Pharmacokinetics and pharmacodynamics of two formulations of verapamil

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The pharmacokinetics and pharmacodynamics of sustained release verapamil were compared with the conventional formulation in 10 healthy adult volunteers after single and multiple dosing. The mean time of maximum plasma concentrations of verapamil were significantly prolonged and the absorption rate constants significantly reduced after sustained release verapamil on both day 1 and day 10. On day 10 there was no significant difference between formulations in the relative bioavailability of verapamil. However, the area under the plasma concentration-time curve and maximum concentration ($C_{\max}$) for both formulations increased significantly with repeat dosing. On day 10, the difference in $C_{\max}$ between formulations was significant. The day 10 mean peak/trough plasma verapamil concentration ratio was significantly less following the sustained release dose form. The mean PR interval was significantly prolonged by both formulations on day 1 and day 10. There were no differences between formulations other than a significantly longer PR interval following the conventional formulation 2 h after dosing on day 10.

Keywords verapamil sustained release pharmacokinetics pharmacodynamics bioavailability

Introduction

Verapamil is a calcium channel blocking agent used in the treatment of angina pectoris, hypertension and supraventricular tachycardia. It has a short plasma half-life of approximately 2–7 h (McAllister & Kirsten, 1982; Schomerus *et al.*, 1976). A sustained release formulation is desirable if the drug is to be used in a once daily regimen. The present study was designed as a pharmacokinetic and pharmacodynamic evaluation of such a formulation after single and multiple dosage in healthy volunteers.

Methods

Twelve normotensive healthy drug-free volunteers (six male, six female, aged 20–48 years) within 20% of ideal body weight, participated in

the study. The protocol was approved by Guy's Hospital Ethics Committee and written consent was obtained.

One group of six volunteers received sustained release verapamil (Securon® SR) 240 mg daily for 10 days, while the second group was given conventional verapamil (Securon®) 120 mg once on day 1 of the study and then twice daily for the remaining 9 days. The second dose of sustained release verapamil was given 30 h after the initial dose. Thereafter, dosing of sustained release verapamil was 24 hourly at 08.00 h. After a 12 day washout, volunteers were crossed over to the alternative regime. Pharmacokinetics and pharmacodynamics were assessed on day 1 and day 10 of each treatment.

On day 10 of conventional verapamil, treatment was given twice daily, the final dose being

taken immediately after the 12 h blood sample. PR intervals and heart rates were measured blind from the 12 lead ECG (lead II) and plasma verapamil concentrations were determined by the method of Cole *et al.* (1981). The area under the plasma verapamil concentration-time curve was calculated by the trapezoidal method, and pharmacokinetic variables were determined by the method of Johnston & Woollard (1983).

Unless otherwise indicated, statistical comparisons were made using Student's *t*-test for paired data. Mean $\pm$ s.d. values are given.

Results

The lower limit of detection for the verapamil assay was 2 ng ml^{-1} with coefficients of variation of 4.4% at 5 ng ml^{-1} and 1.2% at 200 ng ml^{-1} . Pharmacokinetic and pharmacodynamic analyses of data were performed on 10 volunteers who completed the trial. One of the original 12 volunteers was withdrawn after the first dose of sustained release verapamil because of second degree heart block 4 h after dosing. One further volunteer was excluded from the final analysis because of poor compliance. Minor side-effects reported (mainly intermittent headache on pharmacokinetic days only) were thought to be due to caffeine withdrawal rather than the test drug. The pharmacokinetic variables for both formulations after the first dose and following 10 days of treatment are given in Table 1 and the mean plasma verapamil concentration-time profiles in Figure 1.

On both test days (day 1 and day 10), the $C_{\max}$ was significantly lower after sustained release

Figure 1 (a) Day 1 mean ($n = 10$) plasma verapamil concentration after the first dose of conventional verapamil 120 mg (●) and sustained release verapamil 240 mg (■). There were statistically significant differences ($P < 0.05$) in plasma concentrations between treatments at all time points other than at 0 h, 3 h, and 4 h. (b) Day 10 mean ($n = 10$) plasma verapamil concentration after repeat dosing with conventional verapamil 120 mg twice daily (●) and sustained release verapamil 240 mg once daily (■). There were statistically significant differences ($P < 0.05$) in plasma concentrations between treatments at all time points other than at 0 h, 3 h, 4 h, 14 h, 24 h and 30 h.

Table 1 Pharmacokinetic variables (mean $\pm$ s.d., $n = 10$) after the first dose and 10 days of administration of two formulations of verapamil

Variables	Conventional verapamil		Sustained release verapamil	
	120 mg once daily (day 1)	120 mg twice daily (day 10)	240 mg once daily (day 1)	240 mg once daily (day 10)
Concentration at 0 h (ng ml ⁻¹)	—	40.1 $\pm$ 18.1	—	43.7 $\pm$ 15.6
Concentration at 12 h (ng ml ⁻¹)	6.1 $\pm$ 2.6	27.8 $\pm$ 10.5*	37.4 $\pm$ 14.7	75.7 $\pm$ 32.4*
$C_{\max}$ (ng ml ⁻¹)	123 $\pm$ 43	272 $\pm$ 117*	76 $\pm$ 40	165 $\pm$ 73*
$t_{\max}$ (h)	1.05 $\pm$ 0.28	1.05 $\pm$ 0.37	6.7 $\pm$ 3.1	5.6 $\pm$ 2.4
k_a (h ⁻¹)	2.6 $\pm$ 0.69	3.78 $\pm$ 3.53	0.49 $\pm$ 0.28	0.42 $\pm$ 0.28
$t_{1/2}$ (h)	5.8 $\pm$ 2.6	6.0 $\pm$ 1.8	13.7 $\pm$ 6.5 ¹	12.1 $\pm$ 3.3 ¹
AUC (ng ml ⁻¹ h)	450 $\pm$ 130 ²	1107 $\pm$ 411 ^{3*}	1206 $\pm$ 434 ²	1909 $\pm$ 676 ^{3*}

1: Apparent terminal elimination half-life data; 2: AUC_(0-∞); 3: AUC_{ss} = AUC_(0-24 h).

* $P < 0.01$ relative to day 1.

verapamil ($P < 0.01$). Also, the day 1 and day 10 verapamil absorption rate constants were significantly reduced ($P < 0.02$). The bioavailability of verapamil from the sustained release dose form relative to the conventional formulation was 132% on day 1 ($P < 0.05$) and 92% on day 10 ($P > 0.1$). There was a significant ($P < 0.01$) increase in bioavailability ($AUC_{ss}/AUC_{(0-\infty)}$) of each formulation between day 1 and day 10. There was no significant difference in bioavailability between formulations on day 10. After 10 days, the mean peak/trough ratio was 11.04 for conventional verapamil and 4.46 for sustained release verapamil ($P < 0.01$, non-parametric sign test).

There were no significant differences ($P > 0.05$) in the mean pre-dosing PR intervals on any of the four study days. Statistically significant PR prolongations occurred on all four study days, but the only difference between treatments was a longer PR interval on day 10 2 h after the morning dose of conventional verapamil 120 mg twice daily ($P < 0.01$ by two way analysis of variance).

Discussion

The plasma concentration-time profiles suggest that drug release from sustained release verapamil was suitably modified and that the peaks and troughs of the conventional verapamil formulation were avoided, thus conferring the benefit of a possible reduction in side-effects, as well as avoiding the need for multiple daily dosage.

The study was performed in healthy volunteers and, as shown previously, no change in plasma verapamil half-life following multiple dosing with the conventional tablet could be demonstrated (Eichelbaum & Somogyi, 1984). On day 10 of administration of the conventional tablet, the study design limited blood sampling to the 12 h dosage interval after the morning dose and it could be argued that this period was too short for an accurate determination of half-life. In patients, repeat dosing has led to a

significant increase in the plasma verapamil half-life (Freedman *et al.*, 1981; Shand *et al.*, 1981; Schwartz *et al.*, 1982). Both formulations led to an increase in verapamil AUC on repeat dosing and it has been suggested that this effect results from impaired clearance or, less likely, a further distribution of verapamil into deeper tissue compartments during repeat dosing (Schwartz *et al.*, 1985).

On day 10 markedly different plasma concentrations of verapamil were found at 2 h and at 12 h after the 08.00 h and 20.00 h doses of conventional verapamil. This diurnal effect has been suggested for other drugs (Guisson *et al.*, 1983), and could reflect the effect of food (Woodcock *et al.*, 1986), hepatic blood flow (Woodcock *et al.*, 1981a,b) or posture (Daneshmend *et al.*, 1981) on the pharmacokinetic profile.

Verapamil-induced changes in PR interval are significantly greater in the young than in older individuals (Abernethy *et al.*, 1985). Since hypertensive patients tend to be older than the group of healthy volunteers studied, the small but statistically significant time-related changes on each study day found in this investigation may not be applicable to patients. The only difference of possible clinical importance was found on day 10 when the conventional verapamil formulation induced a significantly greater prolongation of the PR interval than the sustained release dose form 2 h after dosing. This suggests that safety advantages could result from use of the sustained release verapamil formulation, particularly as PR interval changes have been related to plasma verapamil concentrations (Anderson *et al.*, 1982). The smoother plasma concentration time profile with reduced peaks and troughs after sustained release verapamil may therefore represent a safety advantage for this formulation.

We conclude that plasma concentrations are well maintained with this formulation of sustained release verapamil (Securon® SR) supporting previous description of its antihypertensive efficacy (Konig & Eckardt, 1984; Pozenel, 1985; Zachariah *et al.*, 1986).

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