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Pharmacokinetics of (+)-, (−)- and (±)-verapamil after intravenous administration

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1 The pharmacokinetics of (+)-, (−)-, and (±)-verapamil were studied in five healthy volunteers following i.v. administration of the drugs.

2 Pronounced differences of the various pharmacokinetic parameters were observed between the (−)- and (+)-isomers. The values for CL, V, V_z, and V_{ss} of the (−)-isomer were substantially higher as compared to the (+)-isomer, whereas terminal $t_{½z}$ was nearly identical for both isomers.

3 No dose dependency of the pharmacokinetics could be observed in two subjects who received 5, 7.5 and 10 mg of (−)- and 5, 25 and 50 mg of (+)-verapamil.

4 Protein binding for the two isomers was also different. The *fu* of (−)- (0.11) was almost twice as much as that of (+)-verapamil (0.064).

5 Pharmacokinetic parameters of (±)-verapamil, which was administered to three subjects who had received (+)- and (−)-verapamil, were very similar to the averaged values of the isomers given separately.

6 Due to the higher CL of (−)-verapamil the extraction ratio of the (−)-isomer is substantially higher. Thus, it can be anticipated that following oral administration of racemic verapamil bioavailability of (−)-verapamil will be substantially less. Since the (−)-isomer is more potent than the (+)-isomer, the present findings could explain the reported differences in the concentration-effect relationship after i.v. and oral administration of racemic verapamil.

Keywords (+)-verapamil (−)-verapamil (±)-verapamil pharmacokinetics

Introduction

The i.v. and oral pharmacokinetics of the calcium antagonist drug verapamil have been studied in detail. Following intravenous administration, the systemic clearance of verapamil is high and approaches hepatic blood flow. Due to this high hepatic extraction, verapamil undergoes extensive 'first-pass' elimination when given orally and therefore despite its almost complete absorption absolute bioavailability is on average only 20–30% (Schomerus *et al.*, 1976; Eichelbaum *et al.*, 1980, 1981a; Freedman *et al.*, 1981; Johnston *et al.*, 1981; Kates *et al.*, 1981; Somogyi *et al.*, 1981; Woodcock *et al.*, 1981a, b; Anderson *et al.*, 1982). The drug preparation available for clinical use is a racemic mixture of the (+)- and (−)-isomer. *In vitro* experiments and studies in the intact animal have demonstrated that the (−)-isomer is much more potent than the (+)-isomer (Kaumann & Serur, 1975; Raschack, 1976; Saikawa & Arita, 1980; Satoh *et al.*, 1980; Nawrath *et al.*, 1981).

Studies from this laboratory have demonstrated pronounced differences in the plasma concentration effect relationship of verapamil on atrioventricular conduction in man depending on the route of administration. Both after single i.v. and oral administration of racemic verapamil a close relationship between verapamil plasma

concentration and effect on P-R interval could be established. But the slope of the oral plasma concentration response curve was significantly less than the slope of the i.v. plasma level response curve. After oral administration on average two to three times higher verapamil plasma levels were required in order to elicit the same increase in P-R interval as after i.v. administration. As a possible mechanism for the different slopes of the concentration effect curves were proposed stereo-selective presystemic first-pass elimination, the more potent (—) isomer being preferentially metabolized after oral administration during hepatic first-pass metabolism (Eichelbaum *et al.*, 1980). Our observations have been recently confirmed (McAllister *et al.*, 1982; Reiter *et al.*, 1982). So far no studies have been carried out either in animals or man to see whether or not the pharmacokinetics of (−)- and (+)-verapamil are different. Knowledge of the relevant intravenous pharmacokinetic parameters of the two isomers should allow an estimate of the extraction ratio which in turn could be used to predict bioavailability of the isomers after oral administration. We therefore decided to study the pharmacokinetics of (+)-, (−)-, and (±)-verapamil following i.v. administration.

Methods

Five healthy male volunteers (aged 23 to 27 years, weight 68 to 91 kg) consented freely to participate in the study. The study had been approved by the Ethics Committee of the University of Bonn. The subjects had normal kidney and liver function as assessed by physical examination and appropriate laboratory tests. ECG recordings (standard 12 leads) revealed no signs of conduction disturbances. Two of the subjects were smokers, three were non-smokers, and they were taking no other drugs. Twenty-four hours before and throughout the study, no alcoholic beverages nor coffee were permitted.

All subjects received in random order either 5 mg (−)- or (+)-verapamil dissolved in 30 ml of physiological saline at a constant rate over 5 min. In addition, to three of the subjects 10 mg of (±)-verapamil was administered. In order to see whether or not there is a dose dependency of verapamil pharmacokinetics, two of the subjects received in addition to the 5 mg dose in random order 7.5 and 10 mg of (−)- and 25 and 50 mg of (+)-verapamil. Venous blood samples were collected in heparinized glass tubes via an indwelling intravenous cannula in the contralateral arm to that in which the intravenous dose had been administered at the following time points: at the end of infusion, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360, 420, 540, 660 and 720 min after the end of the infusion. Blood samples were centrifuged and the plasma stored at −20°C until analysed.

Plasma protein binding

Protein binding of (+)- and (−)-verapamil was determined by equilibrium dialysis at 37°C of 1 ml aliquots of plasma against 0.05 M potassium phosphate buffer (pH 7.4) at 10, 50, 250 and 500 ng/ml plasma. Incubation was carried out for 4 h, and the concentration of verapamil was determined in equilibrated plasma and buffer. In addition, protein binding was also determined for each subject at each study day from three blood samples taken at three different times after verapamil administration.

Drug analysis

Plasma verapamil levels were determined by a specific and sensitive mass fragmentographic method using d_7-verapamil deuterated in the isopropyl group as internal standard. Instead of a packed column as described previously (Spiegelhalder & Eichelbaum, 1977), a 25 m high performance fused silica capillary column with an i.d. 0.32 mm coated with SE-54 (Hewlett-Packard) was used. The lower limit of detection using capillary column is about 0.2 ng/ml of plasma.

Pharmacokinetic analysis

The intravenous verapamil plasma concentration time data were fitted by the following multi-exponential equation:

$$C = \sum_{i=1}^{n} \frac{C_1}{\lambda_i T} \cdot (e^{\lambda_i T} - 1)\, e^{-\lambda_i t}$$

where C is the plasma concentration, C_i the ith coefficient, λ_i the exponent of the ith exponential term, T the duration of the infusion and t is the time since start of the infusion. The equation describes the peak and the post-infusion plasma concentration time data. A non-linear least-squares fit to the data was performed using the LSNLR program kindly provided by Drs A. I. Nichols and C. C. Peck on a Sirius microcomputer system (Peck & Barrett, 1979). Data were weighted according to the reciprocal of the

square of the individual plasma concentrations. The choice of the best fit equation was determined from plots of the distribution of residuals and visual inspection of the goodness of fit.

From the coefficients and exponents of the best fit equation, the following pharmacokinetic parameters were calculated: V, the volume of the central compartment; V_{ss}, the volume of distribution at steady-state; V_z, the area volume of distribution; CL, the total systemic plasma clearance, and $t_{½z}$, the half-life of the terminal exponential phase (Wagner, 1976). Details of the full pharmacokinetic analysis can be obtained from the authors on request.

Results

Significant differences in protein binding between (+)- and (−)-verapamil were observed. The free fraction of (−)-verapamil was on average 0.115 ± 0.016 (range 0.10 to 0.138) as compared to 0.063 ± 0.022 (range 0.044 to 0.096) of (+)-verapamil. No concentration dependency in protein binding was observed up to verapamil concentrations of 500 ng/ml. There was no difference in protein binding whether protein binding was determined in plasma before drug administration or in plasma samples obtained after drug administration.

The visual inspection of the verapamil plasma concentration-time curve revealed multicompartment characteristics. In one of the subjects following administration of racemic verapamil a biexponential ($n = 2$) equation adequately fitted to the data, whereas in the remaining four subjects a triexponential ($n = 3$) equation was required to describe the data. Figure 1 shows the plasma concentration-time curves in one subject to whom increasing doses of (−)- and (+)-verapamil had been administered. Table 1 and 2 list the computer estimated coefficients and exponents of the best fit curve and the various pharmacokinetic parameters of (−)- and (+)- and (±)-verapamil. It is quite apparent from the data that pronounced differences in CL, V, V_{ss}, and V_z are observed between (−)- and (+)-verapamil. With the exception of subjects 2 and 4, terminal half-lives of (+)- and (−)-verapamil were very similar. Plasma clearance, V, V_{ss} and V_z were much higher than the corresponding values for (+)-verapamil. In the two subjects who received increasing doses of (−)- and (+)-verapamil, there was no clear indication of the dose dependency in the pharmacokinetic parameters of either isomer. Total systemic plasma clearance was almost identical irrespective of the dose, although at a dose of 5 mg somewhat lower CL were observed. In the three subjects who also received 10 mg of racemic verapamil the various pharmacokinetic parameters corresponded quite well to the averaged values of the isomers given to these subjects separately. Assuming an average liver blood flow of 1500 ml/min and a blood to plasma ratio of 0.9 for (−)- and (+)-verapamil, substantial differences in the extraction ratios for (+)- and (−)-verapamil are observed. Based on these extraction ratios it can be anticipated that following oral administration systemic

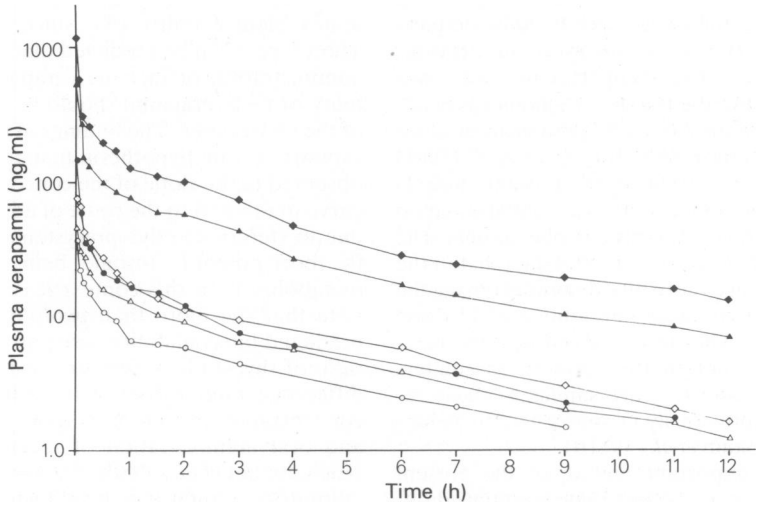

Figure 1 Verapamil plasma concentration-time course following intravenous infusion of different doses of (−)- (5: ○—○; 7.5: △—△ and 10 mg: ◇—◇) and (+)- (5: ●—●; 25: ▲—▲; 50 mg: ◆—◆) verapamil to subject 4.

Table 1 Computer generated coefficients (C) and exponents (λ) of the best fit equation describing verapamil plasma concentrations after intravenous administration of (+)-, (−) and (±)-verapamil.

Subject	*Weight (kg)*	*Isomer*	*Dose (mg)*	C_1 *(ng/ml)*	C_2 *(ng/ml)*	C_3 *(ng/ml)*	λ_1 *(min^{-1})*	λ_2 *(min^{-1})*	λ_3 *(min^{-1})*
1	70	(+)	5	426.5	20.6	9.6	0.60	0.018	0.0027
		(−)	5	242.9	18.9	9.7	0.60	0.044	0.0030
		(±)	10	454.8	55.4	25.4	0.45	0.034	0.0040
2	68	(+)	5	155.9	4.5	21.3	0.03	0.017	0.0037
		(−)	5	37.7	15.8	5.8	0.05	0.183	0.0023
		(±)	10	187.2	28.6	27.0	0.35	0.017	0.0026
3	70	(+)	5	84.8	18.3	8.39	0.16	0.011	0.0022
		(−)	5	33.1	13.4	7.03	0.17	0.048	0.0030
		(±)	10	170.9	24.9	—	0.16	0.003	—
4	92	(+)	5	349.9	15.7	15.2	0.64	0.013	0.0029
		(+)	25	1101.4	47.7	55.3	0.44	0.037	0.0023
		(+)	50	3867.9	169.3	140.0	0.64	0.045	0.0030
		(−)	5	58.9	19.4	4.6	0.62	0.050	0.0014
		(−)	7.5	91.1	19.7	6.2	0.60	0.031	0.0015
		(−)	10	166.9	19.2	8.4	0.42	0.025	0.0016
5	76	(+)	5	201.9	20.6	13.8	0.26	0.020	0.0030
		(+)	25	767.0	70.2	48.5	0.21	0.010	0.0029
		(+)	50	1550.9	163.0	85.6	0.21	0.016	0.0029
		(−)	5	33.5	20.1	8.0	0.41	0.053	0.0031
		(−)	7.5	34.1	9.9	11.1	0.12	0.016	0.0031
		(−)	10	49.2	26.9	13.9	0.11	0.022	0.0029

availability of (−)-verapamil will be only about half that of (+)-verapamil.

Discussion

Following i.v. administration of (+)-, (−)- and (±)-verapamil the drug exhibits multicompartment characteristics. In contrast to our previous reports where a two compartment model was required to describe the data (Schomerus *et al.*, 1976; Eichelbaum *et al.*, 1981) but in accordance with the data reported by Freedman *et al.* (1981) and Kates *et al.* (1981), in the present study in four out of five subjects a triexponential equation was required to satisfactorily describe the data. The difference seems to be due to the fact that in the present study two more blood samples during the early distribution phase were obtained. In those three subjects who also received racemic verapamil, the relevant pharmacokinetic parameters (CL, V_{ss}, V_z, and $t_{½z}$) are similar to those reported by us previously in young healthy volunteers (Eichelbaum *et al.*, 1981b).

The most important finding of the present study, however, is the fact that pronounced differences in the pharmacokinetics and protein binding of (+)- and (−)-verapamil are observed. CL, V, V_{ss}, V_z, and *fu* of the (−)-isomer are much higher than the corresponding values for (+)-verapamil. The half-lives of the terminal phase, however, are very similar for both isomers. Due to the higher systemic clearance of the (−)-isomer, the extraction ratio (E) of this isomer will be substantially higher than the extraction ratio of the (+)-isomer. After oral administration the extraction ratio (E) determines bioavailability (F), since $F = 1 - E$. Therefore it can be predicted that following oral administration of racemic verapamil bioavailability of (−)-verapamil should be only half that of the (+)-isomer. The findings of this study lend support to our hypothesis that the differences observed in the slope of the concentration effect curve in relation to the route of administration is due to stereo-selective presystemic elimination, the more potent (−)-isomer being preferentially metabolized. In this context it is interesting to note that the more than twofold difference in predicted bioavailability based on the extraction ratio of this study is very similar to the 2.2 fold difference observed previously in the slope of the concentration effect regression following i.v. and oral administration of racemic verapamil (Eichelbaum *et al.*, 1980). Data obtained in this laboratory comparing the effects of (−)- and (+)-verapamil on atrioventricular conduction and echocardiographic parameters have shown that the (−)-isomer is about 10 times more

Table 2 Pharmacokinetic parameters of verapamil following intravenous administration of (+)-, (−) and (±)-verapamil.

Subject	*Isomer*	*Dose (mg)*	V *(l/kg)*	V_{ss} *(l/kg)*	V_z *(l/kg)*	*CL (ml/min)*	*CL (ml min^{-1} kg^{-1})*	$t_{½z}$ *(h)*
1	(+)	5	0.14	3.11	4.51	859	12.3	4.24
	(−)	5	0.24	4.37	5.43	1140	16.3	3.86
	(±)	10	0.24	2.72	3.71	1030	14.7	2.92
2	(+)	5	0.37	2.57	2.85	713	10.5	3.14
	(−)	5	1.15	5.68	8.53	1321	19.4	5.07
	(±)	10	0.56	3.52	4.17	745	11.0	4.39
3	(+)	5	0.59	3.54	5.08	796	11.4	5.16
	(−)	5	1.24	6.56	7.82	1650	23.6	3.83
	(±)	10	0.68	3.96	4.57	1196	17.1	4.35
4	(+)	5	0.13	1.96	2.48	661	7.28	3.99
	(+)	25	0.21	3.41	3.93	827	9.00	5.05
	(+)	50	0.12	2.45	2.96	835	9.1	3.76
	(−)	5	0.61	8.46	9.65	1211	13.2	8.47
	(−)	7.5	0.65	8.61	10.19	1449	15.8	7.48
	(−)	10	0.52	8.10	9.79	1443	15.7	7.21
5	(+)	5	0.25	2.33	3.14	726	9.6	3.81
	(+)	25	0.35	2.66	3.86	840	11.1	4.03
	(+)	50	0.34	2.67	4.11	919	12.1	3.93
	(−)	5	1.00	5.50	6.43	1527	20.1	3.69
	(−)	7.5	1.66	5.52	6.62	1537	20.2	3.78
	(−)	10	1.36	5.05	6.55	1418	18.7	4.05
(+) mean			0.27	2.74	3.66	797	10.24	4.08[a]
% C.V.[b]			54.4	18.8	23.4	10	16.4	
(−) mean			0.93	6.42	7.89	1411	18.1	4.81[a]
% C.V.[b]			49.0	24.7	21.95	11	17.4	
(±) mean			0.49	3.40	4.15	990	14.27	3.75[a]
% C.V.[b]			45.0	18.5	10.4	23	21.5	

[a] Harmonic mean; [b] coefficient of variation.

potent than the (+)-isomer (manuscript in preparation).

In a recent study Reiter *et al.* (1982) observed similar differences in the concentration effect curve after single i.v. and oral administration. During intravenous steady-state infusion, however, the slope of the concentration response relationship was much less than after single i.v. bolus. On the basis of their study they concluded that stereo-selective first-pass metabolism was rather unlikely to explain the differences in concentration response relationship. In view of our findings, however, their observations are not surprising. Due to the substantial differences in the systemic plasma clearance of (−)- and (+)-verapamil, steady-state concentration of (−)- and (+)-verapamil will be different and the ratio of (+)- and (−)-isomer will change during prolonged infusion.

It remains to be proven, however, by appropriate experiments that stereo-selective first-pass metabolism of verapamil occurs. Due to the pronounced day to day intraindividual variation in first-pass metabolism of verapamil administration of the isomers on separate days leads to erroneous results, as it has been demonstrated by us in a previous relative bioavailability study (Eichelbaum *et al.*, 1981b). In this previous study stable isotope techniques, which permit the simultaneous administration of two preparations, have been successfully used to overcome these difficulties. Studies are now in progress in this laboratory using isomers labelled with stable isotopes thus allowing the simultaneous administration of the two isomers to investigate the stereo-selectivity of verapamil first-pass metabolism.

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References

Anderson, P., Bondesson, U. & Sylven, C. (1982). Clinical pharmacokinetics of verapamil in patients with atrial fibrillation. *Eur. J. clin. Pharmac.*, **23**, 49–57.

Eichelbaum, M., Birkel, P., Grube, E., Gütgemann, U. & Somogyi, A. (1980). Effects of verapamil on P-R-intervals in relation to verapamil plasma levels following single i.v. and oral administration and during chronic treatment. *Klin. Wochenschr.*, **58**, 919–925.

Eichelbaum, M., Albrecht, M., Kliems, K., Schäfer, K. & Somogyi, A. (1980). Influence of meso-caval shunt surgery on verapamil kinetics, bioavailability and response. *Br. J. clin. Pharmac.*, **10**, 527–529.

Eichelbaum, M., Dengler, H. J., Somogyi, A. & Von Unruh, G. E. (1981a). Superiority of stable isotope techniques in the assessment of the bioavailability of drugs undergoing extensive first-pass elimination. Studies of the relative bioavailability of verapamil tablets. *Eur. J. clin. Pharmac.*, **19**, 127–131.

Eichelbaum, M., Somogyi, A., Von Unruh, G. E. & Dengler, H. J. (1981b). Simultaneous determination of the intravenous and oral pharmacokinetic parameters of (±)-verapamil using stable isotope-labelled verapamil. *Eur. J. clin. Pharmac.*, **19**, 133–137.

Freedman, S. B., Richmond, D. R., Ashley, J. J. & Kelly, D. T. (1981). Verapamil kinetics in normal subjects and patients with coronary artery spasm. *Clin. Pharmac. Ther.*, **30**, 644–652.

Johnston, A., Burgess, C. D. & Hamer, J. (1981). Systemic availability of oral verapamil and effect on PR interval in man. *Br. J. clin. Pharmac.*, **12**, 397–400.

Kates, R. E., Keefe, D. L., Schwartz, J., Harapat, S., Kirsten, E. B. & Harrison, D. C. (1981). Verapamil disposition kinetics in chronic atrial fibrillation. *Clin. Pharmac. Ther.*, **30**, 44–51.

Kaumann, A. J. & Serur, J. R. (1975). Optical isomers of verapamil on canine heart: prevention of ventricular fibrillation induced by coronary artery occlusion, impaired atrioventricular conductance and negative inotropic and chronotropic effects. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **291**, 347.

McAllister, R. G. jr. & Kirsten, E. B. (1982). The pharmacology of verapamil. IV. Kinetic and dynamic effects after single intravenous and oral doses. *Clin. Pharmac. Ther.*, **31**, 418–426.

Nawrath, H., Blei, J., Gegner, R., Ludwig, C. & Xiang-Gang, Zong (1981). No stereospecific effects of the optical isomer of verapamil and D-600 on the heart. In *Calcium antagonism in cardiovascular therapy*, eds. Zanchetti, A. & Krikkler, D. M., pp. 52–63. Excerpta Medica.

Peck, C. C. & Barrett, B. B. (1979). Nonlinear least-squares regression programs for microcomputers. *J. Pharmacokin. Biopharm.*, **5**, 537–541.

Raschack, M. (1976). Relationship of antiarrhythmic to inotropic activity and antiarrhythmic qualities of the optical isomers of verapamil. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **294**, 285–291.

Reiter, M., Shand, D. G. & Pritchett, E. L. C. (1982). Comparison of intravenous and oral verapamil dosing. *Clin. Pharmac. Ther.*, **32**, 711–720.

Saikawa, T. & Arita, M. (1980). Effects of verapamil and its optical isomers on repetitive slow responses induced by electrical depolarization in canine ventricular myocardium. *Jap. Heart J.*, **21**, 247–255.

Satoh, K., Yanagisawa, T. & Taira, N. (1979). Effects on atrioventricular conduction and blood flow of enantiomers of verapamil and of tetrodotoxin injected into the posterior and the anterior septal artery of the atrioventricular node preparation of the dog. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **308**, 89–98.

Schomerus, M., Speigelhalder, B., Stieren, B. & Eichelbaum, M. (1976). Physiological disposition of verapamil in man. *Cardiovasc. Res.*, **10**, 605–612.

Spiegelhalder, B. & Eichelbaum, M. (1977). Determination of verapamil in human plasma by mass fragmentography using stable-labelled verapamil as internal standard. *Arzneimittel-Forsch.*, **27**, 94–97.

Somogyi, A., Albrecht, M., Kliems, G., Schäfer, K. & Eichelbaum, M. (1981). Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. *Br. J. clin. Pharmac.*, **12**, 51–60.

Wagner, J. G. (1976). Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J. Pharmacokin. Biopharm.*, **4**, 443–467.

Woodcock, B. G., Rietbrock, I., Voehringer, H. & Rietbrock, N. (1981a). Verapamil disposition in liver disease and intensive-care patients: Kinetics, clearance and apparent blood flow relationships. *Clin. Pharmac. Ther.*, **29**, 27–34.

Woodcock, B. G., Schulz, W., Kober, G. & Rietbrock, N. (1981b). Direct determination of hepatic extraction of verapamil in male cardiac patients. *Clin. Pharmac. Ther.*, **30**, 52–56.

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