Once a day verapamil in essential hypertension

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- 1 Pharmacodynamic and therapeutic studies with a new slow release 240 mg verapamil formulation were performed in a total of 73 patients with essential hypertension (WHO I–II, diastolic ≥ 100 mm Hg).
- 2 Chronic administration of slow release 240 mg verapamil, one or two tablets in the morning, resulted in 24 h plasma concentration profiles with trough levels > 40 ng ml⁻¹ in 14 of 16 patients and good 24 h blood pressure control. There was no correlation between plasma verapamil or norverapamil concentration and blood pressure response.
- 3 Monotherapy with slow release verapamil was well tolerated and resulted in good blood pressure control (≤ 95 mm Hg diastolic) in 46 of the 57 patients. Responses were best in older patients and those with low plasma renin or higher control blood pressure.
- 4 Slow release 240 mg verapamil given once daily is a simple and effective regimen.

Keywords calcium antagonist slow release verapamil plasma concentrations monotherapy

Introduction

Influx through the slow calcium channel plays a key role in the regulation of intracellular calcium, the contraction of vascular smooth muscle cells and thereby arteriolar tone (Kuriyama *et al.*, 1982). Calcium channel entry blockers which have been used effectively for other cardiovascular disorders have recently generated widespread interest for the treatment of hypertension. This delayed introduction may be partly due to the calcium antagonists' short half-life and the low systemic bioavailability which can be explained by marked first pass liver metabolism, particularly in the case of verapamil (Eichelbaum *et al.*, 1979; Shand *et al.*, 1981).

Despite great interindividual variability, serum verapamil concentrations in patients treated with a twice daily administration of a slow release preparation of 120 mg verapamil, which exceeded a critical lower limit for peripheral

vasodilation, were associated with good blood pressure control (Schütz *et al.*, 1982). The antihypertensive efficacy of slow release verapamil was indirectly correlated to the patient's age; paralleled the blood pressure responses observed with diuretics (Bühler *et al.*, 1982). The efficacy of antihypertensive drug treatment depends on the patient's compliance. This might be improved by a once daily regimen. We therefore investigated the antihypertensive effectiveness of the new 240 mg verapamil slow release formulation for a once daily administration.

Methods

We have investigated 57 patients with essential hypertension (WHO I and II), 22 females and 35 males, age 23–83 (mean 56.6) years, with a casual

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diastolic pressure of 100–120 mm Hg (Korotkoff V) measured on at least three different occasions during a 4 week placebo period. Blood pressures were recorded in the sitting position from both arms using a standard mercury sphygmomanometer; the mean values were used for analysis. Mean blood pressure was calculated as diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressure. Heart rate and body weight were recorded at each visit. Plasma renin activity was determined in the sitting position and related to the sodium excretion rate (Brunner *et al.*, 1972). Verapamil in a new slow release 240 mg preparation was started orally in the morning. Aiming at a diastolic pressure ≤ 95 mm Hg doses were increased up to a maximum of 480 mg twice daily when necessary. Duration of treatment varied between 31 and 533 (mean 141) days.

Further pharmacodynamic studies were performed in 16 patients. In eight a new slow release verapamil 240 mg given once daily was compared with the marketed verapamil retard 120 mg given twice daily. In another eight, previously titrated to higher doses, slow release verapamil 240 mg was given twice daily and compared to a single morning dose of 480 mg (two tablets of slow release 240 mg verapamil). The 16 patients were treated for at least 4 weeks with their regular daily maintenance dose of slow release 240 or 480 mg verapamil. In the morning of the pharmacodynamic study, patients were fasting and were studied 12 or 24 h after the

last verapamil dose, respectively. After a blood sample was drawn (trough level) and baseline blood pressure was recorded, the oral verapamil dose was given and further blood samples were collected and blood pressure measured after 2, 4, 8, 12 and 24 h.

Verapamil and norverapamil concentrations were determined with high pressure liquid chromatography (Harapat & Kates, 1980). In our laboratory this method has a coefficient of variation of less than 5% in a concentration range from 10 to 800 ng ml⁻¹.

Analysis of variance, (ANOVA), linear regression analyses and ANOVA for repeated measurements were performed. Levels of significance were adjusted for multiple comparisons using the method of Bonferroni (Dixon *et al.*, 1983).

Results

Administration of slow release 240 mg verapamil in a mean dose of 446.3 ± 1.1 mg resulted in an average sitting blood pressure reduction from $173.4 \pm 2.4/107.5 \pm 0.9$ to $149.1 \pm 1.8/88.0 \pm 1.2$ mm Hg ($P < 0.01$), and in 46 of the 57 patients to a target diastolic pressure of ≤ 95 mm Hg. There was a small reduction in heart rate from 78.8 ± 1.1 to 76.8 ± 1.8 beats min⁻¹ ($P < 0.05$); body weight remained unchanged.

Age and pretreatment plasma renin activity were negatively correlated ($r = -0.691$,

Figure 1 Relationship between per cent change in mean blood pressure during long-term treatment with verapamil and (a) the patient's age ($n = 57$, $r = 0.422$, $P < 0.01$) and (b) pretreatment plasma renin activity ($n = 57$, $r = 0.460$, $P < 0.01$).

$P < 0.01$). Pretreatment systolic but not diastolic blood pressure was correlated positively with the patient's age ($r = 0.472$, $P < 0.01$) and negatively with the pretreatment plasma renin activity ($r = -0.409$, $P < 0.01$). The per cent change in systolic, diastolic and mean blood pressure with slow release 240 mg verapamil was weakly correlated with the patient's age ($r = 0.361$, $P < 0.05$, $r = 0.435$, $r = 0.422$, both $P < 0.01$) and negatively with pretreatment plasma renin activity ($r = -0.429$, $r = -0.442$, $r = -0.460$, all $P < 0.01$) (Figure 1). Stratification of patients into three age groups showed a greater per cent fall in diastolic pressure in patients older than 60 years as compared to those below 40 years ($-20.2 \pm 1.2\%$, $n = 22$ vs $-9.2 \pm 4.3\%$, $n = 5$, $P < 0.05$). Patients classified as having low renin

essential hypertension exhibited a greater per cent fall in diastolic blood pressure with slow release 240 mg verapamil as compared to those with high plasma renin activity ($-19.8 \pm 2.1\%$, $n = 22$ vs $-6.0 \pm 2.6\%$, $n = 5$, $P < 0.01$). The 46 patients achieving the target diastolic pressure of ≤ 95 mm Hg (responders) were significantly older (59.8 ± 1.2 years vs 43.3 ± 3.2 years, $P < 0.01$) and exhibited a lower plasma renin activity when compared to the 11 non responders (1.4 ± 0.13 vs 3.1 ± 0.48 ng ml⁻¹ h⁻¹, $P < 0.01$).

Verapamil and norverapamil concentrations and blood pressure profiles over a 24 h period in eight patients treated with 240 mg slow release verapamil and another eight treated with 480 mg verapamil daily are shown in Figure 2. Adequate and similar blood pressure control was achieved

Figure 2 Mean $\pm$ s.e. mean ($n = 8$) blood pressure 24 h profile and mean $\pm$ s.e. mean ($n = 8$) verapamil and norverapamil serum concentration (ng ml⁻¹) curves in 16 patients after a once (○-○) or twice (△-△) daily dose of a) 240 mg or b) 480 mg slow release verapamil; using the 120 mg retard formulation or a new slow release 240 mg formulation.

with twice a day and once a day administration of both previously titrated doses; 24 h values were higher during once a day dosing. Although the serum concentration profiles of verapamil and norverapamil tended to be smoother with a twice daily administration, the serum concentration of the once daily administration was not significantly different from the twice a day regimen at 240 and 480 mg dosing. Metabolite concentrations were higher than those of the parent drug at all times. Individual verapamil serum concentration curves showed a marked variability which was greater with the 480 mg daily dose. There was no correlation between verapamil or norverapamil concentrations and blood pressure response.

Discussion

The new slow release preparation 240 mg verapamil alone in an average daily dose of 446.3 ± 1.1 mg lowered diastolic blood pressure to ≤ 95 mm Hg in 46 of the 57 patients with essential hypertension. This new preparation proved to have sufficient duration of action to allow a once daily administration thereby simplifying treatment and potentially improving patient compliance. There was no relationship between verapamil concentrations or their changes and blood pressure responses during the 24 h of observation. This lack of concentration-response relationship might be explained by the observation that even after 24 h, drug levels usually remained above 100 ng ml^{-1} probably exceeding a critical lower limit for antihypertensive effectiveness. Another contributing factor may be the relatively high norverapamil concentration since in animal experiments this metabolite showed vasodilatory potency of about half that observed with unchanged verapamil (Neugebauer, 1978). Standard verapamil has a short half-life of 3–6 h and a low systemic bioavailability of 10–20% but this tends to be higher with chronic treatment (Shand *et al.*, 1981). The present slow release formulation appears to provide a 24 h blood pressure control.

The lack of a serum concentration-response relationship might indicate that the good antihypertensive effects do not seem to depend on plasma concentrations but to some degree on the cardiovascular reactivity of the individual patient. This is supported by verapamil's greater antihypertensive effectiveness in patients with

older age and lower plasma renin activity which confirms previous studies, some performed with other calcium antagonists as well (Kiowski *et al.*, 1985). With older age, β -adrenoceptor mediated cardiovascular effects tend to be blunted and α -adrenoceptor mediated vasoconstriction relatively prevails. Hence, in patients with low plasma renin activity and older age α -adrenoceptor blocking drugs and particularly calcium antagonists have been found to be more effective (Bühler & Bolli, 1985), in part because cardiovascular homeostatic counter-regulation in response to the fall in blood pressure is less vigorous (Kiowski *et al.*, 1983).

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