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Pharmacokinetics and pharmacodynamics of verapamil in combination with atenolol, metoprolol and propranolol

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1 Treatment of angina pectoris with β-adrenoceptor antagonists and verapamil in combination is effective and increasingly common. The study reported here was designed to show whether the pharmacokinetics of verapamil are influenced by concurrent treatment with three different β-adrenoceptor blockers, and whether there is any pharmacodynamic interaction between these drugs.

2 Twelve healthy volunteers (eight men, four women) aged 21–25 years and weighing 48–82 kg consented to participate in the study. They received verapamil 50 mg three times daily for four 1-week periods, each separated by a 1 week 'washout' period. During three of the four treatment periods, the subjects took either atenolol 100 mg once daily, metoprolol 100 mg twice daily or propranolol 80 mg twice daily; in the remaining period they took verapamil alone.

3 The concentration/time curve and plasma elimination half-life of verapamil and norverapamil, its major metabolite, were not influenced by 1 weeks co-administration atenolol, metoprolol or propranolol.

4 As expected, co-administration of each of the β-adrenoceptor blockers significantly reduced exercise heart rate when compared with verapamil alone.

Keywords atenolol metoprolol pharmacology propranolol verapamil

Introduction

Treatment of angina pectoris with β-adrenoceptor antagonists and verapamil in combination is effective and increasingly common (Lessem, 1983; Winniford *et al.*, 1983). Furthermore, it has recently been suggested that verapamil and other calcium antagonists may be useful in the treatment of older patients with hypertension (Bühler *et al.*, 1983). However, pharmacokinetic interaction might be expected to occur between verapamil and the β-adrenoceptor antagonists propranolol and metoprolol, since all these drugs are lipophilic and show substantial first-pass extraction after oral administration. An interaction of this kind between atenolol and verapamil would not be predicted, since atenolol is relatively hydrophilic. The study reported here was designed to show whether the pharmacokinetics of verapamil are influenced by concurrent treatment with each of three different β-adrenoceptor blockers, and whether there is any pharmacodynamic interaction between these drugs. The trial was an open, within-subject, randomised and balanced crossover comparison of propranolol, metoprolol and atenolol treatment on a background of verapamil administration. The subjects for this study were healthy young volunteers, since the effort required by the subjects was more than one could reasonably expect from patients with cardiac disease.

Methods

Twelve healthy volunteers (eight men, four

women) aged 21–25 years (weight 48–82 kg) gave their written consent to participate in the study. All were normal on clinical history and physical examination, resting and exercise electrocardiogram and on haematological and biochemical screening tests and urinalysis. They were asked to abstain from alcoholic drinks and smoking during and for 24 h before each study day.

Treatments

Subjects received verapamil 40 mg three times daily for four periods of 1 week each, separated by a 1 week wash-out period. During three of the four treatment periods, they took either atenolol 100 mg daily, metoprolol 100 mg twice daily, or propranolol 80 mg twice daily; in the remaining period they took verapamil alone. These doses were chosen to achieve equivalent degrees of β_1-adrenoceptor blockade as measured by reduction in exercise heart rate. The order of the β-adrenoceptor antagonist treatment was randomised and balanced as far as possible.

On day 1 of each week of treatment, the subjects remained in the laboratory until two hours after taking their first dose of tablets. An ECG was recorded and subjects were questioned with regard to possible adverse effects before they were allowed home. Treatments were provided in Dosett containers (Cow & Gate Ltd).

On day 8 of each week of treatment, the subjects fasted overnight before attending the Unit at 08.00 h. Pulse rate and blood pressure sitting and standing were then measured, using a Hawksley random zero sphygmomanometer and taking Phase V of the Korotkov sounds as the diastolic pressure. Venous blood samples (5 ml) were taken into lithium heparin tubes. The subjects then received their final morning dose of verapamil 40 mg, with either atenolol 100 mg, metoprolol 100 mg, propranolol 80 mg, or no β-adrenoceptor antagonist. Sets of observations and blood sampling were repeated at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h afterwards.

The subjects underwent a standard 3 min exercise test 3 h after drug administration. The Siemens Elema electrically braked bicycle ergometer was set at a load which had previously been shown to increase their heart rate to at least 155 beats/min during the last ten seconds of the 3 min exercise period. Subjects remained fasting until after the exercise test, when they were allowed normal intake but no caffeinated drinks.

Assay of plasma concentrations of drugs

Plasma concentrations of verapamil and its major metabolite norverapamil were measured 'blind' by h.p.l.c. (Cole *et al.*, 1981). Concentrations of the three β-adrenoceptor antagonists were also determined by h.p.l.c. at 3 h only. Atenolol was measured by the method of Bhamra *et al.* (1983), and propranolol by that of Holt *et al.* (1980); metoprolol was determined using a modification of the method for propranolol.

Analysis of data

Pharmacokinetic parameters were calculated by standard techniques using the STRIPE computer program (Johnston & Woollard, 1983). The significance of differences between treatments was assessed by one-way analysis of variance.

Results

A female subject was withdrawn from the study for reasons entirely unconnected with the trial, and was not replaced. Full data were therefore obtained from 11 subjects.

Plasma concentrations of verapamil and norverapamil after the four different treatments are shown in Figures 1 and 2. Individual values for the area under the plasma concentration:time curve (AUC) for verapamil and norverapamil are shown in Figures 3 and 4. Figures 5 and 6 show the individual values for plasma elimination half-life of verapamil and norverapamil. There were no significant differences between any of the treatments.

Table 1 shows the mean (or median) and range for the peak concentrations, time to achieve peak concentrations, and elimination and absorption half-lives for verapamil. There were no significant differences between the treatments with respect to these variables.

Table 2 shows the plasma concentrations of the three β-adrenoceptor blockers 3 h after the final dose.

Figures 7 and 8 show the mean values for systolic and diastolic blood pressure (standing) and heart rate (supine), after the four treatments. Results for the heart rate and blood pressure in the sitting position were very similar. Analysis of variance showed significant treatment effects for all three β-adrenoceptor antagonists with respect to standing and supine pulse rate, systolic and diastolic blood pressure.

Individual and mean values for exercise heart rates after the four treatments are shown in Figure 9. All three β-adrenoceptor antagonists significantly reduced exercise heart rate when compared with verapamil alone.

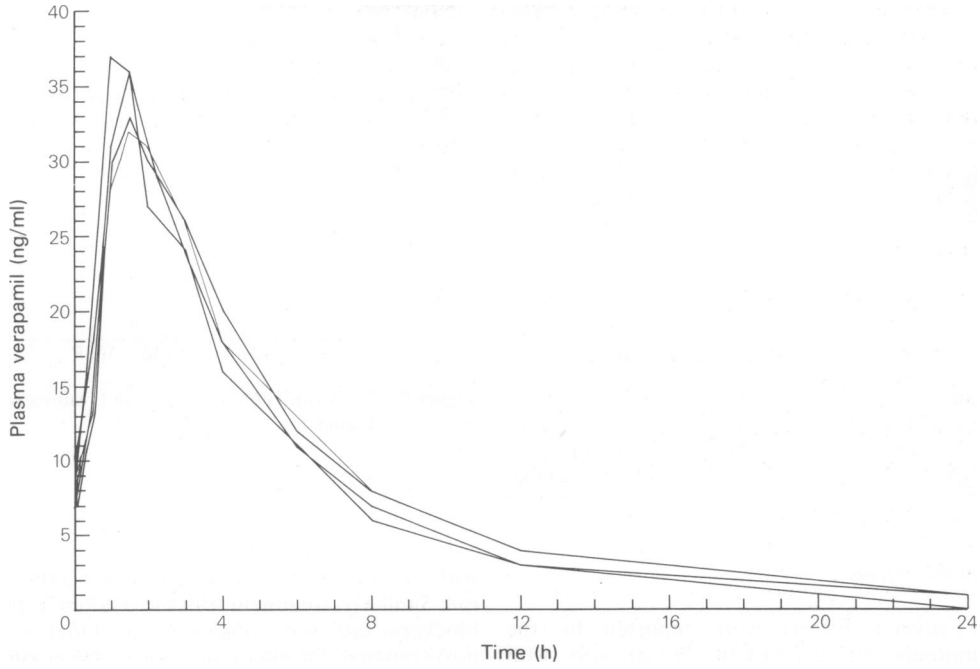

Figure 1 Mean plasma verapamil concentrations in 11 healthy subjects after 1 week of treatment with verapamil 40 mg three times daily with and without concurrent β-adrenoceptor blocker treatment. Key: the curves represent verapamil; verapamil + atenolol; verapamil + metoprolol; verapamil + propranolol. Since the curves do not differ significantly, and in the interests of clarity, no attempt has been made to label these curves.

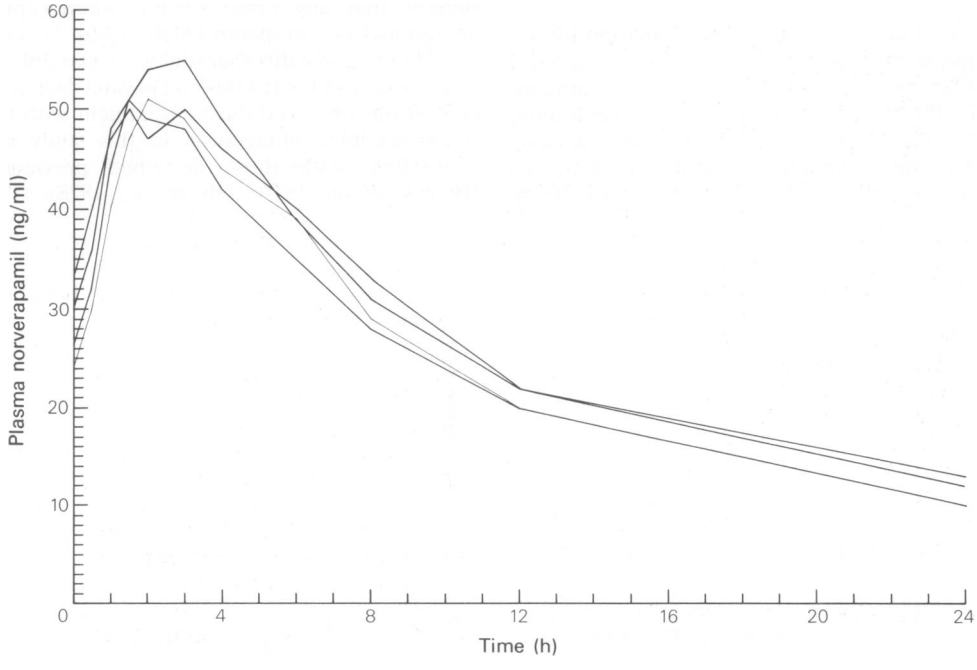

Figure 2 Mean plasma norverapamil concentrations in 11 healthy subjects after 1 week of treatment with verapamil 40 mg three times daily with and without concurrent β-adrenoceptor blocker treatment. Key as for **Figure 1**.

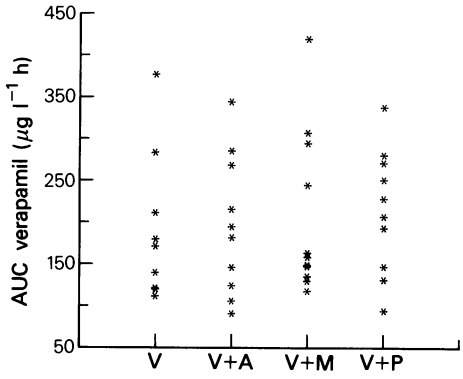

Figure 3 AUC (plasma concentration:time) for verapamil. Key: V = verapamil alone; V + A = V + atenolol 100 mg daily; V + M = V + metoprolol 100 mg twice daily; V + P = V + propranolol 80 mg twice daily.

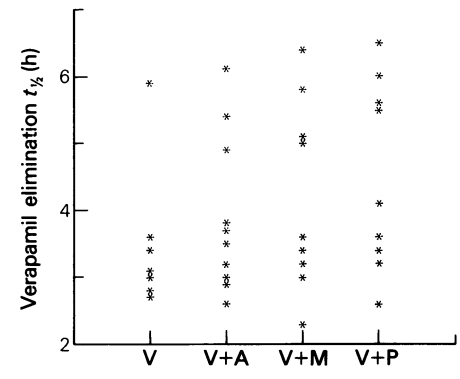

Figure 5 Verapamil elimination $t_{1/2}$ in 11 subjects. Key as for **Figure 3**.

Adverse effects

No adverse effects were reported by the volunteers or noticed by the investigators, with the predictable exception that most volunteers noticed increased fatigue during the exercise test while taking the β-adrenoceptor antagonists.

Discussion

In this study, neither atenolol, metoprolol nor propranolol had any influence on the pharmacokinetics of verapamil after 1 weeks treatment. The absorption, peak plasma concentration, area under the plasma concentration time curve and plasma elimination half-life of verapamil were not influenced by concurrent treatment with any of the three β-adrenoceptor antagonists. Similarly, treatment with the β-adrenoceptor blockers did not influence the kinetics of norverapamil, the major metabolite of verapamil. This result is unlikely to be a false negative, since there was not even a trend towards an effect of the β-adrenoceptor antagonists on verapamil kinetics. Although the marked inter- and intra-subject variability in verapamil kinetics increases the risk of a false negative result, our results strongly suggest that any effect of the adrenoceptor antagonists on verapamil kinetics must be very small compared with other sources of variability.

The exercise heart rates and plasma drug concentrations observed during treatment with the β-adrenoceptor antagonists in this study are compatible with those described previously (Brown *et al*, 1976; Oh *et al.*, 1978). The

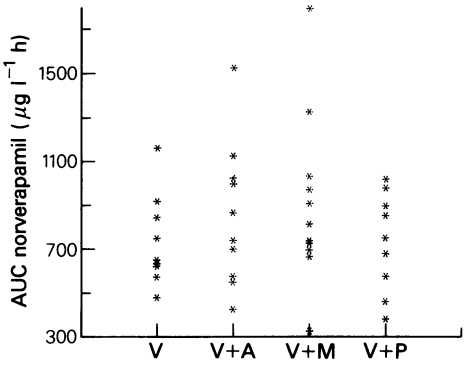

Figure 4 AUC (plasma concentration:time) for norverapamil. Key as **Figure 3**.

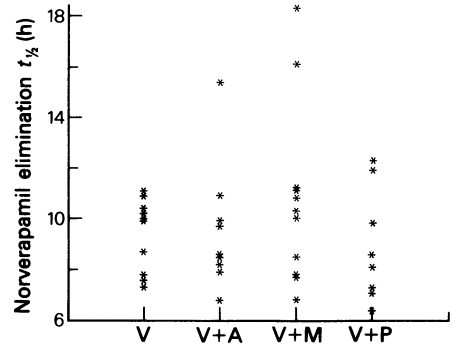

Figure 6 Norverapamil elimination $t_{1/2}$ in 11 subjects. Key as for **Figure 3**.

Table 1 Pharmacokinetic parameters for verapamil, given alone and in combination with atenolol, metoprolol and propranolol in 11 healthy subjects. Median values are shown rather than means where the distribution of the values is not normal or is not continuous.

Treatment	$t_{1/2}$ *absorption (min)*		$t_{1/2}$ *elimination (h)*		*Time to* C_{max} *(h)*		C_{max} *(ng/ml)*	
	Median	*Range*	*Mean*	*Range*	*Median*	*Range*	*Mean*	*Range*
Verapamil alone	26	14–39	3.0	2.2–5.4	1.0	1.0–2.0	41	21–84
Verapamil + atenolol	29	12–91	3.3	2.1–5.6	1.5	1.0–2.0	39	17–80
Verapamil + metoprolol	35	10–140	3.5	1.8–5.9	1.5	1.0–2.0	36	25–58
Verapamil + propranolol	33	12–160	3.9	2.1–6.0	1.5	1.0–3.0	35	23–48

Table 2 Plasma concentrations of atenolol, metoprolol and propranolol 3 h after final dose (taken with final dose of verapamil 40 mg)

Subject	*Plasma drug concentration (ng/ml)*		
	Atenolol	*Metoprolol*	*Propranolol*
1	900	240	136
3	620	661	117
4	827	442	148
5	855	446	70
6	657	562	82
7	824	265	68
8	906	654	200
9	703	376	89
10	685	362	71
11	465	593	240
12	460	389	175

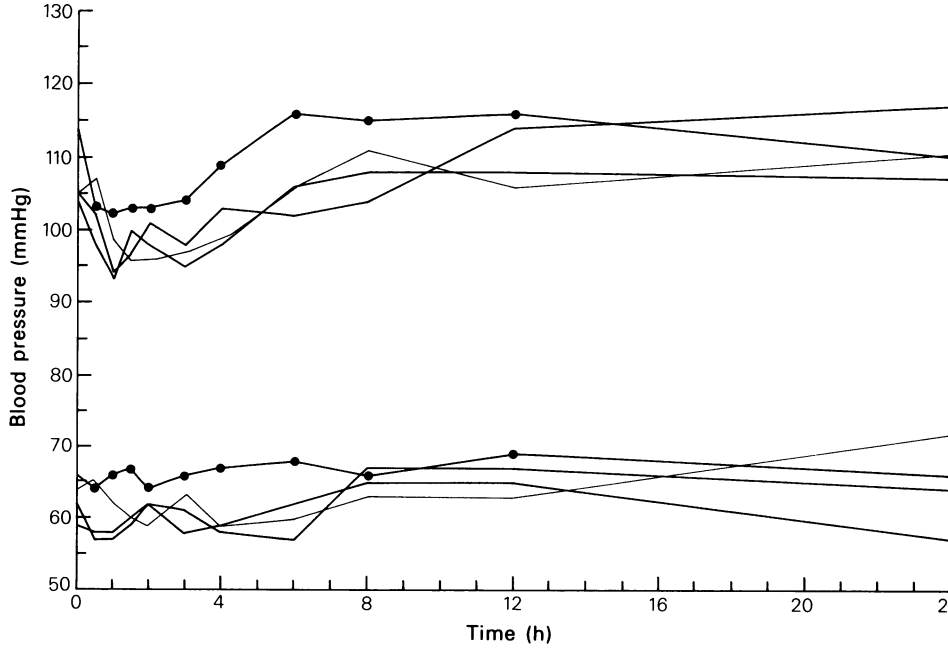

Figure 7 Mean systolic and diastolic blood pressure in erect position after final dose of verapamil alone and in combination with β-adrenoceptor blockers (n = 11). Key: verapamil + placebo (closed circles); verapamil + atenolol; verapamil + metoprolol; verapamil + propranolol. Since the latter three curves do not differ significantly, and in the interest of clarity, no attempt has been made to label these curves.

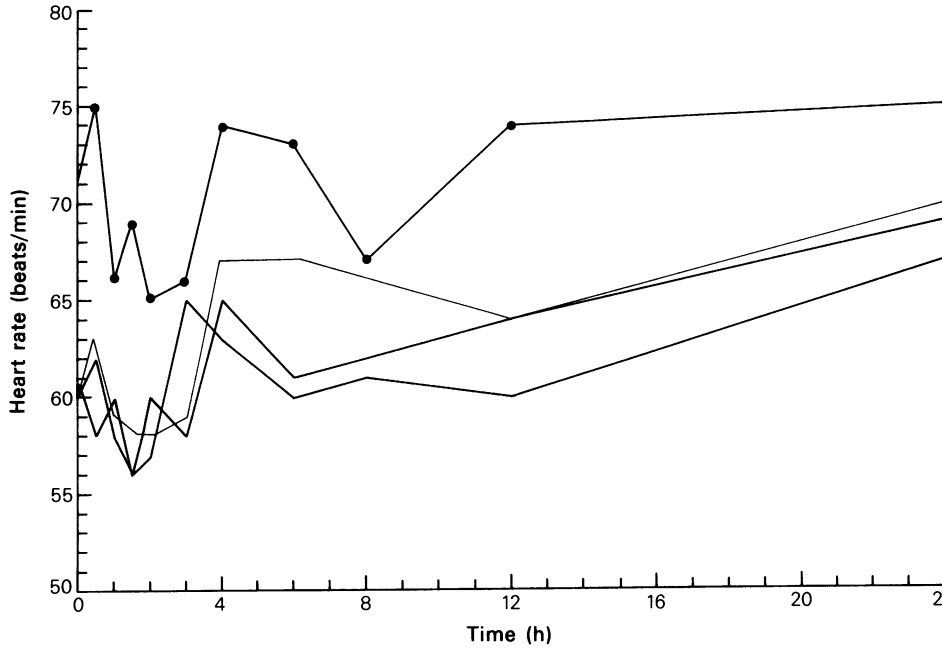

Figure 8 Mean heart rate in supine position after final dose of verapamil alone and in combination with β-adrenoceptor blockers (n = 11). Key as for **Figure 7**.

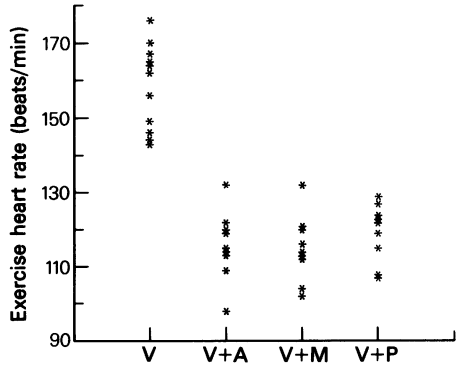

Figure 9 Exercise heart rates 3 h after final dose of verapamil alone and in combination with β-adrenoceptor blockers. Key as for **Figure 3**.

inhibition of exercise tachycardia was similar during treatment with all three β-adrenoceptor antagonists, confirming that the doses chosen produced equivalent degrees of β_1-adrenoceptor blockade. However, no conclusion can be drawn from this study with regard to the influence of verapamil treatment on the pharmacodynamics and kinetics of the β-adrenoceptor blocking drugs. Further experiments are needed to investigate this possibility.

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Group discussion

A. M. Breckenridge

Since you were investigating dynamic parameters was a washout period of 1 week sufficient?

S. J. Warrington

The parameters were actually measured 2 weeks apart, so there were 1 week washout periods before and during treatment. The study was balanced when it started, although the single drop-out will have caused slight imbalance. Order effect and carry-over effect were not apparent from the analysis of variance.

J. H. Silas

In future studies do you have any plans to use a therapeutic dose of verapamil?

S. J. Warrington

We have performed other studies using substantial doses of verapamil. The only problem is that with large doses of verapamil alone the volunteers tend to experience palpitation due to second degree A-V block. Although this condition is not serious it will cause some alarm in those volunteers who notice it. Certainly if you combine large doses of verapamil with the β-adrenoceptor blockers one would expect frequent Wenckebach phenomenon which would be disconcerting for volunteers. As a safety measure, we did on the first occasion monitor the volunteers for several hours after the first dose of the combination of β-adrenoceptor blocker and verapamil. With this low dose of verapamil, we had no such side effects.

J. H. Silas

In future verapamil studies the term 'chronic dosing' should be used to represent 3–4 weeks treatment. Some studies have shown that it may take that long to observe the full anti-anginal effect and there is some prolongation in half-life.

S. J. Warrington

In another study, we did show prolongation of half-life after 1 weeks treatment. Clearly, longer treatment periods are better, but the study tends to fall apart if it lasts longer than a few months.

K. Fox

When you repeat these studies perhaps you should consider the age of the subjects.

S. J. Warrington

It is true that our subjects were young, the problem being that it is only young subjects that can participate in such a study. The trial is strenuous and involves taking much time off work, much drug-taking, and many venepunctures. One has to accept the limitations, and obviously one should not extrapolate too far to patients with heart disease.

E. A. Sotaniemi

Do you think that body weight alone is a good measure of the body size? We have used body mass index which also depends on height. There was a good correlation between body mass index and antipyrine clearance in 200 patients.

S. J. Warrington

Body mass index may be used although surface area would perhaps be an equally good measure. However, the doses were fixed and the variance in the results was no more than one might expect with volunteers of the same size.