R-verapamil: pharmacokinetics and effects on PR interval, blood pressure and heart rate

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- 1 This study in healthy normotensive male volunteers investigated the pharmacokinetics and the effects on electrocardiographic PR interval, blood pressure and heart rate of single oral doses of the single isomer R-verapamil (250, 500 and 1000 mg) in comparison to placebo and 240 mg racemic verapamil.
- 2 After 500 and 1000 mg R-verapamil there were significant prolongations in PR interval, maximal at 1–2 h after dosing and coincident with peak plasma drug concentrations, but these were not significantly different from the maximum prolongation obtained with 240 mg racemic verapamil.
- 3 After 1000 mg R-verapamil there was a significant hypotensive effect, particularly on standing.
- 4 Single doses of 500 and 1000 mg R-verapamil produced peak plasma drug concentrations in the range 1000–3000 ng ml⁻¹. If this concentration range is appropriate for adjuvant cancer chemotherapy it can be predicted that similar steady state concentrations will occur with a dosage regimen of 300 mg 3 times daily.

Keywords R-verapamil pharmacokinetics cardiac effects

Introduction

The concomitant administration of calcium antagonist drugs such as verapamil, diltiazem and dihydropyridine derivatives (nicardipine, nifedipine, niludipine, nimodipine) has been shown to enhance the *in vitro* cytotoxicity of natural product anticancer drugs such as vinca alkaloids and anthracyclines in cancer cells exhibiting Multiple Drug Resistance (MDR) [1, 2, 3].

The detailed mechanisms underlying the development of MDR and its modulation by adjuvant drugs, such as verapamil, have not been clearly established but are thought to involve interference with an energy-dependent drug efflux pump.

For verapamil the total drug concentrations associated with enhanced cytotoxicity *in vitro* are relatively high (2–6 µM) [4]. If no account is taken of protein binding this would correspond in plasma to concentrations of 1000–3000 ng ml⁻¹ but such concentrations of verapamil are difficult to achieve *in vivo* in man without serious cardiovascular side effects, particularly depression of atrioventricular conduction. Verapamil, however, is a racemate and previous studies have shown that R-verapamil is 8–10 times less potent than S-verapamil in its effect on cardiac conduction and

prolongation of PR interval [5, 6]. In addition, following oral administration, the two isomers are subject to stereoselective first pass hepatic metabolism such that the plasma concentrations of R-verapamil are four times higher than those of S-verapamil [7]. However, as a resistance modulator, R-verapamil has been shown to have similar activity to racemic verapamil [8]. Therefore, by administering the single R-isomer it may be possible to achieve the arbitrary target concentrations *in vivo* in man with less risk of cardiovascular side effects.

The principal aim of this study was to investigate relationships between plasma drug concentrations and the pharmacodynamic effects of relatively high oral doses of R-verapamil in healthy volunteers.

Methods

Eight healthy normotensive volunteers, aged 27 ± 7 years, range 19–40 years; body weight 74.5 ± 6.5 kg, range 68–83 kg, gave written informed consent to participate in the study which had received prior approval

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from the Hospital Research and Ethics Committee. All subjects were deemed normal on the basis of routine clinical and laboratory examinations. Pre-study electrocardiographic (ECG) screening confirmed normal sinus rhythm with a PR interval not greater than 180 ms.

Subjects attended the Clinical Pharmacology Research Unit (CPRU) at weekly intervals for a series of four 24 h study days to receive single doses of placebo, 240 mg racemic verapamil and two doses of R-verapamil. The doses of R-verapamil were 250 and 500 mg in the first four subjects (group 1) and 500 and 1000 mg in the final four subjects (group 2) administered as the hydrochloride (96.6% optical purity from Knoll AG Ludwigshafen, Germany). The study design was double-blind but the randomisation was incomplete such that, in each group, the highest dose of R-verapamil was, for safety reasons, always administered as the fourth treatment, following screening (blinded) of the blood pressure, heart rate and PR interval data from the previous study days. On each study day, subjects reported to the CPRU having abstained from food, alcohol, nicotine and caffeine since 22.00 h the previous evening. An intravenous cannula was introduced for blood sampling and after 20 min recumbency baseline measurements of blood pressure, heart rate and PR interval were recorded. Following oral dosing with verapamil or placebo, along with 150 ml water, measurements of blood pressure, heart rate and PR interval were repeated at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h.

Pharmacodynamics

PR interval From a standard lead II ECG recording at a speed of 50 mm s⁻¹, the PR interval was defined as the distance between the beginning of the P-wave to the beginning of the Q-wave. Each measurement was made with the subject in the supine position following a period of not less than 20 min recumbent rest. A digitiser linked to a Nodecrest V 77-600 computer was used to calculate the PR interval from a mean of 10 consecutive cardiac cycles.

Blood pressure and heart rate Supine and erect blood pressure and heart rate were recorded in duplicate by semi-automated sphygmomanometer (Datascop Accutorr 3A, Paramus, New Jersey).

Pharmacokinetics

For both racemic and R-verapamil, plasma concentrations of verapamil and norverapamil were assayed by h.p.l.c. with fluorescence detection using the method of Cole *et al.* [9]. The interassay coefficients of variation at 50, 100 and 500 ng ml⁻¹ verapamil and norverapamil were 6.8%, 5.4% and 4.3% for verapamil and 7.6%, 6.8% and 5.1% for norverapamil. The limit for quantification of the assay was 2 ng ml⁻¹ for both drug and metabolite.

A hierarchy of models were fitted simultaneously to the verapamil and norverapamil data using an 'in house' program employing the Marquardt algorithm [10]. A three compartment model with first order input was most appropriately fitted simultaneously to the plasma

concentrations of verapamil and its metabolite, norverapamil with inverse weighting of the concentration data. The model consisted of two drug compartments with a third compartment for metabolite arising from the central drug compartment.

The area under the plasma drug concentration-time curve (AUC), peak concentration ($C_{\max}$), time to peak concentration ($t_{\max}$) and elimination half-life ($t_{1/2}$) were derived from the model parameters.

Concentration-effect modelling Plasma drug concentration-time data and the corresponding time profile of the placebo-corrected P-R interval were analysed in individual subjects using the concentration-effect modelling approach of Sheiner *et al.* [11] as applied to racemic verapamil by Schwartz *et al.* [12]. Comparisons were made of linear and $E_{\max}$ pharmacodynamic models with effect attributed solely to the parent drug and parent drug and metabolite. The most appropriate model was selected on the basis of the F ratio test applied to the residual sum of squares from the fitting procedure.

Prediction of steady state plasma verapamil concentrations Using the parameters fitted to the single dose data in each individual, a model was derived to predict steady state concentrations. The model for steady state comprised two compartments for drug with first order input from the gut and one compartment for metabolite. Predictions were based upon dosage intervals of two, three and four times daily administration. Since it is known that the clearance of racemic verapamil decreases during continued administration, the predictive model was modified to incorporate a 'correction' factor of 2.4, as suggested by Wagner *et al.* [13] on the assumption that a corresponding reduction in oral clearance would occur with the single isomer.

Prediction of steady state P-R response The predicted steady state plasma drug concentrations and the measured effect model parameters were used to simulate the anticipated steady state P-R profiles during chronic dosing of R-verapamil.

Statistical analysis Analysis of variance (ANOVA) was used to evaluate treatment and time effects for repeated measurements of blood pressure, heart rate and PR intervals. A P value of less than 0.05 was considered significant.

Results

Pharmacokinetics

Mean plasma drug concentrations after the three doses of R-verapamil and the single dose of racemic verapamil are illustrated in Figure 1 and the derived pharmacokinetic parameters for verapamil and norverapamil are summarised in Table 1. Peak plasma drug concentrations ($C_{\max}$) were achieved at about 1.5 h after dosing. There were dose related increases in $C_{\max}$ and AUC values. At the highest dose of R-verapamil (1000 mg)

Table 1 Derived pharmacokinetic parameters for verapamil and norverapamil (mean $\pm$ s.d. – except for median and range for $t_{\max}$)

	Rac-verapamil 240 mg (n = 8)	R-verapamil 250 mg (n = 4)	R-verapamil 500 mg (n = 8)	R-verapamil 1000 mg (n = 4)
<i>Verapamil</i>				
$C_{\max}$ (ng ml ⁻¹)	356 $\pm$ 128	308 $\pm$ 100	892 $\pm$ 492	2103 $\pm$ 673
$t_{\max}$ (h)	1.0 1.0–3.0	1.0 1.0–1.5	1.25 1.0–3.0	1.5 1.0–2.0
AUC (ng ml ⁻¹ h)	1679 $\pm$ 559	1707 $\pm$ 774	3974 $\pm$ 1668	11818 $\pm$ 3739
$t_{1/2}$ (h)	4.4 $\pm$ 0.9	5.6 $\pm$ 1.3	4.0 $\pm$ 0.7	5.5 $\pm$ 1.5
<i>Norverapamil</i>				
AUC (ng ml ⁻¹ h)	1307 $\pm$ 452	1203 $\pm$ 462	3551 $\pm$ 1119	8627 $\pm$ 1900

Figure 1 Mean ($\pm$ s.d.) plasma drug concentrations after 250, 500 and 1000 mg oral doses R-verapamil (∇ , $\square$, $\blacksquare$) and a 240 mg oral dose of racemic verapamil ($\blacktriangle$).

there was a suggestion of nonlinear kinetics. Thus, the mean AUC value of 11818 ng ml⁻¹ h (in the four subjects who received both 500 and 1000 mg) was about 22% greater than the value predicted from the 4835 ng ml⁻¹ h of 500 mg dose data. However, dose normalisation of the different doses failed to demonstrate any statistical differences in $C_{\max}$ and AUC. Terminal elimination half-lives ranged from 4–6 h and were not significantly different after the three different doses of R-verapamil and the single dose of racemic verapamil.

Pharmacodynamics

PR interval PR intervals were increased significantly after all doses of verapamil with maximum increases occurring between 1 and 2 h after dosing. The results for group 2 are illustrated in Figure 2. Maximum prolongations of about 38 ± 8 ms were achieved at about 1 h after dosing with both racemic verapamil and 1000 mg R-verapamil. With racemic verapamil the prolongation in PR interval started to decline towards that observed with placebo values after 4 h but with 1000 mg R-verapamil the effect persisted for the full 12 h.

Blood pressure and heart rate There were no significant changes attributable to R-verapamil in either blood pressure or heart rate in group 1.

Supine blood pressure and heart rate In group 2, supine blood pressure fell from $116/63 \pm 5/7$ mmHg to $104/58 \pm 10/9$ mmHg at 1.5 h after the 1000 mg dose of R-verapamil ($P < 0.05$ for diastolic BP).

Supine heart rate increased transiently (between 1 and 2 h) but significantly after racemic verapamil and also after 500 mg and 1000 mg R-verapamil, with maximum heart rate increments of 16 ± 4 , 13 ± 4 , 22 ± 6 beats min⁻¹ respectively, compared with placebo.

Erect blood pressure and heart rate Erect blood pressure was significantly reduced by all active treatments. The greatest reduction occurred with 1000 mg R-verapamil, at 1–5 h after dosing, with a fall to $93/53 \pm 16/6$ mmHg, as compared with $115/63 \pm 7/7$ mmHg with placebo (Figure 3).

Overall, blood pressure was significantly reduced

Figure 2 Effect of placebo ($\circ$), 240 mg racemic verapamil ($\blacktriangle$), 500 ($\square$) and 1000 mg ($\blacksquare$) of R-verapamil on cardiac conduction (mean $\pm$ s.d. PR intervals).

Figure 3 Effect of verapamil on erect systolic blood pressure (upper panel) and erect heart rate (lower panel) (placebo $\circ$; 240 mg racemic verapamil $\blacktriangle$; 500 $\square$ 1000 mg $\blacksquare$ R-verapamil).

after 1000 mg R-verapamil, compared with 240 mg racemic verapamil and also with 500 mg R-verapamil.

Erect heart rate was transiently but significantly increased after 1 and 2 h (Figure 3) by both the 500 mg and 1000 mg doses of R-verapamil. The maximum increases, at 1 h after dosing, were 18 ± 3 beats min^{-1} after 500 mg and 20 ± 5 beats min^{-1} after 1000 mg R-verapamil.

Tolerability Flushing was the most commonly reported side event occurring in 6/8 subjects who received 500 mg R-verapamil and in 4/4 subjects who received 1000 mg R-verapamil. Gastrointestinal upset was the second most frequently reported adverse event with epigastric pain starting 30 min after dosing and lasting up to 2 h reported by all four subjects who received 1000 mg R-verapamil. Symptomatic, postural hypotension was reported by three subjects; one after 500 mg and two after 1000 mg R-verapamil.

Concentration-effect relationships

The concentration-effect relationships for the placebo-corrected P-R profiles for both racemic and R-verapamil were most appropriately characterised in all individuals by linear relationships with effect attributed to parent drug alone and with the following parameters:

(a) responsiveness – the slope of the linear relationship between concentration and effect, with units of milliseconds per ng ml^{-1}

(b) k_{eo} – which is the first order rate constant characterising the temporal discrepancy between the concentration-time and effect-time profiles.

After 250 mg R-verapamil the placebo-corrected changes in PR interval were small and inconsistent such that no satisfactory fits were obtained to the data in any of the individuals studied. On average, responsiveness was similar for 500 mg and 1000 mg R-verapamil at 0.024 ± 0.007 and 0.022 ± 0.008 ms per ng ml^{-1} , respectively, but significantly different from the value of 0.12 ± 0.07 ms per ng ml^{-1} for racemic verapamil ($P < 0.0001$). Additionally, responsiveness to R-verapamil

Figure 4 Representative fits of the placebo corrected PR profiles following 500 mg ($\square$) and 1000 mg ($\blacksquare$) R-verapamil in three subjects representing the best (a), and 'average' (b) and the worst (c) fitted data sets.

was consistent within individuals with no evidence of any dose-dependency (mean difference of $0.004 (\pm 0.005)$ ms per ng ml^{-1}). The statistical power of the study was greater than 90% to detect a 20% difference in responsiveness.

The value of the rate constant k_{eo} was similar following all doses of verapamil. After racemic, 500 mg and 1000 mg R-verapamil the mean values were 0.8 ± 0.5 , 0.7 ± 0.4 and 0.9 ± 0.6 h^{-1} respectively.

Representative fits for three subjects at 500 mg and 1000 mg R-verapamil are shown in Figure 4. These represent the best, the worst and an 'average' fit.

Simulations

Plasma drug concentration-time profiles Using individual values of the pharmacokinetic parameters derived from the single dose studies, the steady state plasma drug and metabolite concentrations were predicted for several dosage regimens. Data for 300 mg three times daily and 500 mg four times daily regimens are shown in Figure 5.

Predicted peak plasma drug concentrations at steady state were in the range 1800–3000 ng ml^{-1} following 500

Figure 5 Predicted steady state plasma verapamil concentrations during dosage with R-verapamil (a) 300 mg three times daily (◆) and (b) 500 mg three times daily (●) [--- plasma norverapamil concentrations].

Figure 6 Mean predicted prolongation of P-R interval (relative to placebo) at steady state during continuous administration of R-verapamil (300 mg three times daily ◆; 500 mg three times daily ●).

mg R-verapamil given two to four times daily. Predicted plasma concentrations of norverapamil were similar to those of the parent drug and concentrations above 1000 ng ml⁻¹ were maintained for 4 h or more.

Change in PR-interval Placebo-corrected changes in PR interval at steady state were predicted using single dose effect model parameters and the pharmacokinetic model parameters allowing for the change in drug clearance on continuous dosing. Mean changes in P-R interval during 300 mg and 500 mg R-verapamil three times daily regimens are shown in Figure 6. The peak predicted P-R changes occurred 2 h after dosing and, on average, did not exceed 30 ms with the 300 mg three times daily or 50 ms with the 500 mg three times daily regimens. The highest predicted P-R change in an individual was 54 ms which is less than the peak change observed in some individuals with acute administration of 1000 mg R-verapamil.

Discussion

These results show that single doses of 500–1000 mg R-verapamil produce peak plasma verapamil concentrations which are 2 to 5 times higher than with 240 mg racemic verapamil but without producing serious cardio-

toxicity. Both of these doses produced prolongations of the PR interval which were significantly different from placebo but not significantly different from that associated with 240 mg of racemic verapamil. None of the subjects had any degree of A-V block. In contrast, a similar dose of racemic verapamil (9 µg kg⁻¹ min⁻¹ intravenously) was reported by Ozols *et al.* [14] to produce comparable plasma drug concentrations but in association with a severe and unacceptable degree of cardiac toxicity. However, significant falls in blood pressure, particularly on standing, occurred with 1000 mg R-verapamil at approximately the time of maximum plasma drug concentrations. Furthermore, the reported side effects, especially with the 1000 mg dose, included epigastric discomfort which may be either a systemic effect or the result of local gastric irritation caused by the large number of tablets used (200 mg × 5).

The pharmacokinetics of racemic and R-verapamil were consistent with those reported in previous studies [6, 15, 16]. However, after single 500 and 1000 mg doses of R-verapamil peak plasma drug concentrations were relatively short-lived, whereas for most therapeutic purposes a multiple dosing regimen would be employed and plasma concentrations would be more sustained. Thus, it was predicted that a regimen of 500 mg R-verapamil four times daily would produce peak plasma verapamil concentrations at the top of the target range i.e. 3000 ng ml⁻¹. Simplistic application of this target range to adjuvant cancer chemotherapy takes no account of the *in vitro* data which suggest that when both verapamil and norverapamil are used in relatively low concentrations, each of 2 µM, the cytotoxic effect is maximal and equivalent to that of 6 µM racemic verapamil [4]. Thus, to achieve analogous total concentrations *in vivo* requires that R-verapamil may be administered in lower doses to produce a combined verapamil and norverapamil concentration of about 2000 ng ml⁻¹, with a further reduction in the likelihood of cardiovascular side effects. Since norverapamil appears to have only approximately 10% of the potency of the parent compound with respect to coronary vasodilatory activity [17] it is unlikely to exert major haemodynamic effects over the range of concentrations required. A further consideration relevant to drug safety, particularly since cancer is common in middle aged and elderly subjects, is that there is evidence that the elderly

are less susceptible to the negative effects of verapamil on A-V conduction [16].

In conclusion, it is not clear whether or not the range of total verapamil concentrations required *in vitro* can be directly extrapolated to *in vivo* conditions. However, the principal aim of this study was a comparative assessment of cardiotoxic effects and it was not within its scope to investigate or speculate about potentially con-

founding factors such as protein binding, drug penetration into neoplastic tissues and pharmacokinetic interactions with cytotoxic drugs. Nevertheless, these results lend some support to the proposition that R-verapamil is more appropriate than racemic verapamil because relatively high plasma total drug concentrations can be achieved, without serious cardiovascular side effects.

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