between (1) and (3)	Percent Difference (1) and (3)
29	Phenobarbital	11.12	4.14	3.89	6.98	62.77	7.23	65.02
31	Phenobarbital	25.45	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.	Not cal.
35	Phenobarbital	32.39	8.49	7.98	23.90	73.79	24.41	77.64
41	Phenobarbital	16.22	8.49	7.98	7.73	47.66	8.24	50.80
42	Phenobarbital	14.94	9.81	9.22	5.13	34.34	5.72	38.29
44	Phenobarbital	1.92	12.55	11.80	10.63	553.65	9.88	514.58
46	Phenobarbital	2.66	2.16	2.03	0.50	18.80	0.63	23.68
47	Phenobarbital	1.00	4.84	4.55	3.84	384.00	3.55	355.00
48	Phenobarbital	29.99	4.56	4.29	25.43	84.79	25.70	85.70
49	Phenobarbital	17.18	5.55	5.22	11.63	67.69	11.96	69.62
53	Phenobarbital	2.53	32.62	30.66	30.09	1189.33	28.13	1111.86
N		22	20	20	20	20	20	20
X±SD		13.11 ± 10.83	9.59 ± 6.67	8.99 ± 6.30	8.64 ± 8.45	160.99±276.04	8.68±8.16	154.80±256.98
C.V						171.46		166.01

Table 24 : Comparison between Measured and Predicted Phenytoin Serum Concentrations in Patients Receiving Phenytoin along with Phenobarbital and Carbamazepine.

Pt. No.	Others antiepileptics drug	Measured Phenytoin Concentration (1)	Calculated Phenytoin Concentration (2)	Calculated Phenytoin Concentration (3) (adjusting for factors)	Difference between (1) and (2)	Percent Difference (1) and (2)	Difference between (1) and (3)	Percent Difference (1) and (3)
4	Phenobarbital Carbamazepine	12.47	14.25	11.40	1.78	14.27	1.07	8.58
16	Phenobarbital Carbamazepine	14.55	6.84	5.47	7.71	52.99	9.08	62.41
28	Phenobarbital Carbamazepine	9.53	6.79	5.43	2.74	28.75	4.10	43.02
32	Phenobarbital Carbamazepine	7.74	6.42	5.14	1.32	17.05	2.60	33.59
34	Phenobarbital Carbamazepine	5.12	6.42	5.14	1.30	25.39	0.02	0.39
43	Phenobarbital Carbamazepine	11.50	4.84	3.87	6.66	57.91	7.63	66.35
N		6	6	6	6	6	6	6
X ± SD		10.15 ± 3.41	7.59 ± 3.34	6.08 ± 2.67	3.59 ± 2.86	32.73 ± 18.44	4.08 ± 3.61	35.72 ± 27.18
C.V						56.34		76.09

Table 25 : Comparison between The Measured Phenytoin Serum Concentration with The Predicted Phenytoin Concentrations Calculated by Several Different Methods.

No.	Predicted Concentration (μg/mL)					Percent Difference	Percent Difference	Percent Difference	Percent Difference
	Measured	Population	Wagner	K_m=4	V_{max}=7	Between (1) and (2)	Between (1) and (3)	Between (1) and (4)	Between (1) and (5)
	Concentrations (1)	K_m and V_{max} (2)	Method (3)	(4)	(5)	(%)	(%)	(%)	(%)
1	18.66	20.16	7.77	6.76	10.54	8.04	58.36	63.77	43.52
2	50.00	Not cal.	46.53	Not cal.	Not cal.	Not cal.	6.94	Not cal.	Not cal.
3	12.46	16.48	10.18	16.85	16.64	32.26	18.30	35.23	33.55
4	38.86	Not cal.	27.11	Not cal.	Not cal.	Not cal.	30.24	Not cal.	Not cal.
5	16.86	26.89	17.29	38.53	35.86	59.49	2.55	128.53	112.69
6	11.60	6.12	11.82	14.77	11.63	47.24	1.90	27.33	0.26
7	18.48	8.61	17.12	31.82	16.36	53.41	7.36	72.19	11.47
8	6.98	20.35	5.16	5.84	9.31	191.55	26.07	16.33	33.38
9	15.94	61.33	10.28	9.32	126.27	284.76	35.51	41.53	692.16
10	17.00	7.63	6.17	7.41	7.47	55.12	63.71	56.41	56.06
11	54.55	14.92	50.40	Not cal.	90.71	72.65	7.61	Not cal.	66.29
N	11	9	11	8	9	9	11	8	9
X±SD	23.76±16.22	20.28±16.84	19.08±15.82	16.41± 12.34	36.09± 42.82	89.39±89.38	23.50±21.79	55.17±35.08	116.60±218.30
C.V						99.99	92.72	63.59	187.22

Table 26 : Comparison between Measured and Predicted Phenytoin Serum Concentrations Which Calculated by Used Pharmacokinetic Parameters of Individual Patients.

Patients Number	Sex	Age (yr.)	Dose/d (mg.)	Dosage Regimen	Measured Concentration (μg/mL.)	Predicted Concentration (μg/mL.)	Difference (μg/mL.)	Percent Difference(%)	K_m (μg/mL.)	V_{max} (mg/kg/d)
24	F	32	300	P(100)3 caps x hs.	15.94	15.86	0.08	0.50	2.62	8.04
26	M	42	400	P(100)2 caps x 2pc	18.42	16.50	1.92	10.42	7.46	6.94

4. Pharmacokinetic Parameters of Phenytoin in Thai Patients.

According to foreign literatures, (Winter , Katcher and Kimble, 1980), phenytoin has non-linear pharmacokinetics or capacity limited metabolism. The model which appears to fit this metabolic pattern is the one originally proposed by Michaelis and Menten. The pharmacokinetic parameters are V_{max} (maximum metabolic capacity) and K_m (phenytoin concentration at which metabolic capacity is one half of V_{max}) . Clearance and Half-life are varied depended on concentrations so that they were not valid to use to calculate concentrations and/or dosage regimen of phenytoin.

Table 27 showed pharmacokinetic parameters, K_m and V_{max} of nine patients whose dosage regimens were adjusted. Since two different dosages were administered and their corresponding plasma concentrations were measured, the pharmacokinetic parameters of individual patient could be calculated. K_m ranged from 1.34 to 45.18 mg/kg/d, 12.86 $\pm$ 14.25 (mean $\pm$ SD) and V_{max} ranged from 6.34 to 13.58 μg/mL, 8.76 $\pm$ 2.62 (mean $\pm$ SD). This findings was partly supported by Taylor and Diescaviness (1986) who reported that V_{max} ranges from 1.4 to 14 mg/Kg/d and the mean was 7 mg/Kg/d while the reported K_m ranges from 1 to 15 μg/mL. Other study published the range of values for V_{max} and K_m to be 3.8 to 31.3 mg/Kg/d and 0.1 to 26.9 mg/L., respectively (Ludden et al. ,1976) and mean is 4 μg/ml. which was inconsistent with our study. The percent of coefficients of variation of V_{max} and K_m were reported to be 25% and 50% respectively (Martin, Tozer, Sheiner and Riegelman ,1977). Coefficients of variation of V_{max} and K_m in this study were 29.91% and 110.81%. In support of previous research, this study found that V_{max} were less varied when compared to K_m. Houghton, Richens, and Leighton (1975) studied steady-state serum phenytoin concentrations in over 100 adult epileptic patients receiving 300 mg of phenytoin sodium dialy and concluded that genetic difference and the effect of saturation kinetics are much more important determinants of steady-state serum phenytoin concentrations than are age, weight, height and sex.

Table 28 compared the pharmacokinetic parameters of patients that calculated by using one of the population pharmacokinetic parameter to those calculated from patient individual plasma concentrations and their corresponding dosages. The partially population K_m was 6.23 ± 6.98 while the individual K_m was 12.86 ± 14.25 and the partially population V_{max} was 7.06 ± 1.77 while the individual V_{max} was 8.76 ± 2.62. These values were not much differences.

Table 27 : Pharmacokinetic Parameters of Phenytoin in Thai Patients.

Patients Number	Sex	Age	Dose/d (mg.)	K_m	V_{max}
4	F	26	400,300	7.27	8.65
8	M	32	300,350	1.34	4.95
12	M	28	300,350	16.08	12.25
23	F	20	200,300	5.29	8.01
24	F	32	200,250,300	2.62	8.04
26	M	42	300,350,400	7.46	6.94
40	M	20	300,400	1.59	6.34
45	M	32	300,200	45.18	10.08
52	F	13	300,200	28.91	13.58
X±SD.				12.86±14.25	8.76±2.62
C.V				110.81	29.91

Table 28 : Comparison of The Pharmacokinetic Parameters of The Patients Calculated by Using Partially Population Data and Individual Data.

Patients Number	Fix K_m=4, V_{max}=	Fix V_{max}=7, K_m=	Individual K_m	Individual V_{max}
4	7.22	3.50	7.27	8.65
8	7.07	3.92	1.34	4.95
12	6.92	4.18	16.08	12.25
23	6.97	4.04	5.29	8.01
24	9.86	1.83	2.62	8.04
26	5.38	7.60	7.46	6.94
40	9.30	2.09	1.59	6.34
45	4.00	24.32	45.18	10.08
52	6.83	4.62	28.91	13.58
N	9	9	9	9
X±SD.	7.06±1.77	6.23±6.98	12.86±14.25	8.76±2.62
C.V	25.07	112.04	110.81	29.91