CHAPTER IV

RESULTS

Twenty nine children, 13 girls (44.83%) and 16 boys (55.17%) were enrolled in this study. Twenty two patients were taking valproic acid in the form of solution,while seven patients were taking in the form of 500mg-Chrono tablet.

1. Patient's demographic data and characteristics

Table VII showed the characteristics of patients, which were sex, age, weight, height, dosage forms and dosage regimen of valproic acid. The patients' ages ranged from 3 to 15 years with mean age of 6.38±2.34 years. Patients' weights ranged from 14.1 kg to 60.0 kg (mean weight of 28.45±12.40 kg). The doses of valproic acid ranged from 7.04 to 52.94 (mean = 25.09± 10.37) mg/kg. The treatment outcome was classified into 2 group, which were seizure-controlled and seizure-uncontrolled groups. The seizure-controlled patient referred to the patient who has had no seizure since start taking the medication. There were twenty-three patients (79.31%) who had had no seizure with treatment of valproic acid and six patients (20.69%) who still had seizures whereas they were received the high dose.

Laboratory findings

As shown in Table VIII, most of the laboratory data were within normal ranges except for the alkaline phosphatase and creatinine concentrations. The alkaline phosphatase levels observed in the majority of the enrolled patients were higher than normal range of general population, which is not considered abnormal in children.

Table VII Characteristics of the 29 patients participated in this study

Patient No.	Sex	Age (year)	Body weight (kg)	Height (cm)	Dosage form	Dosage regimen (mg/kg/day)	Clinical response
1	female	7	19	110	Solution	26.31	Controlled
2	male	5	25	109	Solution	16.00	Controlled
3	female	8	31	NA	Solution	19.35	Controlled
4	male	9	31	126	Solution	29.03	Controlled
5	male	5	15	90	Solution	26.07	Controlled
6	male	7	36	119	Solution	16.67	Controlled
7	female	11	32	135	Solution	18.75	Controlled
8	female	5	18.3	111	Solution	21.86	Controlled
9	male	11	28.7	134	Solution	17.42	Controlled
10	male	11	17	120	Solution	35.29	Uncontrolled
11	female	5	17	103	Solution	52.94	Uncontrolled
12	male	8	56.8	145	Solution	7.04	Controlled
13	male	6	24.4	119	Solution	16.39	Controlled
14	female	3	15.9	98	Solution	25.16	Controlled
15	male	8	20.7	116	Solution	28.99	Controlled
16	female	5	22	104	Solution	47.73	Controlled
17	male	4	14.1	NA	Solution	42.55	Uncontrolled
18	female	5	22	131	Solution	22.73	Controlled
19	male	5	30	118	Solution	20.00	Controlled
20	female	4	16.6	106	Solution	24.10	Controlled
21	female	7	15.2	105	Solution	39.47	Uncontrolled
22	male	5	30.2	131	Solution	16.56	Controlled
Mean		6.38	24.45			25.93	
SD	-	2.34	9.82	-	-	11.39	-
23	male	15	40	158	Chrono	31.25	Controlled
24	female	13	42	155	Chrono	23.81	Uncontrolled
25	male	12	52	139	Chrono	28.85	Uncontrolled
26	female	12	33	136	Chrono	22.73	Controlled
27	female	11	34	149	Chrono	14.71	Controlled
28	male	9	26	131	Chrono	19.23	Controlled
29	male	11	60	148	Chrono	16.67	Controlled
Mean		11.70	41.00			22.46	
SD	-	1.91	11.71	-	-	6.11	-
Mean		7.66	28.45			25.09	
SD	-	3.20	12.40	-	-	10.37	-

NA= not available

Table VIII Mean Laboratory values of all 29-patients

Laboratory	normal range	mean±SD
Hematology Laboratory		
WBC ($10^3/\mu L$)	4.4-11.3	9.0±3.04
HGB (g/dL)	11.5-15.5	12.8±0.99
HCT (%)	35.0-45.0	38.1±3.15
PLT ($10^3/\mu L$)	172-450	310.8±106.47
Electrolyte (mmol/L)		
Sodium	136-145	141.2±7.55
Potassium	3.5-5.1	4.4±0.27
Chloride	98-107	101.6±3.0
Carbondioxide	22-29	21.5±2.62
Calcium	2.2-2.62	2.49±0.11
Phosphorus	0.81-1.58	2.2±2.74
Liver function test		
Alkaline Phos. (U/L)	50-136	194.7±62.68
Aspartate Am. Trans. (U/L)	15-37	26.2±13.54
Alanine Am. Trans. (U/L)	30-65	34.2±12.98
Albumin (g/L)	43.1-53.3	44.4±3.0
Total bilirubin (μmol/L)	0-17.1	7.6±3.29
Direct bilirubin (μmol/L)	0.0-5.0	2.52±1.05
Renal function test		
Urea (mmol/L)	2.5-6.4	4.8±1.12
Creatinine (μmol/L)	53-115	45.6±6.96
Lipid profile		
Triglyceride (mmol/L)	0.34-2.28	1.0±0.47
Cholesterol (mmol/L)	3.8-5.2	4.8±0.65

Table IX and Table X demonstrated number of patients with febrile convulsion and type of seizures observed in the patients participated in this study. Approximately one-third of the patients have history of febrile convulsion and majority (nearly eighty percent) of the patients, had partial seizures. Three-fourth of the generalized seizure patients had the history of febrile convulsion whereas approximately half of the partial seizure patients had history of prior febrile convulsion. Two patients with LGS did not have history of febrile convulsion.

Table IX Number of patients with febrile convulsion

Patient with Febrile Convulsion	Number of patient	percentage
No	19	65.52
Yes	10	34.48
Total	29	100.00

Table X Percentage of difference type of seizure of the patients participated in this study

Diagnosis	Number of Patient	Percentage
Type of Seizure		
Partial Seizures	**23**	**79.31**
- simple partial seizures	1	4.35
- complex partial seizures	5	21.74
- secondary generalized	17	73.91
Generalized Seizure	**4**	**13.79**
- Absence	1	25.00
- Generalized Tonic Clonic	3	75.00
Indefinite seizures	**2**	**6.90**
- Lennox-Gastuat Syndrome	2	100.00
Total	**29**	**100.00**

Table XI showed the number of patients who had relatives with seizure disorders. Approximately, there were twenty per cent of the patients who had history of seizure in their family. Among them, two had febrile convulsions.

Table XI Percentage of patients with history of seizure of the other members in the patient's family

History of seizure in the family	Number of patient	Per cent
Yes	6	20.69
No	23	79.31
Total	29	100.00

Classification of the patients according to epilepsy syndrome was shown in Table XII. Thirteen patients (44.83%) were classified as symptomatic epilepsy, whereas sixteen patients (55.17%) were classified into idiopathic/cryptogenic group.

Table XII The cause of first seizure of patients

Cause of First Seizure	Number of Patient	Percent
Symptomatic	13	44.83
Idiopathic /Cryptogenic	16	55.17
Total	29	100.00

2. Total, unbound concentration and free fraction

2.1 Therapeutic concentration

The total and unbound valproic acid concentrations were measured from the serum taken before morning dose (trough) and at 5th hour after morning dose of each patient and were shown in Table XIII. According to the total concentration, there were 13 patients (44.83%) whose concentrations were within the therapeutic range (accepted total therapeutic concentration = 50-100 μg/mL). There were 5 patients (17.24%) who had trough concentration in sub-therapeutic range and 11 patients (37.93%) who had at least one concentration above the therapeutic range. Considering the unbound concentrations, recent studies reported the per cent bound of valproic acid to be about 90, which implies that the unbound therapeutic range should be 5 to 10 μg/mL. In this study, there were eleven (37.93%) patients whose unbound valproic acid concentrations either at trough or at 5th hour after morning dose were sub-therapeutic range and fourteen (48.28%) patients whose had those concentrations above therapeutic range. None of the patients showed any symptoms indicating adverse effect.

Table XIII Serum albumin, total and unbound valproic acid concentrations and free fraction

A. Solution dosage form

Patient No.	Serum Albumin (g/L)	Total VPA (μg/mL)		Free VPA (μg/mL)		Free fraction	
		Trough Level	5th hour Level	Trough Level	5th hour Level	At Trough	At 5th hour
1	37.6	82.45	98.09	12.6	15.58	0.150	0.158
2	45.7	49.35	73.14	3.95	6.25	0.080	0.085
3	43.6	63.15	84.39	4.64	8.35	0.073	0.099
4	41.4	76.79	102.18	8.93	17.28	0.120	0.170
5	46.3	80.27	110.99	6.86	12.8 2	0.085	0.116
6	44.5	66.63	89.79	6.36	9.71	0.095	0.108
7	44.9	63.86	97.29	6.73	9.20	0.105	0.095
8	45.8	50.47	71.69	3.77	6.48	0.075	0.090
9	51.6	54.92	78.55	5.78	7.21	0.105	0.092
10*	38.7	72.12	122.09	7.84	19.02	0.109	0156
11*	42.2	90.51	110.49	11.12	21.38	0.123	0.194
12	47.1	53.27	71.58	4.25	6.10	0.080	0.085
13	48.4	50.98	83.13	4.38	6.28	0.086	0.076
14	47.6	32.96	54.71	2.68	4.17	0.081	0.076
15	46.7	53.77	65.75	3.55	5.80	0.066	0.088
16	45.5	127.10	142.47	18.94	21.99	0.149	0.154
17*	46.2	82.97	106.48	8.60	12.57	0.104	0.118
18	41.0	69.40	98.94	7.37	14.19	0.106	0.143
19	46.1	63.54	86.95	6.22	7.18	0.098	0.083
20	40.2	59.02	94.80	6.43	13.94	0.109	0.147
21*	46.8	47.27	82.27	2.03	6.70	0.043	0.081
22	42.6	47.83	76.69	3.13	6.66	0.065	0.087
Mean	**44.57**	**65.39**	**91.02**	**6.63**	**10.86**	**0.096**	**0.114**
SD	**3.36**	**19.85**	**20.13**	**3.81**	**5.43**	**0.026**	**0.036**

Table XIII Serum albumin, total and free valproic acid concentration and free fraction (continue)

B. Chrono dosage form

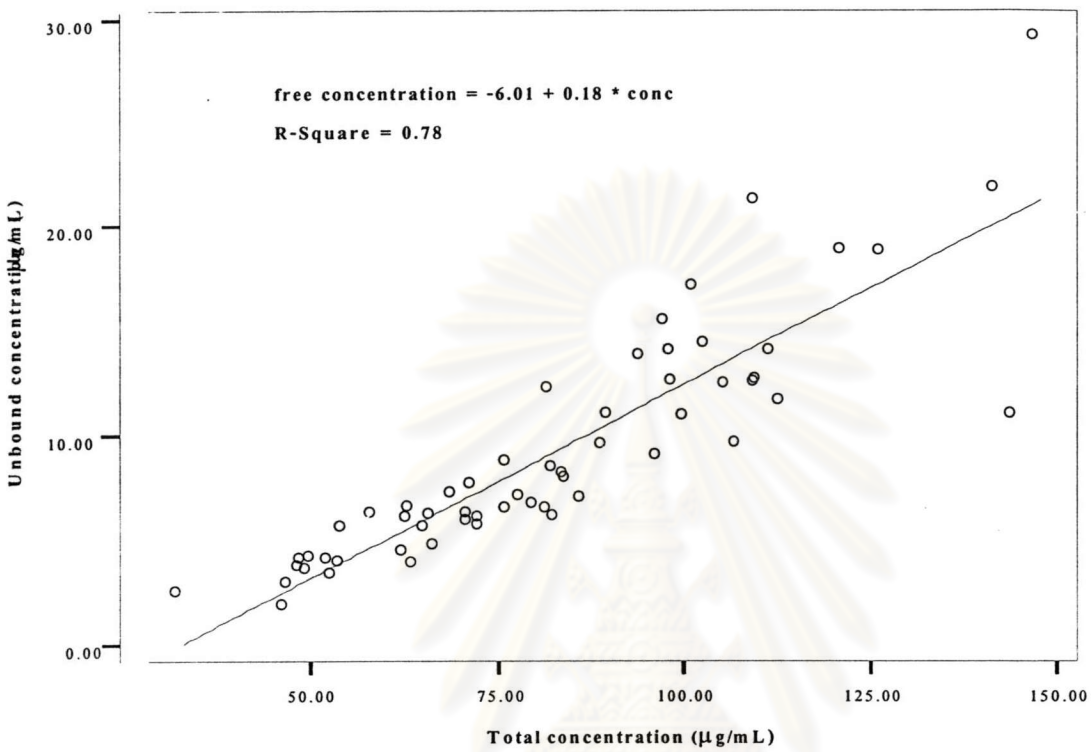
Patient No.	Serum Albumin (g/L)	Total VPA (μg/mL)		Free VPA (μg/mL)		Free fraction	
		Trough Level	5th hour Level	Trough Level	5th hour Level	At Trough	At 5th hour
23	41.3	99.24	103.54	12.73	14.55	0.128	0.141
24*	45.7	112.76	110.49	14.16	12.66	0.126	0.115
25*	44.5	147.90	144.71	29.3	11.12	0.198	0.077
26	45.0	100.78	84.68	11.08	8.08	0.110	0.095
27	44.3	49.69	67.24	4.26	4.90	0.086	0.073
28	42.8	64.28	73.17	4.05	5.84	0.063	0.080
29	43.9	113.96	108.03	11.81	9.79	0.104	0.091
Mean	**43.93**	**98.37**	**98.84**	**12.48**	**9.56**	**0.116**	**0.096**
SD	**1.47**	**32.77**	**26.47**	**8.43**	**3.53**	**0.043**	**0.024**

* uncontrolled seizure

2.2 Relationship of total and unbound concentration

Figure VII demonstrated the correlation between the total and the unbound concentrations of valproic acid. The unbound concentrations were found to be significantly positive correlated to the total concentrations (r^2 = 0.776, $p<0.001$). The lower unbound concentrations (<100μg/mL) and higher concentrations (≥100μg/mL) were correlated to their corresponding total concentrations with correlation coefficient equals to 0.76 ($P<0.001$) and correlation coefficient equals to 0.32 ($p<0.05$) respectively. According to the slope of graph, the unbound concentrations increase at higher concentrations greater than those at lower concentrations.

A.



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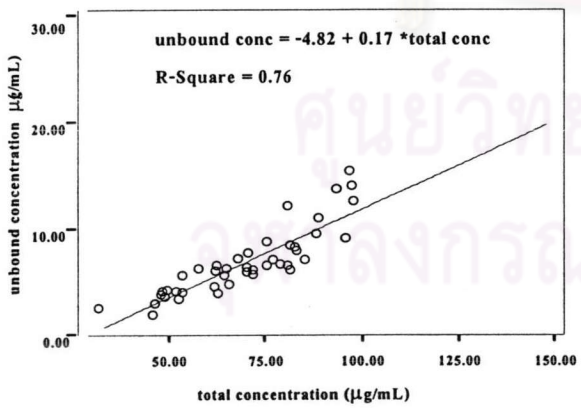

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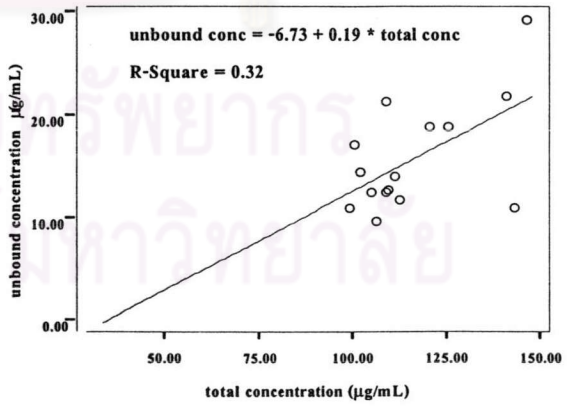


Figure VII. Relationship between total and unbound concentration of VPA

A. all concentrations, B. concentrations<100µg/mL, C. concentrations≥100µg/mL

2.3 Free fraction

By dividing the data of this study into three groups of different concentration ranges which were <50μg/mL, 50-100 μg/mL and >100 μg/mL, the free fractions found in each group were 7.1%, 9.8% and 13.46%, respectively. There were significant differences in the free fractions among the three groups as shown in Table XIV.

Table XIV Comparison of the free fractions between different concentration ranges

Concentration range	Percent of free fraction	Comparison groups	*p value*
A. < 50 μg/mL	7.1	A VS B	.039
B. 50 – 100 μg/mL	9.8	B VS C	.000
C. >100 μg/mL	13.46	C VS A	.000

2.4 Equation to predict free fraction

Graphic presentation of the relationship between free fractions and concentrations was presented in Figure VIII. From multiple regression analysis, the equation obtained for prediction of the free fraction based on the total concentration was:

Free fraction = 0.035 + 0.0008(total concentration) ($r^2 = 0.46$, $p<0.001$)

Free fraction = 0.0279+ 0.0009(total concentration) ($r^2 = 0.411$, $p<0.001$)

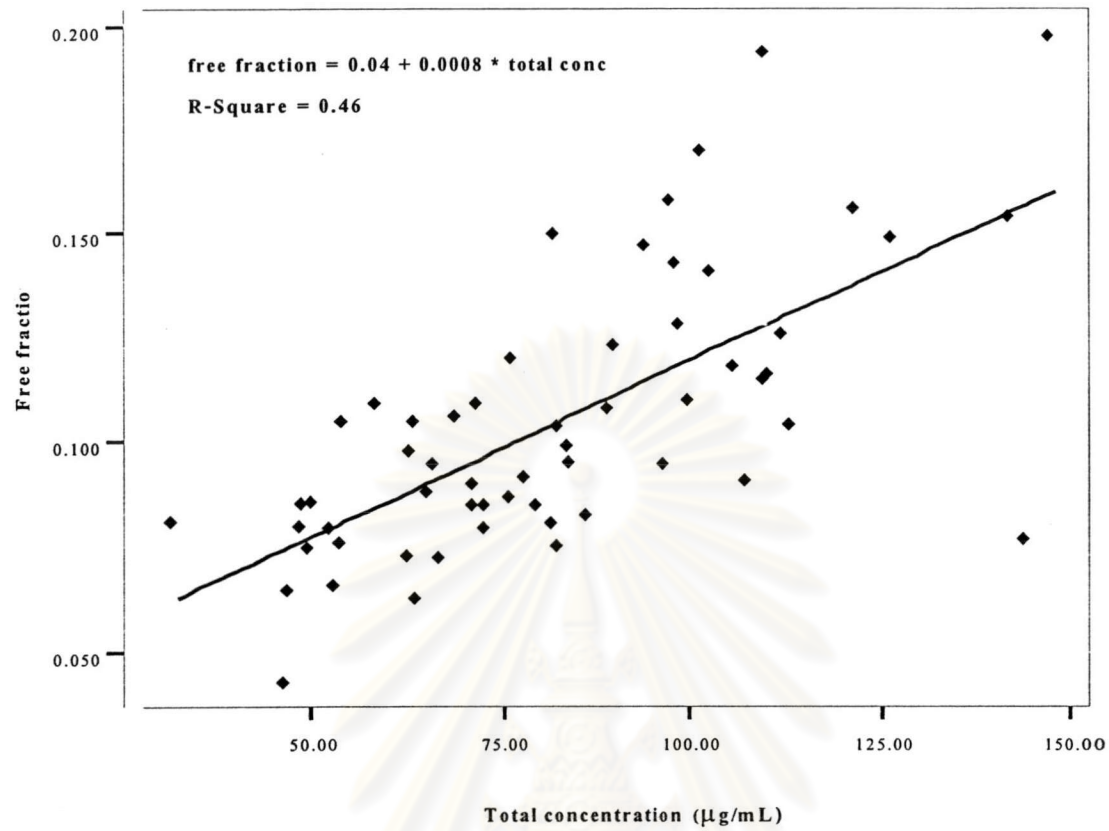
; concentration <100 μg/mL)

Free fraction = 0.0857 + 0.0004(total concentration)($r^2 = 0.034$, $p=0.510$)

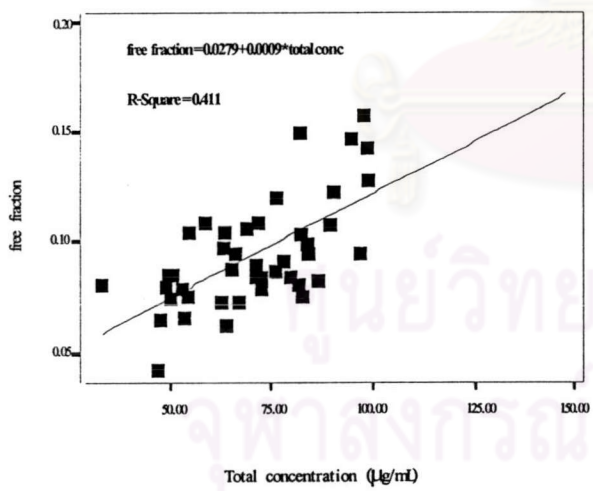
; concentration ≥100 μg/mL)

In this study, minimum correlation was found between the serum albumin and the free fraction of higher concentrations;≥100μg/mL ($r^2=0.148$, $p=0.157$). The higher relationship was found between albumin and the concentration <100μg/mL ($r^2=0.369$, $p<0.001$), and the variable rate of free fraction was lower (Figure IX).

A.



B



C

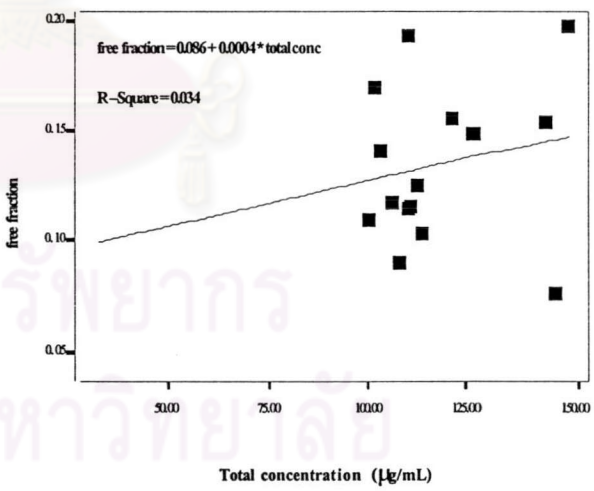
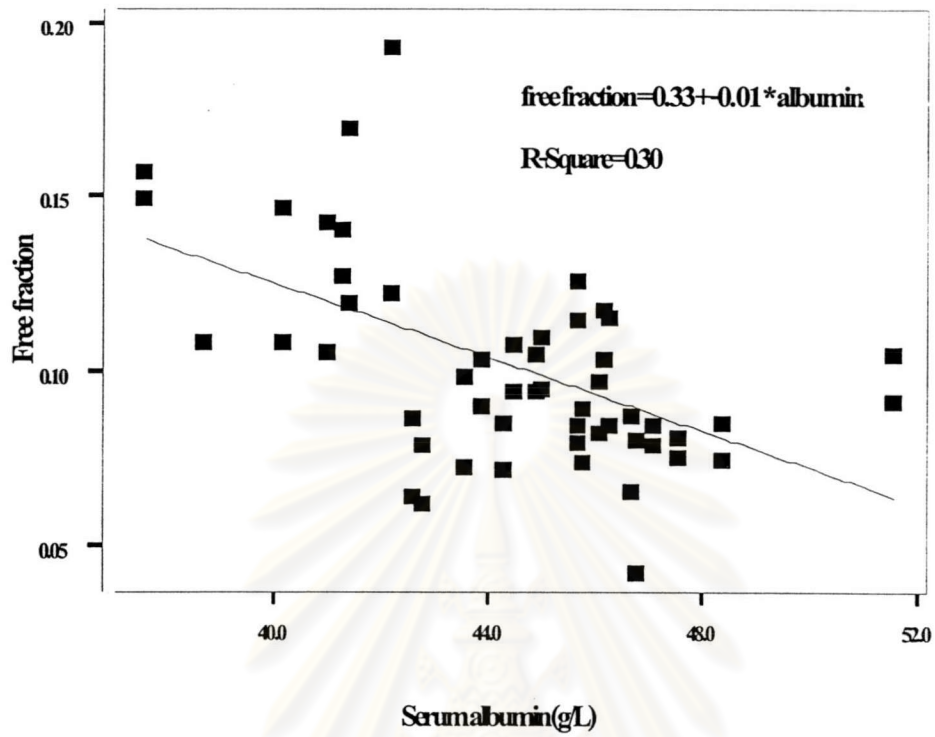


Figure VIII Scatter of relationship between free fraction and total concentration

A. all concentrations, B. concentrations<100µg/mL, C. concentrations≥100µg/mL

A



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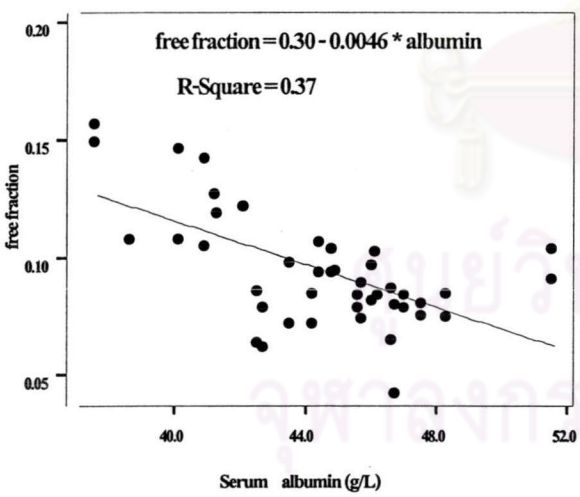

C.

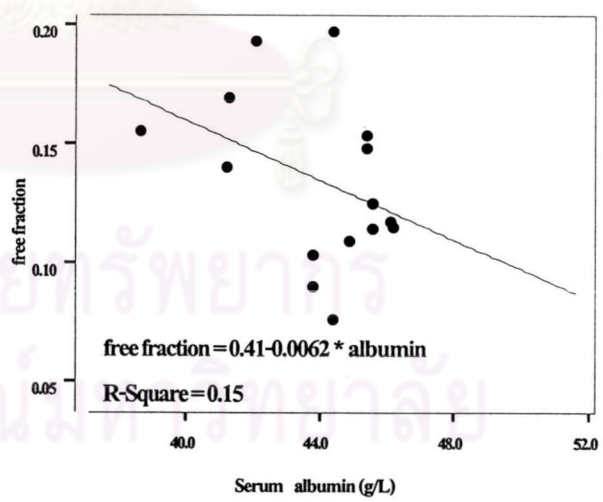

Figure IX Scatter of relationship between free fractions and albumin

A. all concentrations B. concentrations<100μg/mL, B. concentrations≥100μg/mL

3. Pharmacokinetic parameters

3.1 Total and unbound valproic acid pharmacokinetic parameters

The pharmacokinetic parameters were shown in Table XV and summarized in Table XVI. Because there were twenty-two children who took valproic acid in solution form while seven patients took Chrono-talet form. The pharmacokinetic parameters were calculated and considered either for solution only, Chrono only and both dosage forms together. The pharmacokinetic parameters were calculated for both total and unbound concentration and each parameters were compared.

The pharmacokinetic parameters calculated after administered valproic acid solution were:

1. Elimination rate constant (Ke)
2. Clearance (Cl)
3. Volume of distribution (Vd)
4. Half-life ($t_{1/2}$)

Only pharmacokinetic parameter could be calculated after administered Chrono valproic acid was clearance (Cl).

Most pharmacokinetic parameters studied except for the half-life of free drug were significantly greater than those of the total drug as shown in Table XVI. By categorize patients into two subgroups according to their age which were those who are younger than 10 years and those who were older than 10 years-old, the pharmacokinetic parameters were compared by using t-test as showed in Table XVII(A). Neither clearance nor other pharmacokinetic parameters of either total or free drugs showed any significantly different between the younger and the older patients. In addition, the pharmacokinetic parameters were compared between boy and girl and showed no significant difference as showed in Table XVII(B).

The total and unbound clearances of Chrono dosage form were shown in Table XVIII. There were no significant differences in either total or unbound valproic acid clearances between solution and Chrono dosage form.

Talble XV Pharmacokinetic parameter of patients (solution)

Patient	sex	age	weight	height	dosage	dose	K (hr^{-1})		Vd (L/kg)		Cl (mL/kg/hr)		halflife (hr)	
No.		(years)	(kg)	(cm)	form	mg/kg/d	total	free	total	free	total	free	total	free
1	female	7	19	110	solution	26.31	0.029	0.039	0.384	1.808	11.103	69.758	23.979	17.958
2	male	5	25	109	solution	16.00	0.066	0.076	0.135	1.347	8.856	103.010	10.564	9.061
3	female	8	31	*	solution	19.35	0.048	0.099	0.261	1.677	12.592	164.176	14.348	7.018
4	male	9	31	126	solution	29.03	0.057	0.132	0.258	0.859	14.747	113.354	12.137	5.250
5	male	5	15	90	solution	26.07	0.050	0.096	0.203	0.895	10.110	86.080	13.902	7.204
6	male	7	36	119	solution	16.67	0.054	0.079	0.136	0.864	7.396	66.440	12.777	8.739
7	female	11	32	135	solution	18.75	0.074	0.055	0.102	1.485	7.587	81.889	9.327	12.568
8	female	5	18.3	111	solution	21.86	0.059	0.090	0.213	1.483	12.447	133.949	11.846	7.674
9	male	11	28.7	134	solution	17.42	0.055	0.034	0.149	2.990	8.173	101.669	12.577	20.382
10	male	11	17	120	solution	35.29	0.081	0.136	0.149	0.544	12.060	74.178	8.557	5.084
11	female	5	17	103	solution	52.94	0.080	0.258	0.218	0.228	17.417	58.992	8.685	2.683
12	male	8	56.8	145	solution	7.04	0.054	0.066	0.073	0.691	3.921	45.366	12.905	10.548
13	male	6	24.4	119	solution	16.39	0.081	0.060	0.097	1.772	7.898	106.434	8.504	11.540
14	female	3	15.9	98	solution	25.16	0.085	0.074	0.131	2.122	11.067	156.430	8.201	9.403
15	male	8	20.7	116	solution	28.99	0.067	0.164	0.253	1.007	16.977	164.761	10.336	4.236
16	female	5	22	104	solution	47.73	0.038	0.050	0.365	1.805	13.904	89.838	18.213	13.924
17	male	4	14.1	*	solution	42.55	0.083	0.127	0.181	0.942	15.043	119.111	8.333	5.478
18	female	5	22	131	solution	22.73	0.051	0.094	0.196	0.743	9.923	69.580	13.669	7.404
19	male	5	30	118	solution	20.00	0.070	0.032	0.141	3.687	9.797	117.628	9.943	21.724
20	female	4	16.6	106	solution	24.10	0.068	0.111	0.163	0.677	11.027	74.804	10.236	6.271
21	female	7	15.2	105	solution	39.47	0.185	0.398	0.082	0.280	15.201	111.414	3.752	1.741
22	male	5	30.2	131	solution	16.56	0.067	0.108	0.144	1.054	9.680	113.690	10.282	6.423

Talble XV Pharmacokinetic parameter of 29 patients (Chrono)

Patient	sex	age	weight	height	dosage	dose	K (hr^{-1})		Vd (L/kg)		Cl (mL/kg/hr)		halflife (hr)	
No.		(years)	(kg)	(cm)	form	mg/kg/d	total	free	total	free	total & free		total	free
23	male	15	40	158	Chrono	31.25	-	-	-	-	12.840	95.461	-	-
24	female	13	42	155	Chrono	23.81	-	-	-	-	8.887	73.979	-	-
25	male	12	52	139	Chrono	28.85	-	-	-	-	8.215	46.640	-	-
26	female	12	33	136	Chrono	22.73	-	-	-	-	10.212	98.849	-	-
27	female	11	34	149	Chrono	14.71	-	-	-	-	10.480	133.787	-	-
28	male	9	26	131	Chrono	19.23	-	-	-	-	11.659	162.040	-	-
29	male	11	60	148	Chrono	16.67	-	-	-	-	6.257	64.300	-	-

* can not measure

Table XVI Comparisons between total and unbound valproic acid pharmacokinetic parameters (solution dosage form)

Pharmacokinetic parameters Solution (N=22)	Mean±SD (range)	*p* value
Elimination rate constant of total ($K_{e\ total}$) (hr^{-1})	0.068±0.03 (0.029-0.185)	0.021
Elimination rate constant of unbound ($K_{e\ unbound}$) (hr^{-1})	0.103±0.08 (0.013-0.398)	
Volume of distribution ($V_{d\ total}$) (L/kg)	0.183±0.08 (0.073-0.384)	0.000
Volume of distribution of unbound ($V_{d\ unbound}$) (L/kg)	1.316±0.84 (0.228-3.687)	
Clearance (Cl_{total}) (ml/hr/kg)	12.37±4.16 (3.91-17.42)	0.000
Clearance of unbound ($Cl_{unbound}$) (ml/hr/kg)	101.03±33.39 (45.37-164.76)	
Half life (hr) ($t_{1/2\ total}$)	11.50±4.05 (3.75-23.98)	0.040
Half life of unbound (hr) ($t_{1/2\ unbound}$)	9.20±5.34 (1.74-21.72)	

Table XVII Comparison valproic acid pharmacokinetic parameters

A. between younger and older children

B. between male and female

A.

Pharmacokinetic parameters	Total drug	*p* value	Unbound drug	*p* value
Elimination rate constant (hr^{-1})				
< 10 years	0.68±0.32	0.584	0.107±0.89	0.718
≥ 10 years	0.70±0.13		0.075±0.05	
Clearance (ml/kg/hr)				
< 10 years	11.54±3.37	0.250	106.34±36.62	0.209
≥ 10 years	9.41±2.15		85.64±25.26	
Volume of distribution (L/kg)				
< 10 years	0.19±0.086	0.154	1.26±0.79	0.386
≥ 10 years	0.13±0.027		1.67±1.23	
Half-life (hr)				
< 10 years	11.72±4.27	0.447	8.65±4.95	0.469
≥ 10 years	10.15±2.13		12.68±7.65	

B.

Pharmacokinetic parameters	Total drug	*p* value	Unbound drug	*p* value
Elimination rate constant (hr^{-1})				
male	0.065±0.012	0.646	0.083±0.046	0.236
female	0.072±0.044		0.127±0.114	
Clearance (ml/kg/hr)				
male	10.23±3.47	0.225	91.47±42.09	0.892
female	11.68±2.65		93.65±43.00	
Volume of distribution (L/kg)				
male	0.16±0.056	0.147	1.39±0.975	0.674
female	0.21±0.102		1.23±0.686	
Half-life (hr)				
male	10.90±1.92	0.498	9.64±5.80	0.681
female	12.23±5.71		8.66±4.99	

Table XVIII Comparison between valproic acid clearance of patients who were receiving Chrono tablet and those receiving solution

Pharmacokinetic parameters	Mean±SD (range)	*p* value
Clearance (solution) (Cl_{total}) (ml/hr/kg)	12.37±4.16 (3.91-17.42)	0.306
Clearance (Chrono) (Cl_{total})(ml/hr/kg)	9.79±2.21 6.26 – 12.84	
Clearance of unbound (solution) ($Cl_{unbound}$) (ml/hr/kg)	101.03±33.39 (45.37-164.76)	0.765
Clearance of unbound (Chrono) ($Cl_{unbound}$) (ml/hr/kg)	96.44±40.25 46.64 – 162.04	

Table XIX The relationship of pharmacokinetic parameters of total and unbound valproic acid

Models	**model r^2**
Elimination rate constant (hr^{-1}) $K_{e\ unbound} = -0.0413 + 2.113(K_{e\ total})$	0.563
Clearance (mL/kg/hr) $Cl_{unbound} = 57.43 + 3.88(Cl_{total})$	0.155
Volume of distribution (L/kg) $Vd_{unbound} = 1.187 + 0.708(V_{d\ total})$	0.005
Half-life (hr) $(t_{1/2\ unbound}) = 2.0 + 0.63(t_{1/2\ total})$	0.224

3.2 Equations to predict concentration and pharmacokinetic parameters

As showed in Table XIX there were marked relationship only in elimination rate constants of total and unbound drug, whereas the other pharmacokinetic parameters showed low relationship the correspondent between the total and unbound pharmacokinetic parameters.

Table XX and XXI showed relationship between concentrations and daily doses. Considering the total concentration, the relationship between dose and trough concentrations was more obvious than that between doses and the level obtained at the 5^{th} hour after morning doses. In the contrary, the relationship between doses and unbound concentration at 5^{th} hour after morning dose was higher than that of the trough concentration.

Using stepwise multiple linear regression analysis, the models deployed to predict the clearance of total and free drug were developed along with the correlation coefficient (r^2) of the models, independent variables entering the models were shown in Table XX. The results revealed that daily dose and weight were the two most significant independent variables for prediction of clearance of total valproic acid, while model generated to predict clearance of unbound drug required more independent variables.

From stepwise multiple linear regression analysis, models generated to predict volume of distribution of total and free drug along with the correlation coefficient (r^2) of the models, independent variables entering the models were shown in Table XIX, XX and XXI. The results revealed that trough concentration was the most significant independent variable required ($P<0.001$) to predict volume of distribution of valproic acid, prediction from demographic data only showed very low power. The model demonstrated significant relationship between volume of distribution of total valproic acid and the free

fraction of valproic acid in serum concentrations drawn at trough (r^2 = 0.374,P< 0.05) and at 5th hour after morning dose (r^2= 0.342.P< 0.05).

According to stepwise multiple linear regression analysis, models generated to predict half-life of total and free drug along with the correlation coefficient (r^2) of the models, independent variables entering the models were shown in Table XX an XXI. The results revealed that age and trough concentration were the two most significant independent variables predictor (P <0.001) for prediction half-life of total valproic acid, while half-life of total drug related to half-life of unbound drug with r^2= 0.224 (P<0.001)

Since there were no significant difference between clearance of patients who were received valproic acid as solution and as Chrono form, their data were combined. Analysis of the relationship of the clearance and the independent variables was showen in Table XXII and XXIII, which demonstrated that daily dose and weight of patients were the two most significant data required to predict clearance of total drug. Clearance was found to have low significant positive correlation with the clearance of unbound drug (r^2=0.189,P<0.05) while it was markedly correlated to the daily dose and weight.

Table XX Prediction models for the total concentration and pharmacokinetic parameters of valproic acid (solution dosage form)

A. from demographic data

B. from demographic data plus trough total concentration

A.

Models : solution (N=22)	**model r^2**
Total concentration (μg/mL)	
C_{trough} = 36.54 + 1.1(daily dose)	0.408
C_5^{th} = 62.39 + 1.1(daily dose)	0.390
Clearance (Cl_{total}) (mL/kg/hr)	
Cl_{total} = 4.813 + 0.247(daily dose)	0.693
ln Cl_{total} = 1.752 + 0.024(daily dose)	0.635
ln Cl_{total} = 2.316 + 0.0157(daily dose) – 0.0145(weight)	0.739
Volume of distribution ($V_{d\ total}$) (L/kg)	
$V_{d\ total}$ = 0.103 + 0.003(daily dose)	0.184
ln $V_{d\ total}$ = -2.221 + 0.0167(daily dose)	0.189
Half-life ($t_{1/2\ total}$) (hr)	
ln ($t_{1/2\ total}$) = -1.037 + 0.656(age)	0.525

B.

Models : solution (N=22)	**model r^2**
Clearance (Cl_{total}) (mL/kg/hr)	
Cl_{total} = 7.42 + 7.9E-02(age) – 3.9E-02 (weight) + 0.28(daily dose) – 4.6E-02(C_{trough})	0.755*
Volume of distribution ($V_{d\ total}$) (L/kg)	
$V_{d\ total}$ = -0.0005 + 0.0028(C_{trough})	0.459
ln $V_{d\ total}$ = -2.703 + 0.014(C_{trough})	0.403
Half-life ($t_{1/2\ total}$) (hr)	
$t_{1/2\ total}$ = 4.791 + 0.103(C_{trough})	0.254
ln ($t_{1/2\ total}$) = -2.592 + 0.538(age) + (3.344E-02)(C_{trough})	0.606

C_{trough} : total trough concentration, C_5^{th} : total concentration at 5th hour after morning dose

daily dose (mg/kg/day), weight (kg), age (year), * significant of variable > 0.05

Table XXI Prediction models for the unbound concentration and pharmacokinetic parameters of valproic acid (solution dosage form)

A. from demographic data

B. from demographic data plus trough total concentration

A.

Models : solution (N=22)	**model r^2**
Unbound concentration (μg/mL)	
$C_{trough\ unbound}$ = 1.55 + 0.196 (daily dose)	0.343
$C_5^{th}{}_{unbound}$ = 2.3 + 0.33(daily dose)	0.480
$C_5^{th}{}_{unbound}$ = 38.95 + .028(daily dose) – 0.79(Alb)	0.708
Elimination rate constant of unbound ($K_{e\ unbound}$) (hr^{-1})	
$K_{e\ unbound}$ = 1.61E-02 + 3.34E-03 (Daily dose)	0.203
Unbound clearance ($Cl_{unbound}$) (mL/kg/hr)	
$Cl_{unbound}$ = 162.67+0.16(age) – 0.9(daily dose) –1.57(weight)	0.124*
Volume of distribution of unbound concentration ($Vd_{unbound}$) (L/kg)	
$Vd_{unbound}$ = 0.796 – 0.028(daily dose)	0.217
Half-life of unbound drug ($t_{1/2\ unbound}$) (hr)	
ln ($t_{1/2\ unbound}$) = 1.92 – (5.7E-03)(age) – (2.49E-02)(daily dose) + (3.83E-03)(weight) + (1.62E-02)(Alb)	0.278

B.

Models : solution (N=22)	**model r^2**
Elimination constant of unbound ($K_{e\ unbound}$) (hr^{-1})	
$K_{e\ unbound}$ = 0.124 + 6.6E-03(daily dose) – 2.95E-03 (C_{trough})	0.487
Unbound clearance ($Cl_{unbound}$) (mL/kg/hr)	
$Cl_{unbound}$ = 3.68 + 1.13E-02(age) – 1.76E-02(weight) –1.52E-03(daily dose)–4.66(C_{trough})+ 3.56E-02(Alb)	0.376*
Half-life of unbound drug ($t_{1/2}$ of unbound) (hr)	
ln ($t_{1/2\ of\ unbound}$) = 2.02+(2.08E-02)(C_{trough}) –(5.09E-02)(daily dose)	0.536

age (years), weight (kg)daily dose (mg/kg/day), Alb : serum albumin (g/L), C_{trough}: total trough concentration, * significant of variable > 0.05

Table XXII Prediction model for total and unbound concentrations and clearance of valproic acid from demographic data (Chrono dosage form)

Models (N=7: Chrono)	**model r^2**
Total concentration (μg/mL)	
C_{ave} = -30.67 + 2.63(daily dose) + 1.7(weight)	0.863*
C_{ave} = 1.98 – 5.1(age) + 3.67(daily dose) + 1.8(weight)	0.923*
C_{ave} = -261.35 – 4.75(age) + 4.04(daily dose) + 1.66(weight) + 5.85(Alb)	0.999*
Clearance (Cl_{total}) (mL/kg/hr)	
Cl_{total} = 16.01 – 0.15(weight)	0.647
Cl_{total} = 48.14 – 0.14(weight) – 0.75(Alb)	0.886
Cl_{total} = 38.77 – 0.15(weight) – 0.62 (Alb) – 0.38(age)	0.985
ln Cl_{total} = 2.97 – (1.7E-02)(weight)	0.710
Unbound concentration (μg/mL)	
$C_{unbound\ ave}$ = -18.78 + 0.78(daily dose) + 0.32(weight)	0.804*
$C_{unbound\ ave}$ = -10.18 –1.34(age) + 1.04(daily dose) + 0.35(weight)	0.875*
$C_{unbound\ ave}$ = -69.66 – 1.26(age) + 1.13(daily dose) + 0.3(weight) + 1.32(Alb)	0.939*
Unbound clearance ($Cl_{unbound}$) (mL/kg/hr)	
$Cl_{unbound}$ = 218.37 – 2.97(weight)	0.748
ln $Cl_{unbound}$ = 5.8 – (3.2E-02)(weight)	0.764

daily dose (mg/kg/day), weight (kg), age (year), Alb : serum albumin (g/L),

* significant of variable > 0.05

Table XXIII Prediction model for concentration and clearance of total and unbound valproic acid from demographic data (solution and Chrono dosage form)

Models (N=29 :solution & Chrono)	**model r^2**
Total concentration (μg/mL)	
C_{trough} = 46.98 + 1.05(daily dose)	0.162
C_{trough} = 47.51 + 0.91(weight)	0.173
C_{trough} = -28.65 + 1.76(weight) + 2.08(daily dose)	0.656
C_5^{th} = 63.87 + 1.16(daily dose)	0.309
C_5^{th} = 23.68 + 1.7(daily dose) + 0.93(weight)	0.528
Clearance (Cl_{total}) (mL/kg/hr)	
Cl_{total} = 4.84 + 0.24(daily dose)	0.622
Cl_{total} = 8.55 – 0.086(weight) + 0.19(daily dose)	0.708
ln Cl_{total} = 1.76 + 0.023(daily dose)	0.564
ln Cl_{total} = 2.25 + 0.011(weight) + 0.0165(daily dose)	0.708
Unbound concentration (μg/mL)	
$C_{t\ unbound}$ = 3.04 + 0.176(daily dose)	0.146
$C_{t\ unbound}$ = -12.03 + 0.34(weight) + 0.4(daily dose)	0.569
$C_5^{th}{}_{unbound}$ = 1.99 + 0.34(daily dose)	0.499
$C_5^{th}{}_{unbound}$ = 35.64 + 0.9(daily dose) – 0.73(Alb)	0.683
Unbound clearance ($Cl_{unbound}$) (mL/kg/hr)	
$Cl_{unbound}$ = 130.28 – 1.07(weight)	0.147
ln $Cl_{unbound}$ = 4.914 – 0.013(weight)	0.204

daily dose (mg/kg/day), weight (kg), age (year), Alb : serum albumin (g/L),

$C_{trough\ unbound}$: trough unbound concentration,

$C_5^{th}{}_{unbound}$: unbound concentration at 5th hour after morning dose