CHAPTER IV

RESULTS AND DISCUSSION

I. Phenobarbital level dose ratio of Thai paediatric patients in different ages.

Sixty-nine out-patients of paediatric neurologic clinic who met the criteria of this study were analyzed. Table 1 showed the characteristics of the patients and the dosage regimen of phenobarbital. The ages of the patients in this study were between 3 months to 28 years old. The average age of the patients was 8.07 years. There were twelve adults in this study (about 17.39% of all patients). The average age of adults was 20.52 years, and the average age of paediatric patients was 5.45 years, 28 females and 41 males were included in this study. Weights ranged from 6 to 82 kilograms (mean = 25.34 kilograms). Phenobarbital was prescribed once (n = 26), and twice (n = 43) a day orally. Patients received phenobarbital for treatment of generalized seizures (n = 28) ,febrile seizure (n = 15), and partial seizures (n=10)

Table 1 : Characteristics of the patients

Patient Number	Age (year)	Sex	Body Weight (kg)	Dosage regimen		Seizure type*
				Dose (mg/kg/day)	Interval (time/day)	
1	1.66	F	10	6.00	1	FS
2	0.58	M	8.6	6.98	2	GS
3	0.66	F	6.85	4.38	1	no data
4	1.25	M	7.1	4.22	2	no data
5	1.92	F	10.8	6.94	1	PS
6	1.66	F	15	4.00	2	GS
7	0.33	M	6.7	6.43	2	no data
8	0.25	M	6	7.50	2	no data
9	1.92	M	10	6.00	1	GS
10	0.25	F	6	6.25	2	no data
11	1.83	F	11.5	15.65	2	no data
12	4	F	15	6.00	2	FS
13	2.33	M	9.7	6.18	2	GS
14	3.08	F	14	5.45	2	GS
15	2.5	M	10	6.00	2	FS
16	4	F	18	5.00	1	FS
17	3	M	13	5.77	2	PS
18	4.83	M	13	6.90	2	GS
19	4.83	M	16	4.69	2	GS
20	4	F	10	6.00	2	no data
21	2.08	M	12	7.50	2	GS
22	4.92	F	12	5.00	2	GS
23	4	M	16	5.62	2	FS

continued...

Patient Number	Age (year)	Sex	Body Weight (kg)	Dosage regimen		Seizure type*
				Dose (mg/kg/day)	Interval (time/day)	
24	4.92	F	18	5.00	2	GS
25	3.17	F	13	4.62	1	FS
26	4.75	M	20	4.50	1	FS
27	2.5	M	12.5	4.80	1	FS
28	2.25	M	13	5.77	1	FS
29	3.5	M	20	4.50	2	FS
30	4.5	M	13	4.60	2	PS
31	2.5	F	18.5	4.86	1	GS
32	2.42	M	16	7.50	2	GS
33	3.5	F	18.5	4.86	1	FS
34	2	M	10	3.00	2	FS
35	7.25	F	19	3.16	2	no data
36	5.33	M	15	4.00	1	FS
37	5.66	F	18	5.00	1	GS
38	5.17	M	16	7.50	1	no data
39	5.58	M	25	4.80	2	GS
40	9.92	M	27	4.44	1	GS
41	8.66	F	23	4.50	2	GS
42	8	F	27	6.67	2	no data
43	6.17	F	13	3.46	1	GS
44	8	M	24	5.00	2	no data
45	6.08	M	20	6.00	1	GS
46	7.5	F	20	6.00	2	FS

continued..

Patient Number	Age (year)	Sex	Body Weight (kg)	Dosage regimen		Seizure type*
				Dose (mg/kg/day)	Interval (time/day)	
47	14	M	56.5	3.16	2	no data
48	13.25	M	42	2.86	1	PS
49	12	M	35	4.93	2	PS
50	11	F	38	3.16	1	PS
51	11	M	21	5.70	2	no data
52	11.42	F	36	3.33	1	GS
53	12	M	40	3.00	1	PS
54	13	M	56	3.21	2	no data
55	12	F	26	4.62	2	FS
56	11	M	21.5	4.62	1	GS
57	14.83	F	52	2.30	2	GS
58	25	M	82	2.92	2	no data
59	19	M	60	3.00	2	GS
60	16	F	49	2.45	2	PS
61	17.25	M	52	2.30	1	PS
62	25	F	55	2.22	1	GS
63	22	M	52	3.46	1	GS
64	28	M	47	2.55	2	no data
65	22	M	49	4.18	2	GS
66	15	M	48	2.86	2	GS
67	23	F	57	4.20	2	GS
68	18	M	40	3.00	1	GS
69	16	M	56.5	3.18	2	PS

continued..

Patient Number	Age (year)	Sex	Body Weight (kg)	Dosage regimen		Seizure type*
				Dose (mg/kg/day)	Interval (time/day)	
mean (SD)	8.07 (7.03)	-	mean = 25.34kg	-	-	-
range	0.25-28	-	6 - 82	-	-	-
n	69	F = 28 M = 41	69	69	69	69

*FS = Febrile Seizure (n = 15)

GS = Generalized Seizure (n = 28)

PS = Partial Seizure (n=10)

Table 2 showed dosage regimen , measured serum phenobarbital concentrations , treatment time, concomittant antiepileptic drugs and phenobarbital level dose ratio of each patient in sequentially from the youngest patient (0.25 years) to the oldest patients (28 years). Two serum samples were collected from each patient , their concentrations were analyzed and the mean concentration was calculated.

Table 3 showed the mean level dose ratio of the patients in each age. The average level dose ratio of each age which was not significantly different from that of the adjacent age were then grouping into the same group. Phenobarbital level dose ratio could finally be divided into four groups according to the age as shown in table 4 , including., 1 month to 3 years , 3 to 5 years , 5 to 14 years and more than 14 years. The phenobarbital level dose ratios were increased in the older age groups.

Table 2 : Dosage regimen, measured serum phenobarbital concentrations and level dose ratio of patients.

Patient number	Age (years)	Dosage (mg/kg/day)	Concomittant AED	Treatment time(years)	C1 (μg/ml)	C2 (μg/ml)	$\bar{C}$ (μg/ml)	L/D Ratio
8	0.25	7.50	-	0.08	21.5	23.2	22.35	2.98
10	0.25	6.25	-	0.08	32.5	31.3	31.9	5.1
7	0.33	6.43	-	0.02	24.4	26.8	25.6	3.98
2	0.58	6.98	-	0.02	31.3	33.4	32.35	4.63
3	0.66	4.38	-	0.58	9.5	7.3	8.4	1.92
4	1.25	4.22	-	1.08	6.3	8.2	7.25	1.72
1	1.66	6.00	-	0.58	21.4	21.9	21.65	3.61
6	1.66	4.00	-	0.08	16.5	17.4	16.95	4.24
11	1.83	15.65	Lamotrigene	0.83	64.34	50.56	57.45	3.83
5	1.92	6.94	-	0.04	41.2	48.4	44.8	6.46
9	1.92	6.00	-	1.83	28.2	30.8	29.5	4.92
34	2.00	3.00	-	0.50	8.8	9.8	9.3	3.1
21	2.08	7.50	-	2.00	21.4	23.5	22.45	2.99
28	2.25	5.77	-	1.50	22	21.6	21.8	3.77
13	2.33	6.18	-	0.66	15.9	20.4	18.15	2.94
32	2.42	7.50	-	1.83	26.8	32.32	29.56	3.94
15	2.50	6.00	-	1.66	22.5	25.7	24.1	4.01
27	2.50	4.80	-	1.50	21.8	20.9	21.35	4.44
31	2.50	4.86	-	0.25	15.2	17.3	16.25	3.34
17	3.00	5.77	-	2.25	21.10	27.00	24.05	4.16

Table 2 continued...

Patient number	Age (years)	Dosage (mg/kg/day)	Concomittant AED	Treatment time(years)	C1 (μg/ml)	C2 (μg/ml)	$\overline{C}$ (μg/ml)	L/D Ratio
14	3.08	5.45	-	1.00	27.50	25.90	26.7	4.89
25	3.17	4.62	-	0.75	20.60	21.90	21.25	4.59
29	3.50	4.50	-	1.92	20.00	21.90	20.95	4.65
33	3.50	4.86	-	1.17	29.70	24.10	26.9	5.53
12	4.00	6.00	-	1.58	21.50	20.60	21.05	3.5
16	4.00	5.00	-	1.50	14.40	16.10	15.25	3.05
20	4.00	6.00	-	3.33	40.60	45.50	43.05	7.17
23	4.00	5.62	-	0.08	17.40	15.90	16.65	2.96
30	4.50	4.60	-	0.75	20.50	18.40	19.45	4.22
26	4.75	4.50	-	3.42	20.30	21.40	20.85	4.63
18	4.83	6.90	-	4.58	36.50	39.10	37.8	5.47
19	4.83	4.69	-	1.50	25.00	21.70	23.35	4.97
22	4.92	5.00	-	2.17	25.10	21.90	23.5	4.7
24	4.92	5.00	-	3.25	20.10	19.40	19.75	3.95
38	5.17	7.50	Diazepam	0.66	28.20	30.90	29.55	3.94
36	5.33	4.00	-	3.58	24.00	27.20	25.6	6.4
39	5.58	4.80	-	4.58	21.60	26.10	23.85	4.96
37	5.66	5.00	-	0.25	24.70	28.20	26.45	5.29
45	6.08	6.00	-	0.83	43.80	51.14	47.47	7.91
43	6.17	3.46	-	1.17	16.20	15.30	15.75	4.55
35	7.25	3.16	-	6	19.50	17.80	18.65	5.9
46	7.50	6.00	-	2.42	42.70	10.30	41.5	6.91

Table 2 continued...

Patient number	Age (years)	Dosage (mg/kg/day)	Concomittant AED	Treatment time(years)	C1 (μg/ml)	C2 (μg/ml)	$\bar{C}$ (μg/ml)	L/D Ratio
42	8.00	6.67	Valproic acid	3	48.90	45.20	47.05	7.05
44	8.00	5.00	-	0.04	30.40	27.30	28.85	5.77
41	8.66	4.50	-	4.42	22.60	19.30	20.95	4.65
40	9.92	4.44	Valproic acid	3	34.60	37.30	35.95	8.09
50	11.00	3.16	-	2.42	19.50	22.70	21.1	6.67
51	11	5.70	-	1.17	10.60	12.30	11.45	2
56	11.00	4.62	-	0.92	20.00	22.98	21.49	4.65
52	11.42	3.33	-	9.17	17.20	15.80	16.5	4.95
49	12	4.93	-	0.33	38.50	39.60	39.05	7.92
53	12	3.00	-	3.58	14.70	12.40	13.55	4.51
55	12	4.62	Diazepam	10	15.60	18.80	17.2	3.72
54	13	3.21	-	4.25	13.90	14.30	14.1	4.39
48	13.25	2.86	-	9.25	21.40	20.20	20.8	7.27
47	14	3.16	-	2.75	25.10	24.80	24.95	7.89
57	14.83	2.30	-	10.42	25.20	28.60	26.9	11.69
66	15.00	2.86	-	4	15.69	19.34	17.52	6.12
60	16.00	2.45	-	12	24.50	21.70	23.1	9.42
69	16.00	3.18	-	16	33.30	36.40	34.84	10.95
61	17.25	2.30	Phenytoin	13	30.70	26.20	28.45	12.36
68	18.00	3.00	-	7.5	31.20	28.30	29.75	9.91
59	19.00	3.00	-	5	26.70	28.40	27.55	9.18
63	22.00	3.46	-	11.25	32.10	36.00	34.05	9.84

Table 2 continued...

Patient number	Age (years)	Dosage (mg/kg/day)	Concomittant AED	Treatment time(years)	C1 (μg/ml)	C2 (μg/ml)	$\overline{C}$ (μg/ml)	L/D Ratio
65	22.00	4.18	Diazepam +Valproic acid	16	44.30	47.90	46.1	11.02
67	23.00	4.20	-	11.33	29.50	33.20	31.35	7.46
58	25.00	2.92	Phenytoin	6	27.80	29.50	28.65	9.81
62	25.00	2.22	-	12	15.05	17.34	16.19	7.29
64	28.00	2.55	Phenytoin	28	19.50	17.00	18.25	7.15

Table 3 : Mean phenobarbital level dose ratio of patients in each age.

Age group (years)	n	L/D ratio mean (SD)
1 mo - 1	5	3.72 (1.28)
1 - 2	6	4.13 (1.56)
2 - 3	8	3.57 (0.55)
3 - 4	5	4.76 (0.50)
4 - 5	10	4.46 (1.26)
5 - 6	4	5.15 (1.01)
6 - 7	2	6.23 (2.38)
7 - 8	2	6.40 (0.71)
8 - 9	3	5.82 (1.20)
9 - 10	1	8.09
10 - 11	-	-
11 - 12	4	4.57 (1.93)
12 - 13	3	5.38 (2.23)
13 - 14	2	5.83 (2.04)
14 - 15	2	9.79 (2.69)
15 - 16	1	6.12
16 - 17	2	10.18 (1.08)
17 - 18	1	12.36
18 - 19	1	9.91
19 - 20	1	9.18
>20	6	8.76 (1.66)

Table 4: Phenobarbital level dose ratio of patients in each age group

Age group	n	mean age [years (SD)]	mean level dose ratio (SD)
1 month- 3 years	19	1.63 (0.82)	3.79 (1.11)
3-5 years	15	4.07 (0.70)	4.56 (1.05)
5-14 years	21	9.05 (2.78)	5.60 (1.60)
>14 years	14	19.65 (4.48)	9.29 (1.88)
Total	69	8.07 (7.03)	5.62 (2.44)

There were few patients who used other anti-epileptic drug concomittantly with phenobarbital (about 13%). Valproic , phenytoin, and diazepam were the concomittant anti-epileptic drugs used by patients including in this study and there was only one patient who used lamotrigene. Table 5 showed the comparative mean phenobarbital level dose ratios in monotherapy (only phenobarbital) and polytherapy (phenobarbital with other anti-epileptic drugs).

When phenobarbital was used concomittantly with valproic acid the level dose ratio seem to be higher which was not surprising since it occurred predictably in the majority of patients taking these two drugs together. The mechanism by which valproic acid causes phenobarbital accumulation is thought to involve inhibition of phenobarbital metabolism. Concomittantly used phenobarbital with phenytoin showed higher level dose ratio than the average monotherapy level dose ratio of the same age group. The mechanism could be due to the inhibition of phenobarbital biotransformation since both drugs are hydroxylated by hepatic microsomal enzyme. The two patients who used only diazepam concomittantly with phenobarbital showed lower level dose ratio. Since the pharmacokinetic interaction between phenobarbital and diazepam has never been reported and the number of patients concomittantly used phenobarbital with this drug including in this study were too few , further observation with more patients must be done before any mechanism could be discussed or any conclusion could be made.

Table 5 : Phenobarbital level - dose ratio of monotherapy and polytherapy regimens.

Age group (year)	Monotherapy		polytherapy (+VPA)		Polytherapy(+PHT)		polytherapy(+Dia)		Polytherapy(+LMT)	
	n	L/D Ratio mean (SD)	n	L/D Ratio mean (SD)	n	L/D Ratio mean (SD)	n	L/D ratio mean(SD)	n	L/D Ratio mean(SD)
1 mo-3 years	18	3.78(1.14)	-	-	-	-	-	-	1	3.83
3-5 years	15	4.56(1.05)	-	-	-	-	-	-	-	-
5-14 years	17	5.57(1.51)	2	7.57(0.74)	-	-	2	3.83(0.16)	-	-
>14 years	10	8.98(1.75)	1	11.02*	3	9.77(2.60)	1	11.02*	-	-
Total	60		3		3		3		1	

* patient number 65 used both diazepam and valproic acid

VPA = Valproic acid

PHT = Phenytoin

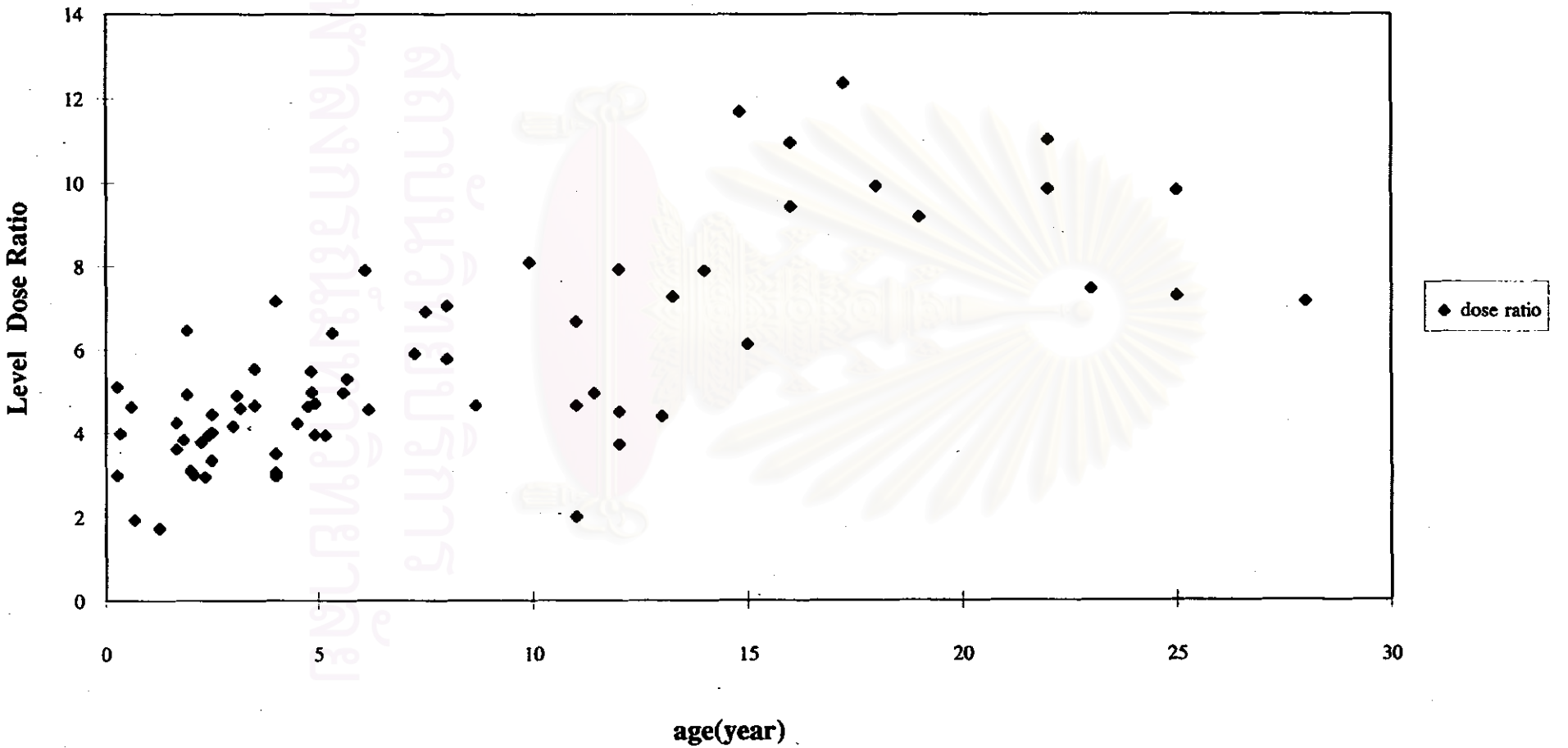
Dia = Diazepam

LMT = Lamotrigene

Figure 1 showed the relationship of the phenobarbital level dose ratio and the age of the patients. Form the age range 3 months to 28 years , the phenobarbital level dose ratio varied between 1.72 and 12.36. The phenobarbital level dose ratios increased with age (L/D = 3.59 + 0.25 age, n = 69, r = 0.727, $p < 0.0001$)

Figure 1: Relationship between phenobarbital level dose ratio and age.

L/D =3.59+0.25age,r=0.727 ,P<0.0001



Predicted concentrations were calculated using several method , i.e , the mean level dose ratios of traditional age groups (1 month to 2 years , 2 to 5 years , 5 to 12 years , 12 to 15 years and more than 15 years) ,the mean level dose ratios of different age groups according to this study (1 month to 3years , 3 to 5 years , 5 to 14 years , more than 14 years) , the pharmacokinetic equation [C_{ss} =(dose(mg/kg/day)*$T_{1/2}$)/ (Vd*0.693)] using the pharmacokinetic parameters as reported by Morselli (12) and the equation derived from the linear regression analysis between level dose ratios and ages , i.e., L/D = 3.59 + 0.25(age). The difference between the calculated concentration by four methods and the observed concentration were show in table 6. The average calculated concentrations and the coefficient of variations by different methods were not significantly different.

Table 6 : Comparison between observed and calculated concentration

Patient	Cobs	Ccal*		Ccal**		Ccal***		Ccal****	
Number	µg/ml	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs
8	22.35	29.55	132.2	28.43	127.2	27.39	122.55	22.5	100.67
10	31.9	24.62	77.18	23.69	74.26	22.84	71.6	18.75	58.78
7	25.6	25.33	98.94	24.37	95.2	23.61	92.23	19.29	75.35
2	32.35	27.5	85.01	26.45	81.76	26.07	80.59	20.94	64.73
3	8.4	17.26	205.5	16.6	197.62	16.45	195.83	13.14	156.43
4	7.25	16.63	229.4	15.99	220.55	16.47	227.17	12.66	174.62
1	21.65	23.64	109.2	22.74	105.03	24.03	110.99	18	83.14
6	16.95	15.76	92.98	15.16	89.44	16.02	94.51	12	70.8
11	57.45	61.66	107.3	59.31	103.24	63.34	110.25	46.95	81.72
5	44.8	27.34	61.03	26.3	58.7	28.25	63.06	20.82	46.47
9	29.5	23.64	80.14	22.74	77.08	24.42	82.78	18	61.02
34	9.3	12.66	136.1	11.37	122.26	12.27	131.94	14.43	155.16
21	22.45	31.65	141	28.43	126.36	30.83	137.33	36.08	160.07
28	21.8	24.35	111.7	21.87	100.32	23.96	109.91	27.75	127.29
13	18.15	26.08	143.7	23.42	129.04	25.79	142.09	29.72	163.75
32	29.56	31.65	107.1	28.43	96.18	31.46	106.43	36.08	122.06
15	24.1	25.32	105.1	22.74	94.36	25.29	104.94	28.86	119.75
27	21.35	20.26	94.89	18.19	85.2	20.23	94.75	23.09	108.15
31	16.25	20.51	126.2	18.42	113.35	20.48	126.03	23.38	143.88
17	24.05	24.35	101.3	26.31	109.34	25.04	104.12	27.75	115.38

Table 6 : continued.....

Patient	Cobs	Ccal*		Ccal**		Ccal***		Ccal***	
Number	µg/ml	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs
14	26.7	23	86.14	24.85	93.07	23.76	88.99	26.21	98.16
25	21.25	19.5	91.76	21.07	99.15	20.25	95.29	22.22	104.56
29	20.95	18.99	90.64	20.52	97.95	20.09	95.89	21.64	103.29
33	26.9	20.51	76.24	22.16	82.38	21.7	80.67	23.38	86.91
12	21.05	25.32	120.3	27.36	129.98	27.54	130.83	28.86	137.1
16	15.25	21.1	138.4	22.8	149.51	22.95	150.49	24.05	157.7
20	43.05	25.32	58.82	27.36	63.55	27.54	63.97	28.86	67.04
23	16.65	23.72	142.5	25.63	153.93	25.8	154.95	27.03	162.34
30	19.45	19.41	99.79	20.98	107.87	21.69	111.52	22.13	113.78
26	20.85	18.99	91.08	20.52	98.42	21.5	103.12	21.64	103.79
18	37.8	29.12	77.04	31.46	83.23	33.1	87.57	33.19	87.8
19	23.35	19.79	84.75	21.39	91.6	23.5	100.64	22.56	96.62
22	23.5	21.1	89.79	22.8	97.02	24.1	102.55	24.05	102.34
24	19.75	21.1	106.8	22.8	115.44	24.1	122.02	24.05	121.77
38	29.55	42	142.1	42	142.13	36.62	123.92	43.28	146.46
36	25.6	22.4	87.5	22.4	87.5	19.69	76.91	23.08	90.16
39	23.85	26.88	112.7	26.88	112.7	23.93	100.34	27.7	116.14

Table 6 : continued.....

Patient	Cobs	Ccal*		Ccal**		Ccal***		Ccal***	
Number	µg/ml	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs
37	26.45	28	105.9	28	105.86	25.03	94.63	28.85	109.07
45	47.47	33.6	70.78	33.6	70.78	30.66	64.59	34.62	72.93
43	15.75	19.38	123.1	19.38	123.05	17.76	112.76	19.96	126.73
35	18.65	17.7	94.91	17.7	94.91	17.07	91.53	18.23	97.75
46	41.5	33.6	80.96	33.6	80.96	32.49	78.29	34.62	83.42
42	47.05	37.35	79.38	37.35	79.38	37.29	79.26	38.48	81.78
44	28.85	28	97.05	28	97.05	27.95	96.88	28.85	100
41	20.95	25.2	120.3	25.2	120.29	25.9	123.63	26	124.11
40	35.95	24.86	69.15	24.86	69.15	26.95	74.96	25.62	71.26
50	21.1	17.7	83.89	17.7	83.89	19.77	93.7	18.23	86.4
51	11.45	31.92	278.8	31.92	278.78	30.45	265.94	32.89	287.25
56	21.49	25.87	120.4	25.87	120.38	21.96	102.19	26.66	124.06
52	16.5	18.65	113	18.65	113.03	19.74	119.64	19.21	116.42
49	39.05	33.38	85.48	27.61	70.7	32.79	83.97	35.5	90.91
53	13.55	20.31	149.9	16.8	123.98	20.03	147.82	21.6	159.41
55	17.2	31.28	181.9	25.87	150.41	36.14	210.12	33.26	193.37
54	14.1	21.73	154.1	17.98	127.52	29.29	207.73	23.11	163.9
48	20.8	19.36	93.08	16.02	77.02	21.46	103.17	20.59	98.99
47	24.95	21.39	85.73	29.36	117.68	22.44	89.94	22.75	91.18

Table 6 : continued.....

Patient	Cobs	Ccal*		Ccal**		Ccal***		Ccal***	
Number	µg/ml	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs	µg/ml	%Cobs
57	26.9	15.57	57.88	21.37	79.44	16.78	62.38	16.56	61.56
66	17.52	26.34	150.3	26.57	151.66	20.99	119.8	30.94	176.6
60	23.1	22.56	97.66	22.76	98.53	18.6	80.52	26.51	114.76
69	34.84	29.29	84.07	29.54	84.79	24.14	69.29	34.4	98.74
61	28.45	21.18	74.45	21.37	75.11	18.18	63.9	24.89	87.49
68	29.75	27.63	92.87	27.87	93.68	24.27	81.58	31.26	105.08
59	27.55	27.63	100.3	27.87	101.16	25.02	90.82	31.26	113.47
63	34.05	31.87	93.6	32.14	94.39	31.45	92.36	37.44	109.96
65	46.1	38.5	83.5	38.83	84.23	38	82.43	45.23	98.11
67	31.35	38.68	123.4	39.02	124.46	39.23	125.14	45.44	144.94
58	28.65	26.89	93.86	27.13	94.69	28.73	110.28	31.59	110.26
62	16.19	20.45	126.3	20.62	127.36	21.85	134.96	24.02	148.36
64	18.25	23.48	128.7	23.69	129.81	27	147.9	27.59	151.18
Mean(SD)		109.23(37.91)		108.06(35.46)		110.16(39.23)		114.27(38.95)	
%CV		34.71		32.82		35.61		34.08	

Ccal* = calculated concentration by mean L/D of traditional age group

Ccal** = calculated concentration by mean L/D of this study

Ccal*** = calculated concentration by L/D from linear regression

Ccal**** = calculated concentration by pharmacokinetic equation

II The relationship between serum phenobarbital level and theoretical therapeutic range.

The mean serum phenobarbital levels of each patients were examined whether or not they were within the theoretical therapeutic range. Table 7 showed the number and percentage of patients in each age group whose serum level were less than 10 μg/ml, within 10 - 20 μg/ml, within 20 - 40 μg/ml, and more than 40 μg/ml. The serum levels of most patients (60.9%) were within 20 - 40 μg/ml while the lowest percentage of the patient (4.4 %) had their serum level less than 10 μg/ml.

If therapeutic range is 10 - 20 μg/ml , percentage of patients whose serum levels were within therapeutic range will be 24.6%. If therapeutic range is 20 - 40 μg/ml , percentage will be 60.9%. And if therapeutic range is 10 - 40 μg/ml , percentage will be 85.5%.

Table 7 : Number and percentage of patients in each age group whose serum level were within therapeutic range,subtherapeutic range and overtherapeutic range.

Age group (year)	Number of the patients n(%)			
	subtherapeutic	within therapeutic range		over therapeutic
	<10μg/ml	10-20μg/ml	20-40μg/ml	>40μg/ml
1 month - 3 years	3(15.8)	3(15.8)	11(57.9)	2(10.5)
3-5 years	0(0)	4(26.7)	10(66.6)	1(6.7)
5-14 years	0(0)	7(33.33)	11(52.39)	3(14.28)
>14 years	0(0)	3(21.43)	10(71.43)	1(7.14)
Total	3(4.4)	17(24.6)	42(60.9)	7(10.1)
		59(85.5)		

III The relationship between serum phenobarbital level and seizure control.

To justify the relationship between serum phenobarbital level and clinical result, table 8.1 - 8.4 show seizure frequency and phenobarbital serum level at study time in each age group. Most patients in this study were absolutely controlled (about 71.01%). There were six patients whose seizure frequency was still the same as before phenobarbital was used or dosage regimen was adjusted. Among these six patients , there was only one patient (No. 4) whose serum phenobarbital level was lower than 10 μg/ml and soon after the serum level was taken , phenobarbital was discontinued and the patient was prescribed other anti-epileptic drugs. Phenobarbital was continued on the same dosage regimen in four patients [two patients used concomittant antiepileptic drugs , one (patients no. 69) had upper limit serum concentration, another had no reason for continue the same dosage regimen]. In one patient (patient no. 62) , dosage of valproic acid was increased and phenobarbital dosage was decreased.

Table 9 showed mean serum concentrations of controlled patients in each age group which were nearly equal except for age group > 14 years which the mean serum concentration was slightly higher. The overall mean serum concentration calculated from all 49 controlled patients was 22.17 μg/ml.

Table 8.1:Seizure frequency and phenobarbital blood level measured at studying time in patients age group 1month to3 years.

Patient number	Cobs (μg/ml)	Seizure Frequency
1	21.65	0
2	32.35	0
3	8.40	0
4	7.25	↔
5	44.80	↓
6	16.95	0
7	25.60	0
8	22.35	0
9	29.50	↓
10	31.90	↓
11	57.45	0
13	18.15	0
15	24.10	0
21	22.45	↓
27	21.35	0
28	21.80	↓
31	16.25	0
32	29.56	↓
34	9.30	0
n=19	mean(SD)=24.27(12.14)	seizure free =12 (63.2%)

Table 8.2 : Seizure frequency and phenobarbital blood level measured at studying time in patients age group 3 to 5 years.

Patienft number	C obs (μg/ml)	Seizure Frequency
14	26.70	0
17	24.05	0
25	21.25	0
29	20.95	0
33	26.90	0
12	21.05	0
16	15.25	0
18	37.80	↔
19	23.35	0
20	43.05	↓
22	23.50	0
23	16.65	0
24	19.75	0
26	20.85	0
30	19.45	0
n=15	mean(SD)=24.04(7.44)	seizure free =13 (86.67%)

Table 8.3 : Seizure frequency and phenobarbital blood level measured at studying time in patients age group 5 to 14 years.

Patient number	C obs (μg/ml)	Seizure Frequency
35	18.65	0
36	25.60	0
37	26.45	0
38	29.55	0
39	26.85	↓
40	35.95	↓
41	20.95	0
42	47.05	0
43	15.75	0
44	28.85	0
45	47.47	↓
46	41.50	0
50	21.10	0
51	11.45	0
52	16.50	0
56	21.49	0
49	39.05	0
53	13.55	↓
55	17.20	0
48	20.80	↔
54	14.10	0
n=21	mean(SD)=25.71(10.88)	seizure free =16 (76.19%)

Table8.4 : Seizure frequency and phenobarbital blood level measured at studying time in patients age group >14 years

Patient number	C obs (μg/ml)	Seizure Frequency
47	24.95	0
57	26.90	0
58	28.65	0
59	27.55	0
60	23.1	0
61	28.45	↓
62	16.19	↔
63	34.05	0
64	18.25	↔
65	46.1	↓
66	17.52	0
67	31.35	0
68	29.75	↑
69	34.84	↔
n=14	mean(SD)=27.69(7.86)	seizure free =8 (57.14%)

C obs = Observed phenobarbital concentration

Seizure frequency = 0 = no Seizure

↔ = the seizure frequency is still the same as before phenobarbital was used or dosage regimen was adjusted.

↓ = the seizure frequency decreases after phenobarbital was used or dosage regimen was adjusted.

↑ = the seizure frequency increase after phenobarbital was used or dosage regimen was adjusted.

Table 9 : Mean serum concentrations of controlled patients in each age group

Age group (years)	mean serum concentrations of controlled patients	n
1 month - 3	22.82	12
3 - 5	21.52	13
5 - 14	24.70	16
> 14	26.76	8
Total	22.17	49

Table 10 showed the comparison between phenobarbital blood level of patient whose seizure were completely controlled and not completely controlled. If the therapeutic range of phenobarbital is determined to be 10 - 40 μg/ml as traditional , 91.84 percent (45 out of 49 patients) of the controlled patients had their blood level within therapeutic range. Of the total 59 patients whose blood levels were within 10 - 40 μg/ml , 45 patients (76.27 percent) were classified in the controlled group while 14 patients (23.73 percent) were classified in the uncontrolled group.

If the therapeutic range of phenobarbital is recommended to be 10 - 20 μg/ml as Morselli (12) preferred for infants and children , only 26.53 percent (13 out of 49 patients) of the patients in the controlled group had their blood levels fell within this therapeutic range. However , of the total 17 patients whose blood levels were within 10 - 20 μg/ml , 13 patients (76.47 percent) were controlled patients while 4 patients (23.53 percent) were uncontrolled patients. These last two percentages were quite similar whether the therapeutic ranges were recommended to be 10 - 40 μg/ml , 10 - 20 μg/ml or 20 - 40 μg/ml.

When these last two percentages were considered along with the age of the patients , the results showed that when the blood level of the younger patients (from one month to forteen years old) fell in the category of 10 - 20 μg/ml , their seizure were well controlled. In the contrary , when the blood level of the older patients (more than forteen years old) fell in this same category phenobarbital could not completely controlled seizure of the majority patients. Older patients showed higher percentage of completely seizure controlled when their blood level were within 20 - 40 μg/ml.

Table 10 : Comparison between the phenobarbital blood level of patients whose seizure were completely controlled and not completely controlled

Age group (year)	Controlled patients				Uncontrolled patients			
	c<10 (N=3) n (%)	c=10-20 (N=17) n (%)	c=20-40 (N=42) n (%)	c>40 (N=7) n(%)	c<10 (N=3) n(%)	c=10-20 (N=17) n (%)	c=20-40 (N=42) n (%)	c>40 (N=7) n (%)
1 mo.- 3	1 (33.33)	3 (100)	8 (72.73)	1 (50)	2 (66.67)	0 (0)	3 (27.27)	1 (50)
3 - 5	0 (0)	4 (100)	9 (90)	0 (0)	0 (0)	0 (0)	1 (10)	1 (100)
5 - 14	0 (0)	6(85.71)	8(72.73)	2 (66.67)	0 (0)	1(14.28)	3(27.27)	1 (33.3)
> 14	0 (0)	1 (33.33)	6(60)	0 (0)	0 (0)	2 (66.67)	4 (40)	1 (100)
total	1 (33.33)	13 (76.47)	32 (76.19)	3 (42.86)	2 (66.67)	4 (23.53)	10(23.81)	4 (57.14)
		45 (76.27)				14 (23.73)		
	49(71.01)				20(28.99)			

IV. The relationship between phenobarbital serum level and side effects.

Phenobarbital blood levels and side effects of patients in each age group are shown in table 11.1 to 11.4. The side effects which were found in twenty-nine patients (42.03%) from this study included hyperactivity , sedative, ataxia, and aggressive. These side effects were either found from the OPD card (n = 17) or by interviewing from the parents and patients (n = 30). Mean phenobarbital serum concentrations of each age group were ranged from 18.80 to 30.31 μg/ml.

Table 12 showed the relationship between side effects and phenobarbital serum level for the patients in each aged group. Younger patients (1 month - 3 years) showed side effects even when their phenobarbital serum level were less than 10 μg/ml. Older patients showed higher incidences of side effects when their phenobarbital serum concentration were higher than 20 μg/ml.

Table 11.1 : Incidence of side effects and their correspondent phenobarbital blood level found for patients age group 1 month to 3 years.

Patient Number	Side effect	From OPD Card	From parent	Cobs * (μg/ml)
1	Hyperactivity	/	/	21.65
3	Hyperactivity	-	/	8.40
4	Sedative	/	/	7.25
27	Hyperactivity	/	/	21.35
28	Hyperactivity	-	/	21.80
32	Sedative	-	/	32.32
mean				18.80
n=6	n=6	n=3	n=6	n=6

* Cobs = Observed concentration

Table 11.2 : Incidence of side effects and their correspondent phenobarbital blood level found for patients age group 3 to 5 years

Patient Number	Side effect	From OPD Card	From parent	Cobs * (μg/ml)
29	Hyperactivity	/	/	20.95
19	Hyperactivity	-	/	23.35
22	Sedative Ataxia (only first time)	/	/	20.86
23	Hyperactivity	-	/	16.65
24	Hyperactivity	/	/	19.75
26	Hyperactivity	/	/	20.85
30	Hyperactivity	/	/	19.45
mean				20.26
n=7	n=8	n=5	n=7	n=7

* Cobs = Observed concentration

Table 11.3 : Incidence of side effects and their correspondent phenobarbital blood level found for patients age group 5 to 14 years

Patient Number	Side effect	From OPD Card	From parent	Cobs * (μg/ml)
36	Hyperactivity	-	/	25.60
37	Hyperactivity	/	/	26.45
38	Hyperactivity	/	/	29.55
40	Hyperactivity	-	/	35.95
41	Hyperactivity	/	/	20.95
43	Hyperactivity	-	/	15.75
45	Hyperactivity	/	/	47.47
46	Sedative	-	/	41.50
49	Sedative	/	/	39.05
	Aggressive	/	/	
48	Hyperactivity	/	/	20.80
mean				30.31
n=10	n=11	n=7	n=10	n=10

* Cobs = Observed concentration

Table 11.4 : Incidence of side effects and their correspondent phenobarbital blood level found for patients age group >14 years

Patient Number	Side effect	From OPD Card	From parent	Cobs * (μg/ml)
47	Aggressive	-	/	24.95
57	Hyperactivity	-	/	26.90
59	Sedative	/	/	27.55
60	Sedative	-	/	23.10
61	Aggressive	/	/	28.45
64	Sedative	-	/	18.25
mean				24.87
n=6	n=6	n=2	n=6	n=6

* Cobs = Observed concentration

Table 12 : Incidences of side effects in relation to phenobarbital therapeutic range for patients in each age group.

Age group (year)	number of patients in each serum level				Total
	<10 µg/ml n(%)	10-20 µg/ml n(%)	20-40 µg/ml n(%)	>40 µg/ml n(%)	n (%)
1 month - 3	2(66.67)	0(0)	4(36.36)	0(0)	6(31.6)
3-5	0(0)	3(75)	4(40.0)	0(0)	7(46.7)
5-14	0(0)	1(14.28)	7(63.64)	2(66.67)	10(47.62)
>14	0(0)	1(33.33)	5(50)	0(0)	6(42.86)
Total n (%)	2(66.7)	5(29.41)	20(47.62)	2(28.57)	29(42.03)
		25(42.37)			

% = number of patients who had side effect in each serum level of each age group / number of patients in each serum level of each age group

Nineteen patients reported the incidence of hyperactivity , eight patients experienced sedative. Three patients reported aggressive and one patient felt ataxia but only for a very short period. Table 13 showed the percentage of various types of side effects found in each range of phenobarbital serum levels. Hyperactivity was the side effect found most frequently in this study (n=19). At higher serum level, there was no higher incidence of hyperactivity. The same was true for sedative side effect, the highest percentage of sedative incidence was found when the serum levels were less than 10 μg/ml while among the patients with serum level higher than 40 μg/ml only 14.3% reported sedative side effect. Aggressive was found in 3 patients with serum level ranged 20-40 μg/ml. Even though aggressive tend to happen more often with higher concentration , but the number of patients with concentration higher than 40 μg/ml were too few. Therefore ,no relation between any type of side effects and phenobarbital serum level could be concluded.

Table 14 showed the percentage of incidences of each type of side effects in each age group. Higher percentage of side effect were reported for the older children as compared to the 1 month to 3 years age group up to the peak at the age group of 5 to 14 years and then markedly dropped down for the patients with the age higher than 14 years old. The incidences of hyperactivity were reported to be highest for the 3 to 5 years age group patients only one patient in the age group > 14 years complained about hyperactivity and not even one patient with the age higher than 15 years complained about this side effect. However , the incidence of sedative seem to be higher in the adult group (21.48% in patients age >14 years). Aggressive was found in one patient in the age group 5 - 14 years which the patient was 13 years old , and was found in two patients whose age was higher than 14 years. Therefore this side effect was found only in patients who were older than 12 years old.

Table 13 : Incidences of different types of phenobarbital side effects in relation to the therapeutic range.

Type of Side effect	number of side effect in each serum level				Total
	<10 µg/ml N=3 n (%)**	10-20µg/ml N=17 n (%)**	20-40 µg/ml N=42 n (%)**	>40 µg/ml N=7 n(%)**	N=69 n (%)
Hyperactive	1(33.3)	4(23.53)	13(30.95)	1(14.3)	19(27.54)
Sedative	1(33.3)	1(5.88)	5(11.90)	1(14.3)	8(11.59)
Ataxia	0(0)	0(0)	1* (2.4)	0(0)	1(1.45)
Aggressive	0(0)	0(0)	3* (7.14)	0(0)	3(4.35)
Total n (%)	2(66.7)	5(29.41)	22* 20(47.62)	2(28.6)	31* =29(42.29)
		27* 25(42.37)			

** % = $\frac{\text{number of side effect incidences in each serum level}}{\text{number of the patients in each serum level}} \times 100$

* More than one side effects were occured in the same patient

Table 14 : Incidences of different types of phenobarbital side effects in relation to the age.

Age group (year)	Type of side effect				Total
	Hyperactivity n(%)**	Sedative n(%)**	Ataxia n(%)**	Aggressive n(%)**	n (%)
1 month - 3	4 (21.1)	2(10.5)	0(0)	0(0)	6(31.6)
3-5	6(40.0)	1(6.7)	1*(6.7)	0(0)	8(46.7)
5-14	8(38.10)	2(9.52)	0(0)	1*(4.76)	11(52.38)
>14	1(7.14)	3(21.48)	0(0)	2*(14.28)	6(42.86)
Total n (%)	19	8	1	3	31*

* More than one side effects were occured in the same patient

** % = $\frac{\text{number of side effect incidences in each age group}}{\text{number of patients in each age group}} \times 100$

Figure 2 showed relationship between side effect incidences and age of the patients. The hyperactivity side effect was found to be normally distributed. Peak percentage was found during age 3-14 years. In children the incidence of sedative was not varied much with age, but after the patients were 14 years, the incidences trend to be higher than in young children.

Figure 3 showed relationship between side effect incidences and phenobarbital serum level. The side effect incidences were not higher when the serum level were higher indicated that most of the side effects occurred were not blood level dependent.

Figure 2 : Relationship between percentage of side effect incidences and age of the patients.

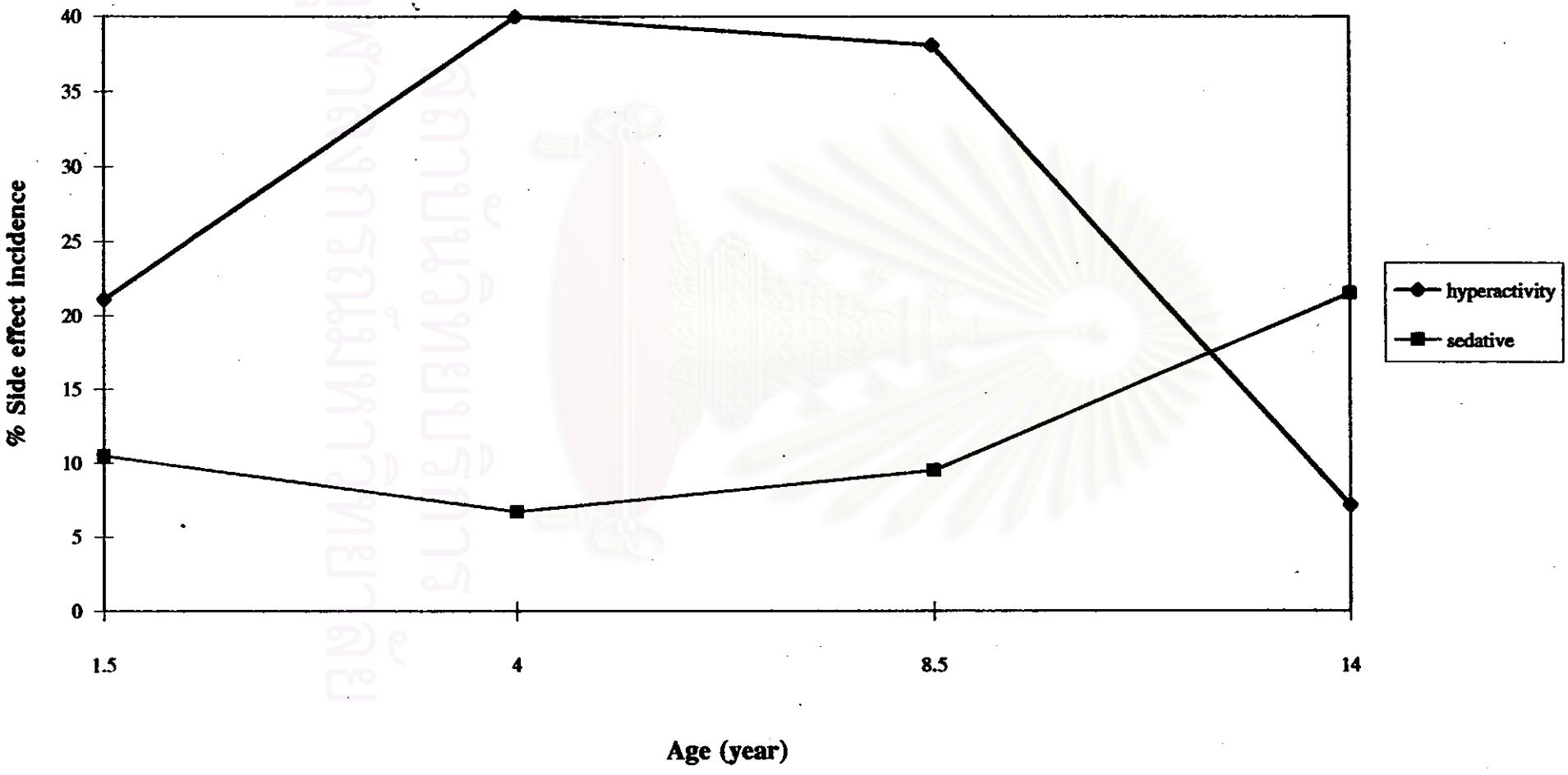


Figure 3 : Relationship between percentage of side effect incidences and phenobarbital serum level.