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A comparative study on the pharmacokinetics of valpramide after intravenous administration in dogs

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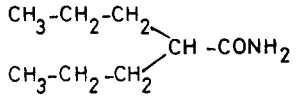
Valpramide (I), a primary amide of valproic acid, is commonly used as an antiepileptic and psychotic drug (Favel et al 1973; Musolino et al 1980; Pisani & Di Perri 1980; Pisani et al 1981, 1982b). After oral administration, valpramide is biotransformed to valproic acid before reaching the systematic circulation, leaving only traces of valpramide in the plasma of epileptics receiving it chronically (Pisani et al 1981). Biotransformation



Valpramide (I)

of valpramide to valproic acid in rats noted after oral administration of valpramide but not after intramuscular (i.m.) administration, was not inhibited in a group of rats pretreated with neomycin (Pisani et al 1982a). Food increased the bioavailability of valproic acid after oral administration of valpramide to healthy volunteers (Pisani et al 1982b). In man, the elimination half life of valpramide and valproic acid is 8–12 h (Pisani & Di Perri 1980). Valpramide has a slower absorption rate than valproic acid, resulting in fewer fluctuations in the drug plasma level during chronic valpramide treatment, which might allow for a dose reduction (Meijer & Klaff 1975; Pisani & Di Perri 1980; Pisani et al 1981). As intravenous (i.v.) administration avoids first pass effects, we have compared the pharmacokinetics of i.v. valpramide with those of valproic acid in five mongrel dogs.

Materials and methods

Four males and one female mongrel (16–21 kg) each received via a catheter into the cephalic vein a bolus injection of 200 mg of sodium valproate (Labaz, France) as a 50 mg ml^{-1} sterile aqueous solution (injected in 10 s), and 400 mg of valpramide (Labaz, France) in a 3·64 mg ml^{-1} sterile 0·9% NaCl(saline) solution. (110 ml of the valpramide solution were injected i.v. within 3 min and the data treated pharmacokinetically as an i.v. bolus). Starting 5 min after each administration, blood samples (7 ml) were taken via an indwelling catheter in the other cephalic vein into heparinized test tubes, for measurement of valpramide and valproic acid. Each blood sample was centrifuged immediately (at 2000 rev min^{-1} for 15 min), the plasma decanted and stored at −20 °C. Before assaying, the plasma was allowed to reach room temperature (22 °C), vortexed, centrifuged and the residual clot removed.

Valpramide and valproic acid were assayed by g.l.c. (Bialer et al submitted for publication). Each sample was extracted into chloroform and chromatographed on the same day and compared with an eight point calibration curve containing plasma (from each dog before either treatment administration-time = 0) spiked with known amounts of valproic acid and valpramide. Valpramide was stable in plasma at room temperature and 37 °C for 24 h. The solubility of valpramide used was 4·385 ± 0·14 mg ml^{-1} (mean ± s.d., n = 10) in purified water and 3·619 ± 0·101 mg ml^{-1} (mean ± s.d., n = 15) in saline. Each plasma sample was assayed three times.

Results and discussion

Mean plasma concentrations of valpramide and valproic acid after i.v. administration to the five dogs are presented in Fig. 1., and the pharmacokinetic parameters are summarized in Table 1. After valproic acid administration, a biphasic exponential decay of plasma concentrations was found in dogs 1, 3 and 5, so that a two-compartment open body model could be assumed (Loscher & Enswein 1978; Loscher 1978). The distribution half life ($t_{1/2\alpha}$) was about 10 min. Owing to a shorter distribution half life in dogs 2 and 4, the biphasic exponential decay of valproic acid plasma concentrations could not be easily determined. After valpramide administrations the $t_{1/2}$ was even shorter and hence a

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Table 1. Summary of pharmacokinetic parameters as calculated after i.v. administration of VPA and VPD.[a]

Pharmacokinetic parameter	Drug and amount administered		
	Valproic acid 200 mg	Valpramide 400 mg	Valproic acid as Valpramide metabolite 400 mg
Terminal slope[b] (min^{-1})	0·009 ± 0·0027	0·0042 ± 0·0011	
Terminal half[c] life (h)	1·24 ± 0·27	2·83 ± 0·51	
AUC ((mg min) $litre^{-1}$)	3713·6 ± 579·1	6153·6 ± 1075·2	2582·2 ± 1192·7
V (litre)[d]	5·81 ± 2·17	15·59 ± 3·54	
Vextrap (litres)[e]		15·98 ± 3·70	
CL (ml min^{-1})	52·65 ± 12·48	66·91 ± 13·74	
fm[f]	0·317 ± 0·121		

[a] Results are given as mean ± s.d. (n = 5).
[b] For valproic acid (two compartment model) it is equal to β, for valpramide (one compartment model) it is equal to ke.
[c] For valproic acid it is equal to t½β, for valpramide it is the elimination half life t½.
[d] V was calculated from the equation CL/ke or CL/β and is equal to Vβ in a two compartment model.
[e] Vextrap was calculated from the ratio D/Cb_0.
[f] fm is the fraction of drug (valpramide) converted to the metabolite (valproic acid) or the absolute bioavailability of valproic acid after i.v. valpramide administration.

one compartment open body model could be assumed.

Plasma concentrations of valproic acid after valpramide administration could be described be using a one compartment open body model and equation (1) (Gibaldi & Perrier 1975a)

$$Cb = \frac{kfD}{Vm(ke - km)}(e^{-kmt} - e^{-ket}) \qquad (1)$$

where Cb is the valproic acid plasma concentration. The constants kf and km are the apparent respective first order rate constants for valproic acid formation and elimination, and ke is the overall elimination rate constant of valpramide. D is the administered dose of valpramide and Vm is the apparent volume of distribution of valproic acid. But as the values of km (valproic acid's ke) and ke (valpramide) were similar, it was difficult to calculate them from the linear terminal slope of equation (1) or by the feathering technique (Gibaldi & Perrier 1975a,b), so the ke of valpramide was calculated from the linear terminal slope of the log Cb vs t plot by the method of least squares. β of valproic acid was also calculated from the linear terminal slope obtained after its i.v. administration. These linear kinetics imply no change in the pharmacokinetic parameters in Table 1 when the valproic acid dose is increased from 200 to 400 mg (Loscher & Enswein 1978; Loscher 1978). The AUC was calculated using the trapezoidal rule. The total body clearance was calculated from the quotient of dose and AUC. The volume of distribution V (or Vβ) was calculated from the ratio of the clearance and linear terminal slope. For valpramide, V was also calculated from the ratio D/Cb_0. (Cb_0 the extrapolated valpramide plasma concentration at time zero). The fraction of valpramide converted to valproic acid (fm) was calculated from the ratio in equation (2) (Rowland & Tozer 1980).

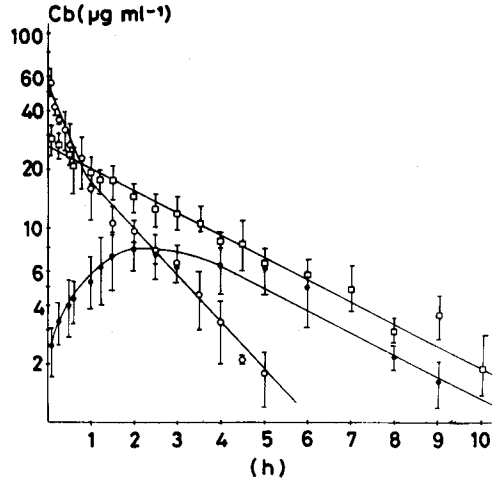

FIG. 1. Mean plasma concentrations of valpramide (400 mg) and valproic acid (200 mg) obtained after i.v. administration to five dogs. □: Valpramide; ● valproic acid after valpramide; ○ valproic acid.

$$\frac{\text{AUC metabolite}}{\text{AUC drug}} = fm\,\frac{\text{Clearance of drug}}{\text{Clearance of metabolite}} = fm\,\frac{\text{Valpramide clearance}}{\text{Valproic acid clearance}} \qquad (2)$$

The clearance of the metabolite was calculated from the data obtained after i.v. administration of valproic acid. As fm was relatively low, urine samples excreted during the studies were assayed for valpramide and small amounts of this drug were found.

Our results show that a relatively low fraction of valpramide is converted to valproic acid after i.v. administration to dogs (fm = 31·5% ± 12·0%). (fm is also equal to the absolute bioavailability of valproic acid after i.v. administration of valpramide). Data obtained after oral administration of valpramide (400 mg in a

Table 2. Pharmacokinetic parameters obtained after oral administration of valpramide to five dogs.

Pharmacokinetic parameter	Dog number 1	2	3	4	5	mean ± s.d.
F[a]	1	0·873	0·422	0·536	0·442	0·655 ± 0·265
fm oral[b]	0·242	0·249	0·4383	0·248	0·328	0·301 ± 0·85
fm i.v.[c]	0·1852	0·290	0·225	0·464	0·419	0·3166 ± 0·121

[a] F—absolute bioavailability of valpramide after oral administration.
[b] fm is the fraction valpramide converted to the valproic acid after oral administration.
[c] fm after i.v. administration.

gelatin capsule) showed an fm similar to that obtained after i.v. administration (Table 2), the average fm (0·301 ± 0·085) not showing a statistically significant difference from the average fm obtained after i.v. administration ($P > 0·05$). The fact that the fm or the ratio between the AUCs of valproic acid did not change significantly after oral and i.v. administrations of valpramide indicates the presence of a first pass effect in the valpramide to valproic acid biotransformation (Harris & Riegelman 1969; Ritschel 1980). The absolute bioavailability of valpramide after oral administration varied among the five dogs and its average value was 65·5% ± 26·5% (Table 2). These data are different from those reported for man by Pisani et al (1980, 1981, 1982a,b) in whom, after oral administration, hardly any valpramide could be found because of a very high first pass effect. This difference in fm might be caused by species differences in its metabolism between dog and man (Williams 1974; Dendrick & Bishoff 1980). As in our study in dogs only low amounts of valpramide were found in the urine, it seems that it was metabolically cleared to other oxidative metabolites in a manner similar to valproic acid metabolism (Schafer & Luhrs 1978; Jakobs & Loscher 1978; Ferrandes & Eymard 1977).

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