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A comparative pharmacokinetic study of valpromide and valproic acid after intravenous administration in humans

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Summary

The pharmacokinetics of valpromide and valproic acid were investigated comparatively in 6 healthy subjects, after intravenous administration of the two drugs. Valpromide was very rapidly and almost completely biotransformed to valproic acid ($f_m = 81.2 \pm 10.5\%$; mean $\pm$ S.D.; $n = 6$). Relative to valproic acid, valpromide has a very short half-life (0.84 ± 0.33 h), a high-clearance value (70 ± 30.5 l/h) and a large volume of distribution ($V_\beta = 75.3 \pm 12.7$ l). The results of this study showed that there was no significant difference between the biotransformation of valpromide to valproic acid after intravenous administration and that obtained after oral administration of valpromide. Therefore, in humans, valpromide appears to be a prodrug of valproic acid after intravenous as well as oral administration.

Introduction

Valpromide-dipropylacetamide (I), a primary amide of valproic acid, is commonly used as an antiepileptic and antipsychotic drug (Favel et al., 1973; Musolino et al., 1980; Pisani and Di Perri, 1980; Pisani et al., 1981, 1982b). It is formulated in several European countries as an enteric-coated tablet under the trade name of

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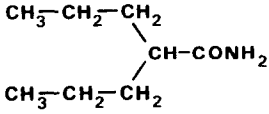
Depamide (Labaz, France—Reynolds, 1982). Previous reports showed that after oral administration of Depamide to humans, valpromide is biotransformed into valproic acid before reaching the systemic circulation (Pisani et al., 1981; Schobben, 1983). Food increased the bioavailability of valproic acid after oral administration of Depamide (Pisani et al., 1982b). Three studies indicated the existence of species differences among humans, dogs and rats in valpromide metabolism or valpromide to valproic acid biotransformation (Pisani and Di Perri,1980; Pisani et al., 1982a; Bialer and Rubinstein, 1983, 1984c).

Up to date, there has not been a single paper on the pharmacokinetics of valpromide after its i.v. administration to humans. Therefore, no estimation of the major pharmacokinetic parameters of valpromide, such as clearance and volume of distribution could be derived. As valpromide is almost completely biotransformed to valproic acid after oral administration, it is also difficult to calculate its half-life. Only in one paper (Schobben, 1983—based on Meyer personal communication), the half-life of valpromide was estimated after its oral administration, and was found to be 45–90 min. In this paper, the protein binding of valpromide was reported to be 30–35%. Unlike valproic acid, valpromide possesses antipsychotic activity (Reynolds, 1982), which can be caused by the very small portion of valpromide which is not biotransformed to valproic acid, and due to its lipophilicity and low protein binding, it will easily cross the blood–brain barrier. Therefore, it is very essential to document the pharmacokinetics of valpromide by administering it i.v. despite its rapid and almost complete biotransformation to valproic acid after oral administration. Valpromide was found to be susceptible to first-pass effect in dogs (Bialer and Rubinstein, 1983). Pisani et al. (1982a) indicated that valpromide is metabolized to valproic acid in the gastrointestinal tract. The present study was undertaken in order to document the pharmacokinetics of valpromide in humans after intravenous administration, and to compare it to the pharmacokinetics of valproic acid. As intravenous administration avoids first-pass effect and gastrointestinal metabolism, this study could investigate the biotransformation of valpromide to valproic acid after this mode of administration.



VALPROMIDE (I)

Materials and Methods

Six volunteers (males) aged between 24 and 32 years, weighing 65–82 kg, were selected for the study on the basis of a negative medical history, physical examination normal routine chemical blood analysis and morphology and urinalysis. Each volunteer received at separate times (in a cross-over design) an i.v. injection (into the

forearm vein) of 400 mg sodium valproate (Labaz, France) as a 50 mg · ml^{-1} sterile solution, and 300 mg of valpromide (Labaz, France) as a 3.64 mg · ml^{-1} sterile 0.9% NaCl (saline) solution. In the two studies, the drugs were injected within 7 min and the data were treated pharmacokinetically as an i.v. bolus. Two volunteers (I.R. and H.Z.) received in preliminary study also 100 mg of valpromide i.v. in a similar manner. Each of the two drugs was administered at 08.00 h, following an overnight fast. Food was withheld for 5 h after administration of the drugs. Venous blood samples (10 ml) were taken via an indwelling catheter from the other forearm vein, at 0, 5, 10, 15, 20, 30, 45, 60 min, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 30, 39 and 48 h after each administration. Between two consecutive studies, there was a washout period of 3 weeks. Sera were immediately separated by centrifugation at 7000 rpm for 15 min and stored at −20°C. Before assaying, the serum was allowed to reach room temperature (22°C), vortexed, centrifuged and the residual clot removed. Valproic acid and valpromide were assayed by GLC (Bialer et al., 1984b). Each sample was extracted into chloroform and chromatographed on the same day, and compared with an eight-point calibration curve (containing serum from each volunteer before each treatment; time = 0), spiked with known amounts of valproic acid and valpromide.

The blood–serum concentration ratio (Rowland and Tozer, 1980a) of valpromide was also calculated by spiking the known amounts of valpromide in 10 samples of blood taken from each volunteer before the drug administration. Valpromide blood concentrations were ranged from 2 to 80 $\mu g \cdot ml^{-1}$. Each blood sample was centrifuged, and the serum was separated according to the procedure mentioned above. Serum levels of valpromide were determined by GLC assay (Bialer et al., 1984b). The protein binding of valpromide was studied by using the ultrafiltration method. This was done in 7 valpromide serum samples at the following drug serum concentrations: 3, 5, 8, 10, 12, 15 and 20 mg · ml^{-1}. Valpromide levels in the filtrate (serum water) were assayed by GLC. Urine samples were collected at 4–6-h intervals for 48 h after the drug administration. The volume of each urine sample was recorded, and 10 ml of each sample was frozen until analyzed. The amount of valproic acid glucuronide in urine was determined by enzymatic hydrolysis of the conjugate metabolite followed by GLC measurement of valproic acid (Klotz and Antonin, 1977; Johno et al., 1982). 0.5 ml of urine was incubated in 0.2 N sodium citrate buffer (pH = 5) at 37°C for 24 h, with 50 μl β-glucuronidase type H-2 (activity 100,000 units · ml^{-1}; Sigma, St. Louis, MO). The incubation mixture was further extracted and assayed as described above. As no valproic acid could be monitored in the urine before the enzymatic hydrolysis, the amount of valproic acid in the urine corresponds to the amount of its metabolite, valproic acid glucuronide. This enzymatic hydrolysis is preferable to an alkaline hydrolysis (Schobben and van der Kleijn, 1982).

The linear terminal slope (β) of the log C_b (valpromide and valproic acid serum concentration) vs t (time) plot was calculated by the method of least-squares. The half-life of the drugs ($t_{1/2\beta}$) was calculated from the quotient: (0.69)/(terminal slope). The AUC (area under the C_b vs t curve) was calculated using the trapezoidal rule, with extrapolation to infinity, by dividing the last experimental serum con-

centration point by the terminal slope (Gibaldi and Perrier, 1982a). The peak serum concentration of valproic acid after valpromide administration (C_{bmax}) and time to reach C_{bmax} (t_{max}) were reported. The total cumulative amount of the excreted metabolite, valproic acid glucuronide, was determined from the urine data (Gibaldi and Perrier, 1982b), and a "sigma minus" analysis (Martin, 1967) of these urine data was performed.

The total body clearance (CL) was calculated from the quotient of dose and AUC. The volume of distribution V_β was calculated from the ratio of the clearance and linear terminal slope. The volume of distribution at steady-state (V_{ss}) was calculated in two ways:

$$V_{ss} = V_1\left(1 + \frac{k_{12}}{k_{21}}\right) \tag{1}$$

$$V_{ss} = \frac{D \cdot AUMC}{(AUC)^2} \tag{2}$$

by using a model-dependent Eqn. 1 (Riggs, 1963) and model-independent Eqn. 2 (Benet and Galeazzi, 1979). The volume of distribution of the central compartment (V_1) and the microscopical rate constants k_{10}, k_{21} and k_{12} were calculated by the usual way (Gibaldi and Perrier, 1982c; Niazi, 1979; Shargel and Yu, 1980). AUMC is the area under the curve of the product of time t and the serum drug concentration C_b, from time zero to infinity (Benet and Galeazzi, 1979). AUMC was calculated by the trapezoidal rule with extrapolation to infinity (Gibaldi and Perrier, 1982d).

Results and Discussion

Mean serum levels of valpromide and valproic acid of 6 healthy volunteers are presented in Figs 1 and 2. The pharmacokinetic parameters are summarized in Table 1. After the i.v. administration of the two drugs, a biphasic exponential decrease in serum concentration was found in all 6 subjects, so that a two-compartment open body model could be assumed (Klotz and Antonin, 1977). This was confirmed by the similarity of the values of V_{ss} of the two drugs which were calculated by model and non-model-dependent equations (Eqns. 1 and 2—Table 1).

Very low serum levels of valpromide were determined for up to 90 min after its administration (300 mg). No valpromide could be monitored after intravenous administration of 100 mg of the drug. The fraction of valpromide converted to valproic acid (f_m) was calculated from the ratio in Eqn. (3) (Rowland and Tozer, 1980b):

$$f_m = \frac{\text{valproic acid clearance}}{\text{valpromide clearance}} \cdot \frac{AUC_{\text{valproic acid}}}{AUC_{\text{valpromide}}} \tag{3}$$

TABLE 1

SUMMARY OF INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS AS CALCULATED AFTER i.v. ADMINISTRATION OF VALPROMIDE AND VALPROIC ACID

Subject name	I.R.		H.Z.		L.A.		A.R.		K.S.		Z.F.		Mean ± S.D.	
Pharmacokinetic parameter	VPD [a]	VPA [b]	VPD	VPA	VPD	VPA	VPD	VPA	VPD	VPA	VPD	VPA	VPD	VPA
β (h^{-1})	1.08	0.058	1.14	0.032	0.80	0.045	0.70	0.042	0.49	0.052	1.26	0.043	0.88 ± 0.33	0.045 ± 0.008
$t_{1/2\beta}$ (h)	0.63	11.9	0.61	21.5	0.87	15.3	0.99	16.2	1.42	13.4	0.54	16.3	0.84 ± 0.33	15.8 ± 3.0
AUC ($mg \cdot l^{-1} \cdot h$)	4.08	667.8	2.76	1140.2	6.43	809.6	6.0	1058.6	8.03	696.2	2.89	960.7	5.01 ± 2.1	888.1 ± 177.7
CL (l/h)	73.5	0.60	108.7	0.35	46.7	0.49	50.0	0.38	37.4	0.58	103.9	0.42	70.0 ± 30.5	0.47 ± 0.10
V_1 (liter)	35.7	6.6	41.1	6.7	29.4	6.2	43.5	6.9	42.9	6.6	69.8	6.3	43.7 ± 13.8	6.6 ± 0.26
V_β (liter)	68.1	10.3	95.3	10.9	58.3	10.9	71.4	9.0	76.3	11.1	82.5	9.8	75.3 ± 12.7	10.3 ± 0.8
V_{ss} [c] (liter)	53.9	10.0	80.5	10.8	68.7	10.5	65.4	8.9	70.6	10.7	92.3	9.6	71.9 ± 13.2	10.1 ± 0.7
V_{ss} [d] (liter)	48.8	9.7	81.2	11.2	63.2	10.3	63.9	9.05	74.4	10.5	93.9	9.62	70.9 ± 14.4	10.0 ± 0.07
k_{10} (h^{-1})	2.06	0.091	2.81	0.052	4.13	0.08	0.8	0.055	0.87	0.088	1.78	0.066	2.08 ± 1.26	0.07 ± 0.017
k_{12} (h^{-1})	1.24	0.46	4.02	0.67	7.48	0.38	1.72	0.25	1.81	0.33	1.93	0.35	3.03 ± 3.28	0.407 ± 0.133
k_{21} (h^{-1})	2.43	0.88	4.20	1.12	12.26	0.55	3.36	0.88	2.79	0.52	5.95	0.686	5.28 ± 4.17	0.773 ± 0.210
f_m (%)	85.1		87.5		60.2		83.4		80.2		90.9		81.2 ± 10.5	
C_{bmax} [e] ($mg \cdot l^{-1}$)		25.4		26.7		17.0		29.4		20.5		29.1		24.7 ± 4.9
t_{max} [f] (h)		1.5		2.5		1.0		2.5		1.5		2.0		1.8 ± 0.60
$t_{1/2\beta}'$ [g] (h^{-1})		10.3		18.6		8.5		14.9		15.4		15.8		13.9 ± 3.8
AUC' [h] ($mg \cdot l^{-1} \cdot h$)		426		748		369		662		419		650		546 ± 159
M_∞ [i] (%)	13.6	33.8	10.2	29.4	5.8	22.5	4.7	16.7	4.3	35.5	3.4	31.9	7.0 ± 4.0	28.3 ± 6.7
$t_{1/2\beta}''$ [j] (h)	12.2	15.1	8.8	13.4	9.5	9.6	9.4	10.5	9.8	15.1	10.5	7.7	10.0 ± 1.2	11.9 ± 2.8

[a] VPD = valpromide. [b] VPA = valproic acid. [c] $V_{ss}{}^{a} = V_1 \left(1 + \frac{k_{12}}{k_{21}}\right)$. [d] $V_{ss}{}^{b} = D \frac{AUMC}{(AUC)^2}$. [e] C_{bmax} = peak serum concentration of VPA after VPD administration. [f] t_{max} = time to reach C_{bmax}. [g] $t_{1/2\beta}'$ of VPA after VPD administration. [h] AUC' = area under curve of C_b vs t of VPA after VPD administration. [i] M_∞ = cumulative amount excreted in the urine of valproic acid glucuronide. [j] $t_{1/2\beta}''$ = VPA half-life calculated from the linear terminal slope of 'sigma minus' of urine data of valproic acid glucuronide.

The clearance of valproic acid was calculated from the data obtained after its i.v. administration. The average f_m after administration of 300 mg valpromide was $81.2 \pm 10.5\%$. In 5 subjects, f_m ranged from 85% to 95%, and only in one subject (L.A.) a relatively low f_m of 60% was found. The terminal half-life of valproic acid after valpromide administration was similar to that obtained after the administration of valproic acid.

Valpromide blood–serum concentration ratio was calculated in the volunteers

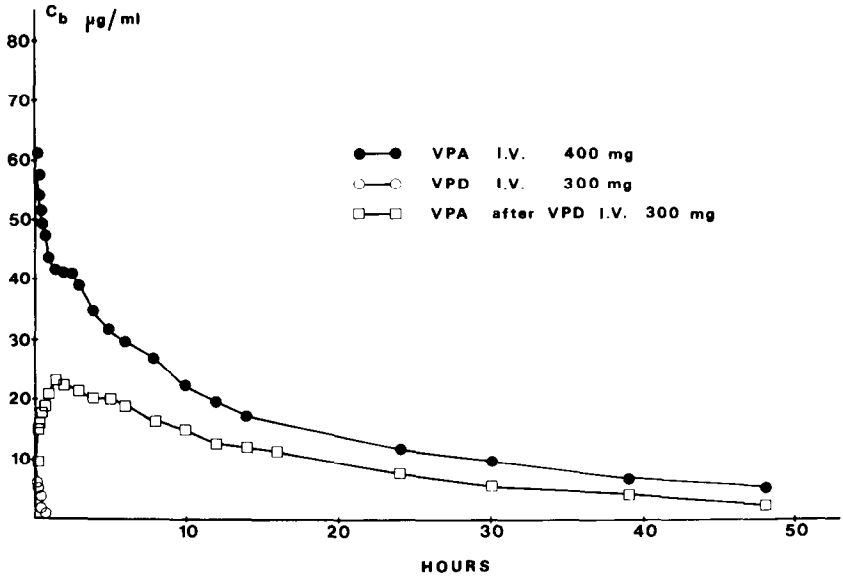


Fig. 1. Mean serum concentration of valpromide (300 mg) and valproic acid (400 mg), obtained after i.v. administration to six healthy subjects. ○, valpromide (VPD); □, valproic acid (VPA) after valpromide; ●, valproic acid.

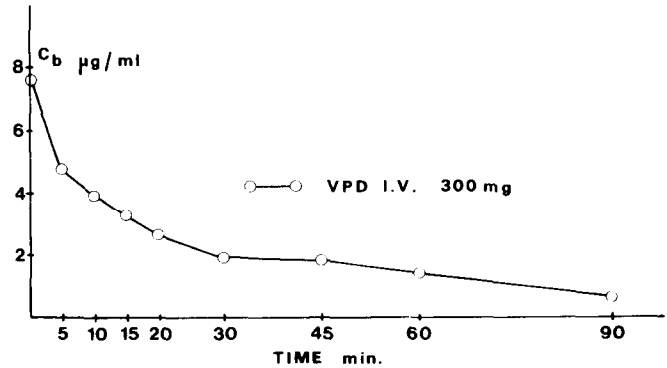


Fig. 2. Expanded scale of mean serum concentration of valpromide (VPD—300 mg), obtained after i.v. administration to six healthy subjects.

and the mean value (±S.D.) was 0.92 ± 0.073. Hematocrit was measured in the six volunteers with a mean of 45%, yielding a mean red blood cell–serum ratio of 0.83. The protein binding degree of valpromide in a concentration range of 3–20 $\mu g \cdot ml^{-1}$ was 53 ± 4% (mean ±S.D.,; n = 7). The mean valpromide free fraction (f_u) was 0.47 ± 0.04 (mean ±S.D.; n = 7), and its range was 0.42–0.54. As valpromide was stable in human serum at room temperature and 37°C for 24 h (Bialer and Rubinstein, 1983), the mean extraction ratio (E) of valpromide was calculated by using Eqn 4.:

$$CL = Q \cdot E \tag{4}$$

where CL is mean total body clearance of valpromide calculated from blood data, and Q is the hepatic blood flow (1350 $ml \cdot min^{-1}$; Rowland and Tozer, 1980c). The mean value of E was 0.94, assuming that after i.v. administration, the biotransformation of valpromide to valproic acid occurred only or primarily in the liver.

Urine analysis showed that no valpromide or valproic acid were excreted unchanged. The cumulative amount (M_∞) of one of the major metabolites of valproic acid–valproic acid glucuronide excreted into the urine within 48 h after drug administration, ranged from 16.7 to 35.5% and 3.4 to 13.6% of the administered dose of valproic acid and valpromide, respectively. The M_∞ value after valpromide administration was lower than that obtained after the administration of valproic acid. The mean terminal half-life ($t_{1/2\beta}$) of valproic acid calculated from a 'sigma minus' analysis of valproic acid glucuronide, after the administration of valproic acid and valpromide were 11.9 ± 2.8 h and 10.0 ± 1.2, respectively. These two values were similar, though the individual values of $t_{1/2\beta}$ did not correlate with the $t_{1/2\beta}$ calculated from serum data, respectively.

The pharmacokinetic parameters calculated after intravenous administration of valproic acid are in good agreement with those of other authors (Klotz and Antonin, 1977; Perucca et al., 1978; Nitsche and Mascher, 1982).

In this study, valpromide was almost completely biotransformed to valproic acid (f_m = 81.2 ± 10.5%). A similar f_m was obtained in the same 6 volunteers after oral administration of a tablet (f_m = 79 ± 24%) and an oral solution (f_m = 77 ± 12%), in a previous study (Bialer et al., submitted for publication). The fact that the f_m or the ratio between the AUCs of valproic acid did not change significantly after oral and i.v. administration, indicates the presence of a first-pass effect in the valpromide to valproic acid biotransformation (Harris and Riegelman, 1969; Ritschel, 1980). This point is strengthened by the very high extraction ratio of valpromide which was found in this study. In a similar in vitro experiment, valpromide was rapidly biotransformed to valproic acid after incubation with rats' liver microsomes (Bialer and Zabida, submitted for publication). As valpromide was found to be stable in serum, it seems that after i.v. and oral administrations, the liver is responsible for its biotransformation to valproic acid.

Despite the similarity in their chemical structure, the pharmacokinetics of valpromide is totally different from that of valproic acid. Relative to valproic acid, valpromide has a very high total body (metabolic) clearance, a very short half-life

and a high volume of distribution of about 1 l/kg. This study shows that in humans, after i.v. administration, valpromide is biotransformed rapidly to valproic acid, similarly to what has been obtained after oral administration. This can be attributed to a high affinity to hepatic enzymes, lipophilicity and a low degree of protein binding. In humans, unlike dogs (Bialer and Rubinstein, 1983), a higher fraction of valpromide dose was biotransformed to valproic acid. Therefore, valpromide seems to be a better prodrug to valproic acid when administered to humans than to dogs.

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