SYSTEMIC AVAILABILITY OF ORAL VERAPAMIL AND EFFECT ON PR INTERVAL IN MAN

A. JOHNSTON, C.D. BURGESS & J. HAMER

Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE

- 1 The plasma levels of verapamil and its major metabolite norverapamil were related to its effect as a Ca-antagonist on atrio-ventricular (AV) conduction, judged from prolongation of the PR interval in six normal volunteers.
- 2 Intravenous administration (0.1 mg kg^{-1}) was compared to oral administration (120 mg) in each subject.
- 3 Intravenous verapamil showed a mean distribution half-life (α) of 8.5 min and elimination half-life (β) of 2.0 h. The volume of distribution was about 112.1. Oral dosage gave an elimination half-life of 2.7 h, and a norverapamil half-life which averaged 4.6 h. The bioavailability of the oral dose averaged 22% (17 to 29%).
- 4 After the oral dose the percentage change in PR interval in the five appropriate subjects correlated significantly with the log plasma verapamil level ($r = 0.732$), but not with the log plasma norverapamil level ($r = 0.078$); norverapamil could not be detected after the intravenous dose. One subject developed Wenckebach type second degree AV block after each dose.

Introduction

Verapamil is an anti-anginal and anti-arrhythmic agent. Its beneficial effects are thought to be produced by inhibition of calcium transport across myocardial cell membrane, (Nayler & Krikler, 1974), which is particularly critical for the normal function of the cells of the atrio-ventricular node.

Data on its physiological disposition in man are scant, with only two published studies comparing plasma drug levels after oral and intravenous administration. (Schomerus *et al.*, 1976; Koike *et al.*, 1979). In the present study verapamil has been given by both routes to six volunteers to assess its systemic availability and its effect on atrio-ventricular conduction using high speed surface electrocardiography.

Methods

Six healthy volunteers, four male and two female, agreed to participate in the study. The subjects weighed between 60 and 73 kg and ranged in age between 21 and 31 years. Normal kidney, liver and cardiac function was confirmed by physical examination, laboratory tests and electrocardiography. Each volunteer was given verapamil on two occasions separated by at least a week. The doses chosen were 0.1 mg kg^{-1} intravenously and 120 mg orally and the subjects fasted for 12 h before and at least 3 h after each dose.

For oral administration the tablets were given with 200 ml of water and blood samples were taken for plasma verapamil and norverapamil estimation prior to and at 20, 30, 40 min and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8 and 12 h after the drug was given. High speed (100 mm s^{-1}) ECG recordings to determine PR interval were made before and at 0.5, 1, 1.5, 2, 2.5, and 3 h. PR interval was calculated from these recordings without the observer being aware of the time relationship to drug administration.

The intravenous dose of verapamil was given over 5 min and blood samples were taken at 0, 5, 10, 20, 30 and 45 min and 1, 1.5, 2, 2.5, 3, 4 and 6 h. High speed ECG recordings were made at 0, 5, 10, 20, 30 and 60 min. The subjects were supine for the period of ECG recording.

The plasma samples were stored frozen until assayed for verapamil and norverapamil using a high pressure liquid chromatography method similar to that of Harapat & Kates (1980). The limit of detection is 10 ng ml^{-1} for both compounds, with coefficients of variation of about 6%.

The pharmacokinetic values were estimated graphically from semi-logarithmic plots of verapamil concentration against time. An apparent bioavailability of the oral preparation was calculated by comparing area under the concentration time curve ($\text{AUC}_{0-\infty}$) extrapolated to infinity of the oral to the intravenous dose and adjusting for dosage by simple proportion.

Figure 1 Plasma verapamil concentrations (mean $\pm$ s.e. mean) in the six subjects after 0.1 mg/kg intravenously.

Figure 2 Plasma verapamil (■) and norverapamil (●) concentrations (mean $\pm$ s.e. mean) in the six subjects after a 120 mg oral dose.

Table 1 Pharmacokinetic parameters calculated for all subjects.

Subject	Weight (kg)	i.v.		Oral		V_d (l)	V_d (l/kg)	Bio-availability %	$AUC_{0-\infty}$	
		$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (h)	Verapamil $T_{1/2\beta}$ (h)	Norverapamil $T_{1/2\beta}$ (h)				i.v. (ng ml ⁻¹ h)	Oral (ng ml ⁻¹ h)
1 M	65	6.0	2.1	1.64	4.2	120.4	1.85	14.0	97.2	252.1
2 M	73	9.9	1.3	2.90	4.3	61.9	0.85	10.8	160.9	286.5
3 F	60	6.0	2.2	3.2	3.6	111.1	1.71	17.1	68.8	235.8
4 M	70	6.0	2.6	2.7	4.3	122.8	1.75	32.8	130.5	734.2
5 M	60	9.0	2.2	3.0	7.3	96.8	1.61	28.4	177.3	1015.5
6 F	60	17.3	1.7	2.65	4.1	162.2	2.7	29.1	75.6	439.7
Mean	64.7	8.5	2.0	2.7	4.6	112.5	1.75	22.0	118.4	494.0
s.d.	5.7	4.9	0.5	0.5	1.3	33.0	0.59	9.2	45.1	316.5

Table 2 Changes in PR interval and heart rate (HR) after oral and intravenous verapamil. (Mean $\pm$ s.e. mean, subject 4 excluded. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$)

Oral verapamil (120 mg)			Intravenous verapamil (0.1 mg/kg)		
Time (min)	HR (beats/min)	PR (ms)	Time (min)	HR (beats/min)	PR (ms)
30	-2.8 ± 3.0	1.8 ± 4.8	5	7.0 ± 1.6	22.0** ± 4.3 **
60	0.6 ± 4.4	23.8* ± 6.3	10	2.4 ± 2.0	22.6*** ± 2.7
90	-0.6 ± 2.4	25.6* ± 6.3	20	1.4 ± 1.9	21.4** ± 3.2
120	-0.2 ± 1.8	24.6* ± 5.8	30	4.2 ± 3.6	16.4*** ± 1.4
150	-2.6 ± 2.5	26.3* ± 6.1	60	1.2 ± 3.9	14.4** ± 2.3
180	-2.6 ± 2.2	17.0 ± 4.1			

Results

The mean plasma concentrations of verapamil after intravenous administration to the six volunteers are plotted in Figure 1. Norverapamil was detectable only after the oral dose and the mean plasma levels of verapamil and metabolite after this dose are shown in Figure 2.

After intravenous administration the plasma level of verapamil declined biexponentially, the mean distribution half-life (α) being 8.5 min and the mean elimination half-life (β) 2.0 h. After oral administration the plasma half-life of verapamil was longer 2.7 h but this difference was not statistically significant. The elimination half-life of norverapamil ranged from 3.6 to 7.3 h with a mean of 4.6 h.

The volume of distribution of verapamil in the subjects was high, about 112 l, consistent with the high lipid solubility of the drug. Overall, the mean bioavailability of the oral dose was 22% and ranged between 17.1 and 29.1%. The pharmacokinetic parameters for all six subjects are given in Table 1.

PR interval was increased significantly in five of the subjects for up to 60 min after the intravenous dose, and for between 60 and 180 min after the oral dose. Changes in PR interval are given in Table 2. One subject (No. 4) developed Wenckebach type second degree A-V block after both treatment periods. After oral administration, the percentage change in PR interval correlated significantly with the log plasma level of verapamil (Figure 3, $r = 0.732$, $P < 0.001$) but not with the log plasma level of the metabolite norverapamil ($r = 0.078$, $P > 0.7$). Subject 4 was excluded from this analysis.

Figure 3 Percentage change in PR interval correlated with log plasma verapamil concentration after oral dose ($r = 0.732$, $P < 0.001$).

Discussion

The low oral bioavailability of verapamil seen in this study reinforces the clinical observation that much larger doses of verapamil are required orally than intravenously to produce a therapeutically similar result (Krikler & Spurrell, 1974).

The half-life of verapamil in this study is shorter

than previously reported by Schomerus *et al.* (1976), 4.4 h and Koike *et al.* (1979), 4.1 h. However, the subjects in both these previous studies were much older, and in the latter study the non-specific spectrofluorimetric method used for the analysis of plasma verapamil may have been biased by the longer half-life of norverapamil.

As a potent calcium antagonist the useful effect of verapamil is to impair conduction in the calcium dependent cells of the atrio-ventricular node, which are responsible for the major delay of the PR conduc-

tion in the conventional electrocardiogram. Figure 3 demonstrates a clear relationship between this prolongation of the PR interval and the plasma verapamil concentration. The lack of significant correlation between the change in PR interval and norverapamil levels suggests that the metabolite does not contribute to the therapeutic action of the drug in man.

The authors wish to thank Abbott Laboratories, U.K. for their financial support.

References

- HARAPAT, S.R. & KATES, R.E. (1980). High performance liquid chromatographic analysis of verapamil. *J. Chromatog.* **181**, 484–489.
- KOIKE, Y., SHIMAMURA, K., SHUDO, I. & SAITO, H. (1979). Pharmacokinetics of verapamil in man. *Res. Comm. Chem. Path. Pharmac.*, **24**, 37–47.
- NAYLER, W. & KRIKLER, D. (1974). Verapamil and the myocardium. *Postgrad. med. J.*, **50**, 441–446.
- SCHOMERUS, M., SPIEGELHALDER, B., STIEREN, B. & EICHELBAUM, M. (1976). Physiological disposition of verapamil in Man. *Cardiovascular Res.*, **10**, 605–612.
- KRIKLER, D. & SPURREL, R.A.J. (1974). Verapamil in the treatment of paroxysmal supraventricular tachycardia. *Postgrad. med. J.*, **50**, 447–453.

(Received September 23, 1980)