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Effect of sustained release on the pharmacokinetics of valproic acid in the dog

Meir Bialer, Michael Friedman and Joseph Dubrovsky

Department of Pharmacy, School of Pharmacy, Hebrew University of Jerusalem, Jerusalem 91120 (Israel)

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Summary

The effect of sustained release on the pharmacokinetics of valproic acid was examined by comparing 4 test sustained-release formulations to a standard tablet and an i.v. preparation of the drug. Drug level monitoring in the plasma was performed by a GLC assay. Results indicate that 3 sustained-release formulations exhibited a more prolonged and uniform absorption rate, yielded more sustained plasma levels after injection, and showed an overall bioavailability of 0.81, 0.78 and 0.40, respectively, relative to an equivalent dose of a conventional tablet. The absorption profile of the various oral formulations were pharmacokinetically analyzed by using the Loo-Riegelman procedure.

Introduction

There has been a renewed interest in the clinical use of sustained-release formulations in recent years. One of the major advantages of a sustained-release dosage form is patient convenience in long-term or chronic therapy, where a simplified regimen might lead to an improvement in compliance and clinical efficacy (Ballard, 1978).

Valproic acid (VPA) is an anti-epileptic drug that has been found to show a much shorter elimination half-life than all other commonly used anti-epileptic agents (Reekers-Ketting et al., 1975; Bruni and Wilder, 1979; Gugler and von-Unruh,

Correspondence: M. Bialer, Dept. of Pharmacy, School of Pharmacy, Hebrew University of Jerusalem, P.O.B. 12065, Jerusalem 91120, Israel.

1980). The mean half-life of VPA ranged from 9.5 to 17.7 h (Bowdle et al., 1980; Gugler et al., 1977; Klotz and Antonin, 1977; Perruca et al., 1978a). Epileptic patients exhibited shorter half-lives, consistent with the induction of valproate metabolites by other anti-epileptic drugs. The mean half-life in epileptic adults was approximately 9 h (Mattson et al., 1978; Perruca et al., 1978b). The relatively short half-life of VPA explains the frequently reported fluctuations in VPA plasma levels during chronic therapy (Levy and Lai, 1982). The oscillations in VPA-free (unbound) plasma levels are greater than those of the total plasma concentration (Levy, 1980). Large, unpredictable, daily fluctuations in VPA plasma concentrations during chronic therapy may be inconvenient in the management of epileptic patients (Cenrard et al., 1981; Rodin and Haidukewych, 1981). Therapeutic drug monitoring is difficult, since sampling at various times of the day results in very different plasma concentrations, most of which are quite far from either minimal or mean VPA plasma levels.

One way of minimizing VPA plasma level fluctuations during chronic therapy is by administering the drug in a sustained-release dosage form. Despite the many brand names of various VPA formulations, a classical sustained-release dosage form of VPA does not exist at present. The benefits of a VPA sustained-release formulation for epileptic patients and their environment is well realized as it will decrease the dosage regimen of the drug during chronic therapy (Reekers-Ketting et al., 1975; Bruni and Wilder, 1979; Cenrard et al., 1980; Klotz, 1982; Morselli and Franco-Morselli, 1980).

Recently, we described a pharmacokinetic analysis in dogs of a novel sustained-release dosage form (Bialer et al., 1984a). This paper deals with a pharmacokinetic analysis in dogs of 4 new test-formulations of VPA in comparison to a standard tablet and i.v. preparation of the drug.

Materials and Methods

The experiments were done on 5 mongrels, 4 males and 1 female, all weighing between 16 and 21 kg. Each dog received an i.v. bolus injection of 200 mg of sodium valproate (Labaz, France) in a 50 mg/ml sterile aqueous solution; oral doses of 400 mg of a sodium valproate standard tablet (Depakine, Labaz) and 400 mg of the 4 new test-formulations of VPA (designated hereafter as formulations A, B, C and D). Formulations A and B were new sustained-release VPA test-formulations in a matrix tablet form. These two matrix formulations contained 200 mg of sodium valproate and a hydrophilic swelling polymer, at a ratio of 1 : 3 (formulation A) and 1 : 1 (formulation B). Formulation C was a double-compressed tablet of VPA. It contained a core which was based on a 1 : 1 mixture of the same hydrophilic swelling polymer and 100 mg of sodium valproate. The core was coated with a second layer of a mixture of 100 mg sodium valproate and 600 mg of ethyl-cellulose. Formulation D contained 200 mg of sodium valproate and 600 mg Eudragit RS (Röhn Pharma, F.R.G.). The tablets were prepared by compressing suitable amounts of the drug–matrix mixtures, using a laboratory press (Perkin-Elmer Hydraulic Press,

U.S.A.), at force of 5000 kg with a 1.0 cm flat-face punch and die. In every study, each dog was administered with two tablets (400 mg). A washout period of at least 3 weeks was conducted between two consecutive studies in each dog. Before assaying, the frozen plasma samples were left to reach room temperature, vortexed, centrifuged and the residual small clot removed.

Valproic acid was assayed by a recently described GLC assay (Bialer et al., 1984b), using a gas liquid chromatograph apparatus (Packard Model 7400) equipped with a flame ionization detector and a dual pen recorder (Unicorder U-225 M).

Results and Discussion

Mean plasma concentrations obtained after the administration of 5 various formulations of VPA to the 5 dogs are presented in Figs. 1 and 2.

After the i.v. administration, a biphasic exponential decline of VPA plasma concentration was found, so that a two-compartment open-body model could be assumed (Loscher and Esenwein, 1978). Corresponding to the model is the bi-exponential equation describing the plasma level Cb:

$$Cb = \frac{D}{V_1}\left(\frac{k_{21}-\alpha}{\beta-\alpha}\cdot e^{-\alpha t} + \frac{k_{21}-\beta}{\alpha-\beta}\cdot e^{-\beta t}\right)$$

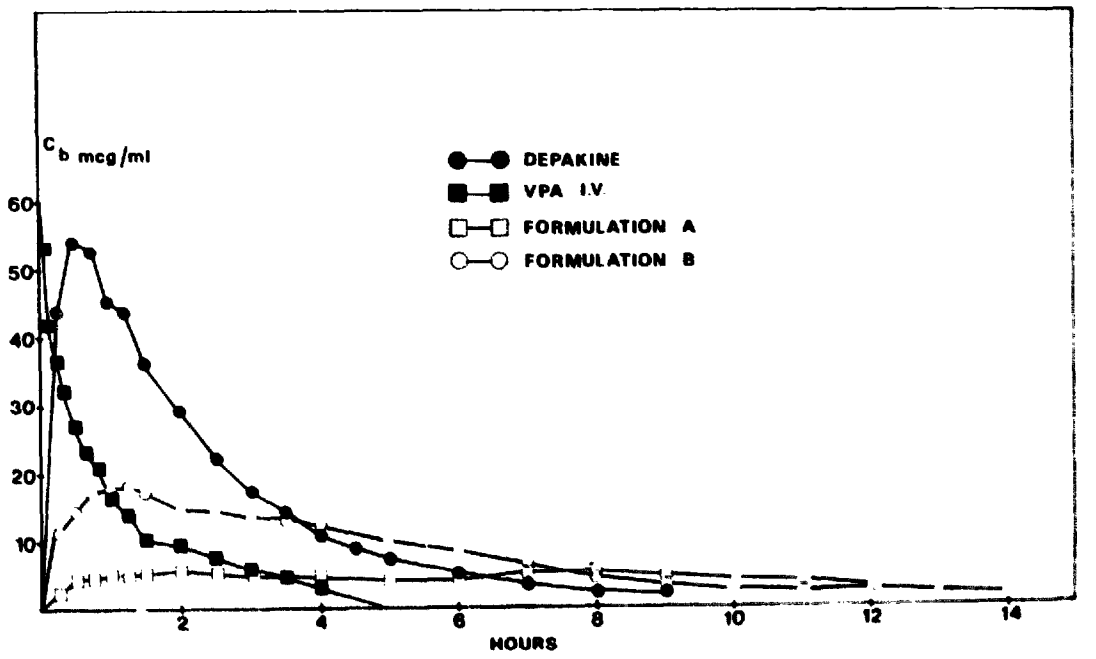

Fig. 1. Mean plasma levels of VPA obtained after i.v. (200 mg) and oral administrations of Depakine and formulations A and B to the 5 dogs.

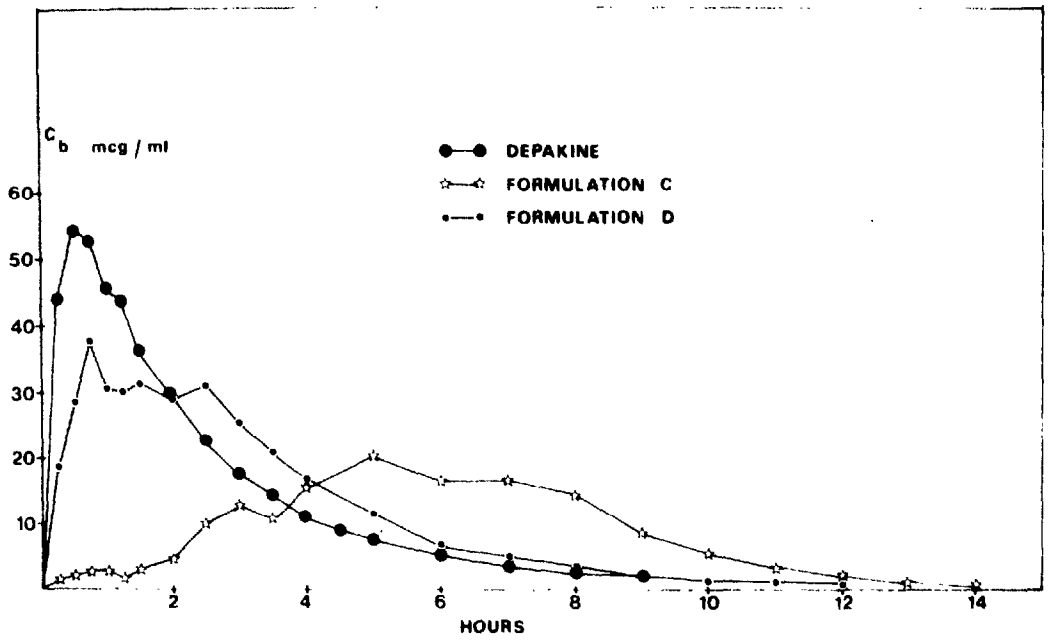

Fig. 2. Mean plasma levels of VPA obtained after administrations of 400 mg of Depakine and formulations C and D to the 5 dogs.

where D is the dose, V_1 is the distribution volume of the central compartment and α and β are hybrid constants of the 3 microscopical first-order rate constants, k_{10}, k_{21} and k_{12} (Gibaldi and Perrier, 1982; Niazi, 1980; Shargel and Yu, 1980). β was calculated from the linear terminal slope of the log Cb vs t plot by the method of least-squares. The AUC was calculated by the trapezoidal rule. The last measured plasma concentration was divided by the least-squares value for the β phase, indicating log-trapezoidal extrapolation to zero concentration (i.e. AUC $0 \rightarrow \infty$). Absolute bioavailability (F) was calculated from the ratio of the AUC obtained after oral and i.v. administration corrected for the various doses. Total body clearance (Cl) was calculated from the quotient of the i.v. dose and the AUC. The volume of distribution (V_β) was calculated from the ratio Cl/β.

Shown in Table 1 are model pharmacokinetic parameters obtained from the i.v. treatment (Gibaldi and Perrier, 1982). Tables 2 and 3 present a summary of the various pharmacokinetic parameters obtained after the administrations of the 5 VPA oral formulations. The peak plasma levels (Cb_{max}) obtained after the administration of formulations A, B and C were lower than those following the conventional tablets of Depakine and formulation D. Peak concentrations were (in mg/l): 8.9 ± 2.6 (mean $\pm$S.D.); 19.8 ± 6.5; 23.8 ± 8.4 and 41.2 ± 25.0, for formulations A, B, C and D, respectively, and 56.4 ± 16.23 for the Depakine treatment. The data thus indicate approximately 60-80% reduction in plasma peak levels, which can be attributed to the slower release of VPA from the sustained-release formulations. Such an attenuated release rate was also manifested in the slower peak time for the sustained-release formulations (A = 180.0 ± 15.53 min; B = 63.0 ± 25.8 min; C = 264.0 ± 114.6

TABLE 1

PHARMACOKINETIC PARAMETERS OBTAINED AFTER I.V. ADMINISTRATION OF SODIUM VALPROATE (200 mg) TO 5 DOGS

Dog no.	β ($min^{-1} \cdot 10^{-3}$)	AUC (mg/l·min)	Cl (ml/min)	V_β (l)	V_1 (l)	k_{12} ($min^{-1} \cdot 10^{-3}$)	k_{21} ($min^{-1} \cdot 10^{-3}$)	k_{10} ($min^{-1} \cdot 10^{-3}$)
1	10.2	3000	66.7	6.51	3.45	24.9	38.4	19.2
2 *	13.0	4330	34.64	2.66	2.34	9.3	51.3	14.8
3	7.07	3256	61.42	8.69	3.13	14.5	49.3	19.6
4	9.2	3780	52.91	5.75	3.70	7.5	22.7	14.3
5	8.77	4202	47.60	5.43	3.45	8.0	38.3	13.8

Key: β = terminal slope; AUC = area under the curve plasma concentration vs time plot; Cl = total body clearance; V_β = apparent volume of distribution ($V_\beta = Cl/\beta$); V_1 = apparent volume of distribution of the central compartment; k_{12}, k_{21} = first-order transfer rate constants from the central compartment to the peripheral and vice versa; k_{10} = first-order elimination rate constant.
* Dog no. 2 was administered with 150 mg of sodium valproate.

min; D = 90.0 ± 51.1 min) as compared to that of Depakine (30.0 ± 10.6 min).

The absorption profiles of VPA formulations A, B, C, D and Depakine were comparatively calculated by using the Loo-Riegelman procedure (Loo and Riegelman, 1968), which assumed that the amount of drug absorbed at any given time point is equal to the sum of the drug amounts presented in the central and peripheral compartments and the amount of drug eliminated by all routes (Loo and Riegelman, 1968; Shargel and Yu, 1980). The cumulative amounts of VPA absorbed following each of the five 400 mg oral treatments are shown in Table 4 and Fig. 3. The amount absorbed throughout the 10 h period was highest after the administration of the plain tablet (Depakine), followed by formulations D, C and formulations B and A.

The incremental absorption rates following the three 400 mg doses of Depakine and formulations A, B, C and D are illustrated in Fig. 4. It is apparent that the high initial absorption rate following the plain dose (Depakine) was drastically decreased in each succeeding interval. Tables 2 and 3 list the absolute and relative bioavailability of formulations A, B, C and D. Though in some dogs the individual bioavailability of Depakine was greater than one, the mean value of Depakine bioavailability was not significantly different from 1.0.

The pharmacokinetic properties of the sustained-release formulations A, B and C as evaluated in the present study, indicated a prolonged absorption of valproic acid, though formulation A exhibited a relatively low value of bioavailability in dogs (0.42). Such effects were manifested in the plasma concentration–time profile where the peak level was attenuated, the peak time delayed and the temporal fluctuations moderated, resulting in more sustained plasma levels for up to 10 h. As the benefits of a VPA sustained-release dosage form for epileptic patients are well realized (Reekers-Ketting et al., 1975; Bruni and Wilder, 1979), formulations A, B and C might have clinical and therapeutic advantages in anti-epileptic therapy.

TABLE 2

SUMMARY OF THE PHARMACOKINETIC PARAMETERS OF VPA OBTAINED AFTER THE ADMINISTRATIONS OF 400 mg OF FORMULATIONS A, B AND DEPAKINE TO 5 DOGS

Pharmacokinetic parameter	Dog no.											
	1			2			3			4		
	A	B	Dep. [c]	A	B	Dep.	A	B	Dep.	A	B	Dep.
$t_{1/2}\beta$(min)	119.4	129	83.13	53.9	165.9	87.77	98	115	64.61	552	159.7	78.59
β ($min^{-1} \cdot 10^{-3}$)	5.78	5.35	7.6	12.8	4.16	8.14	7.04	6.0	11.2	1.25	4.32	8.78
AUC (mg/l·min)	2457	5936	6854	4962	6152	11175	1686	4020	6507	4143	6293	8538
F [a]	0.41	0.99	1.14	0.43	0.54	0.97	0.26	0.62	1.0	0.55	0.83	1.13
t_{max} (min)	120	75	15	480	15	30	30	60	30	150	75	45
Cb_{max} (mg/l)	9.0	15.4	36.4	13.7	23.7	60.6	8.1	13.8	58.9	8.0	15.3	46.6
F [b] relative	0.36	0.87		0.44	0.55		0.26	0.62		0.49	0.73	

Key: $t_{1/2}\beta$ = terminal half-life; F = bioavailability; t_{max} = time to reach peak plasma concentration; Cb_{max} = peak plasma concentration; [a]absolute bioavailability; [b]relative bioavailability to an equal dose of a standard tablet (Depakine); [c]Dep. = Depakine.

TABLE 2 (continued)

Pharmaco-kinetic parameter	5			Mean ± S.D.		
	A	B	Dep.	A	B	Dep.
$t_{1/2}\beta$(min)	50.3	138.3	113.11	237.6 ± 223.6	141.6 ± 18.9	85.44 ± 17.7
β ($min^{-1} \cdot 10^{-3}$)	13.72	4.99	6.1	8.12 ± 4.63	4.96 ± 0.67	8.36 ± 1.9
AUC (mg/l · min)	3638	9408	8442	3377 ± 1311	6488 ± 2189	8303 ± 1847
F [a]	0.43	1.12	1.00	0.42 ± 0.10	0.82 ± 0.24	1.05 ± 0.08
t_{max} (min)	120	90	30	180.0 ± 155.3	63.0 ± 25.8	30.0 ± 10.6
Cb_{max} (mg/l)	5.8	30.8	79.5	8.9 ± 2.6	19.8 ± 6.5	56.4 ± 16.23
F [b] relative	0.43	1.12		0.40 ± 0.09	0.78 ± 0.23	

TABLE 3

SUMMARY OF PHARMACOKINETIC PARAMETERS OBTAINED AFTER TWO ADMINISTRATIONS OF FORMULATIONS C AND D TO 5 DOGS

Pharmaco-kinetic parameter	Dog no.											
	1		2		3		4		5		Mean ± S.D.	
	C	D	C	D	C	D	C	D	C	D	C	D
$t_{1/2}\beta$ (min)	87.0	68.6	73.2	104.9	86.6	70.5	85.1	117.9	73.4	119.0	81.1 ± 6.4	96.2 ± 22.3
β ($min^{-1} \cdot 10^{-3}$)	7.93	10.06	9.43	6.58	7.97	9.78	8.11	5.85	9.40	5.80	8.57 ± 0.69	7.61 ± 1.90
AUC (mg/l·min)	5233	3913	7482	10050	5584	5585	6590	8702	8400	8800	6658 ± 1314	7410 ± 2556
F [a]	0.87	0.65	0.65	0.87	0.86	0.86	0.87	1.15	1.00	1.05	0.85 ± 0.13	0.92 ± 0.19
t_{max} (min)	300	150	420	45	300	150	180	75	120	30	264 ± 104.6	90 ± 51.1
Cb_{max} (mg/l)	17.7	16.4	28.0	88.1	22.0	24.2	37.7	36.7	13.8	40.4	23.8 ± 8.4	41.2 ± 25.0
F [b] relative	0.76	0.57	0.67	0.90	0.86	0.86	0.77	1.02	1.00	1.05	0.81 ± 0.12	0.88 ± 0.19

For explanation of symbols, see Key to Table 2.

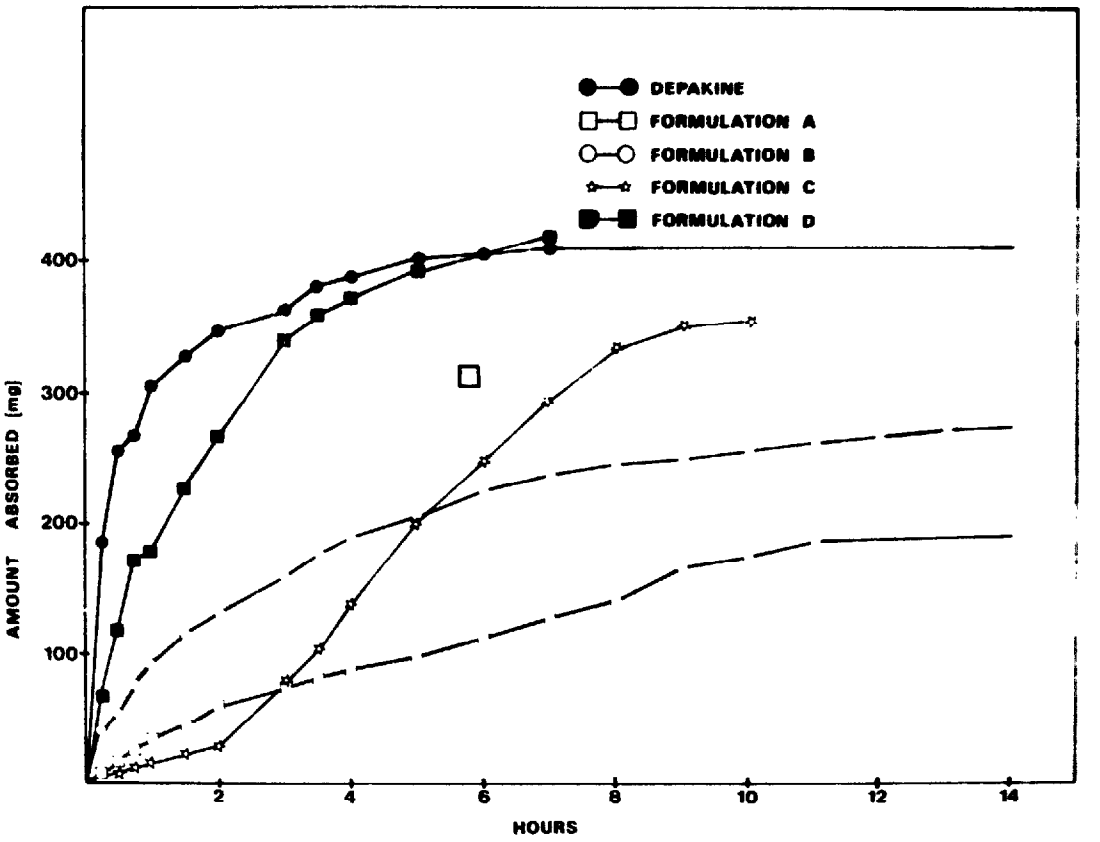

Fig. 3. Cumulative amount of VPA absorbed as a function of time after the administrations of Depakine (400 mg) and formulations A, B, C and D.

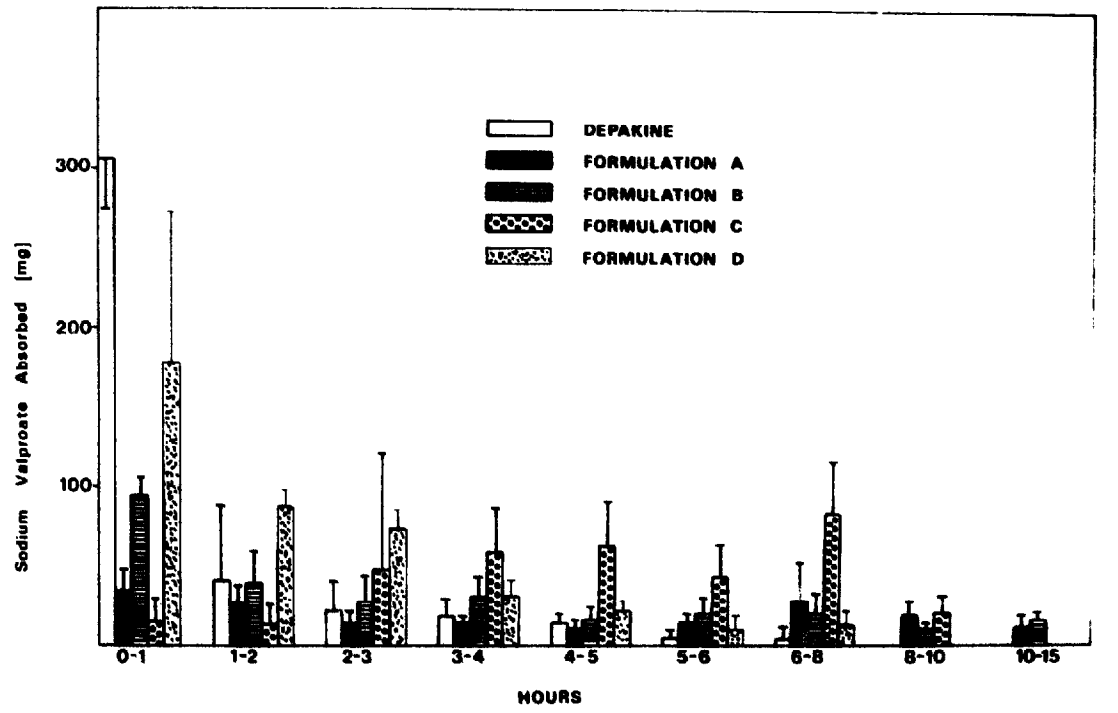

Fig. 4. Timed absorption of VPA from the five 400 mg oral treatments (bars indicate one standard deviation).

TABLE 4

CUMULATIVE AMOUNT OF SODIUM VALPROATE (mg) HAVING ABSORBED INTO THE BODY

Time (min)	Depakine	Formulation A	Formulation B	Formulation C	Formulation D
15	184.1 ± 40.3	7.5 ± 0.9	36.6 ± 21.6	4.9 ± 3.9	66.7 ± 33.2
30	255.6 ± 46.4	18.9 ± 10.3	57.2 ± 18.2	8.8 ± 9.5	117.5 ± 65.5
45	267.2 ± 40.5	27.6 ± 12.4	77.5 ± 18.9	12.3 ± 13.8	169.8 ± 97.6
60	306.2 ± 32.6	34.7 ± 14.1	93.9 ± 11.4	15.2 ± 16.1	178.2 ± 93.5
90	328.4 ± 25.2	45.7 ± 17.4	115.8 ± 17.0	22.2 ± 18.2	226.9 ± 99.0
120	347.3 ± 29.6	60.9 ± 22.9	132.7 ± 29.4	29.2 ± 21.7	265.7 ± 91.5
180	369.1 ± 38.5	75.0 ± 30.1	160.2 ± 45.5	78.0 ± 84.4	338.3 ± 88.7
210	380.9 ± 29.3	83.2 ± 33.3	177.5 ± 49.7	102.7 ± 88.1	357.6 ± 84.6
240	387.5 ± 38.5	89.7 ± 32.9	190.8 ± 46.1	137.5 ± 91.8	370.2 ± 85.1
300	401.9 ± 42.3	99.5 ± 31.1	207.1 ± 47.6	201.9 ± 92.1	392.0 ± 80.4
360	405.8 ± 36.8	114.1 ± 33.2	227.1 ± 49.2	247.4 ± 103.6	381.0 ± 65.9
420	410.1 ± 34.4	129.8 ± 27.7	238.4 ± 51.3	295.4 ± 92.7	417.0 ± 78.9
480	*	142.3 ± 28.8	246.9 ± 52.8	333.5 ± 103.8	*
540		168.1 ± 13.5	250.7 ± 52.5	344.9 ± 95.7	
600		176.6 ± 13.5	257.3 ± 54.6	354.4 ± 96.0	
660		187.9 ± 22.0	263.9 ± 55.0	*	
720		*	269.3 ± 52.8		
780			273.7 ± 51.8		
840			*		
900					

* = no more amount of VPA has been absorbed.

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