Br. J. clin. Pharmac. (1988), **25**, 349–357

The effect of combined therapy on the pharmacokinetics and pharmacodynamics of verapamil and propranolol in patients with angina pectoris

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1 The pharmacokinetics and pharmacodynamics of oral verapamil and propranolol were studied in patients with stable angina pectoris during chronic mono- and dual therapy.

2 The peak plasma concentrations (C_{max}) and areas under the plasma concentration-time curves (AUC) of verapamil were similar during combined treatment with propranolol (mean ± s.d.: C_{max} = 491 ± 397 ng ml^{-1}; AUC = 2075 ± 1524 ng ml^{-1} h) or atenolol (mean ± s.d.: C_{max} = 372 ± 320 ng ml^{-1}; AUC = 1985 ± 1660 ng ml^{-1} h).

3 No differences in C_{max} and AUC were observed during verapamil monotherapy (mean ± s.d.: C_{max} = 287 ± 105 ng ml^{-1}; AUC = 1375 ± 455 ng ml^{-1} h) *vs* combined treatment with propranolol (mean ± s.d.: C_{max} = 312 ± 55 ng ml^{-1}; AUC = 1566 ± 486 ng ml^{-1} h).

4 Treatment with verapamil increased the C_{max} (mean ± s.d.: 227 ± 117 *vs* 116 ± 62 ng ml^{-1}, $P < 0.05$) and AUC (1389 ± 617 *vs* 837 ± 316 ng ml^{-1} h, $P = 0.0625$) of propranolol in all subjects.

5 Transient atrioventricular dissociation occurred in two patients 2 h after dosing with verapamil and propranolol or atenolol.

6 Close observation of patients is essential when β-adrenoceptor antagonists and verapamil are used together.

Keywords verapamil propranolol pharmacokinetics pharmacodynamics combined therapy

Introduction

β-adrenoceptor antagonists and calcium channel antagonists are often used together in patients with angina inadequately controlled by monotherapy. The calcium antagonist verapamil is as effective as β-adrenoceptor antagonists in relieving symptoms and more effective than nifedipine either when used alone or in combination with propranolol (Livesley *et al.*, 1973; Leon *et al.*, 1981; Subramanian *et al.*, 1982a, b; Winniford *et al.*, 1985a). Hence, for the

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optimal control of angina in resistant cases, combined treatment with verapamil and a β-adrenoceptor antagonist would appear logical. Unfortunately, both drugs have a negative ionotropic action and delay atrioventricular conduction and this may result in serious adverse effects when they are used together (Benaim, 1972; Opie, 1980; Wayne *et al.*, 1982). Despite this disadvantage, long term control of symptoms may be achieved with close supervision (McGourty *et al.*, 1985).

A pharmacokinetic interaction may also contribute to the effects of combined treatment. Verapamil undergoes extensive first pass metabolism (10–20% bioavailability), primarily via *O*- and *N*-dealkylation (Eichelbaum *et al.*, 1979). The latter route leads to the formation of norverapamil, the major active metabolite present in plasma. It has been established that β-adrenoceptor antagonists can inhibit oxidative drug metabolism to an extent which is dependent upon their lipid solubility (Bax *et al.*, 1983; Tucker *et al.*, 1984). Therefore, when used in combination with a β-adrenoceptor antagonist the oral clearance of verapamil might be decreased, particularly when a lipid soluble agent like propranolol is used. Since exercise performance, changes in PR interval and the occurrence of heart failure may be related to plasma verapamil concentration (Freedman *et al.*, 1981; Johnson *et al.*, 1981; Schwartz *et al.*, 1982; Weiner *et al.*, 1984), such an interaction may have clinical significance.

Propranolol is also extensively metabolised and its bioavailability is increased by other drugs (Reimann *et al.*, 1981). Furthermore, there is strong evidence that verapamil inhibits its own metabolism (Schwartz *et al.*, 1985) and also that of antipyrine (Bach *et al.*, 1986; Rumiantsev *et al.*, 1986), quinidine (Edwards *et al.*, 1987), carbamazepine (MacPhee *et al.*, 1986) and cyclosporin (Lindholm & Henricsson, 1987). Impairment of the oral clearance of propranolol by verapamil may increase the risk of plasma drug concentration-related adverse effects.

Recent studies have not detected any pharmacokinetic interaction between verapamil and β-adrenoceptor antagonists (Warrington *et al.*, 1984: McInnes *et al.*, 1985, 1986). However, these investigations involved the administration of single and sub-therapeutic doses of the drugs to young, healthy volunteers. We describe three studies performed in small groups of patients with angina pectoris to compare the pharmacokinetics and pharmacodynamics of 1) verapamil during 4 weeks combined treatment with propranolol or atenolol, 2) verapamil during monotherapy and after 4 weeks treatment with propranolol and 3) propranolol during monotherapy and after 4 weeks treatment with verapamil.

Methods

The following features were common to the three studies:

1) They were approved by the Clatterbridge Hospital Ethics Committee and all subjects gave written informed consent

2) Prior to entry routine clinical chemistry (urea and electrolytes and full blood count) was performed and chest X-rays were taken. The results of all investigations were normal in each subject

3) Oral diuretic and glyceryl trinitrate (GTN) treatment remained unaltered but the patients took no other drugs apart from the study tablets

2) Patients recorded the number of angina attacks and of GTN tablets taken during each 4 week treatment period in a diary

3) Unless otherwise stated, verapamil was taken at 08.00 h, 14.00 h and 22.00 h and β-adrenoceptor antagonists at 08.00 h and 22.00 h.

Study 1

The aim of this study was to compare the effect of propranolol with that of atenolol on the pharmacokinetics and pharmacodynamics of verapamil.

Six non-smoking males (mean ± s.d. age 59 ± 10 years) with chronic stable angina, which was well controlled with verapamil (360 mg daily) and a β-adrenoceptor antagonist (atenolol 100 mg, five patients; propranolol 320 mg, one patient) for a mean period of 10 months (range 3–15 months), took part. Three patients had suffered previous myocardial infarctions, five had hypertension which was well controlled and one had diabetes mellitus treated by diet. Two patients were taking thiazide diuretics and two were taking oral nitrate preparations.

Verapamil (120 mg three times daily) was taken throughout the study. Patients were given propranolol (80 mg twice daily) or atenolol (50 mg twice daily) for 4 weeks in a random, single blind fashion followed by crossover to the alternative agent for a further 4 weeks.

At the end of each treatment phase the subjects fasted overnight and then took single oral doses of verapamil (120 mg) and either propranolol (80 mg) or atenolol (50 mg) with 50 ml of water. Patients did not eat or drink for the following 4 h. Samples of venous blood (10 ml) were withdrawn before and at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 h after dosing. The serum was separated

and stored at –20° C until assayed for verapamil and its metabolite, norverapamil. Heart rate and PR interval were measured from an electrocardiogram taken before and at 2 h after dosing. The PR interval was calculated as the mean of four complexes measured from lead II and recorded at 100 mm s^{-1}.

Study 2

The aim of this study was to investigate the effect of propranolol on the pharmacokinetics and pharmacodynamics of verapamil.

Four males (mean ± s.d. age 58 ± 6 years) suffering from angina not fully controlled by verapamil (360 mg daily) took part in the study. Two subjects were smokers and, on previous occasions, three had suffered myocardial infarctions and one had a stroke. Only one subject was receiving an oral nitrate preparation and none was taking diuretics. Following entry into the study, the subjects continued to take verapamil (120 mg three times daily) for 4 weeks. They then followed the protocol described for study 1, except that on the first study day a single oral dose of verapamil (120 mg) alone was taken and an exercise test was performed. Propranolol (80 mg twice daily) was then added to the treatment and the patients were reviewed after 2 weeks to ensure that the drug combination was well tolerated. After a further 2 weeks the protocol from the previous study day was followed, single oral doses of both verapamil (120 mg) and propranolol (80 mg) being taken.

Study 3

The aim of this study was to investigate the effect of verapamil on the pharmacokinetics and pharmacodynamics of propranolol.

Six patients (five males, one female; mean ± s.d. 57 ± 9 years) with angina not fully controlled with propranolol (160 mg daily) took part. One subject was a smoker, four had suffered previous myocardial infarctions and two had hypertension which was controlled. Four subjects were taking oral nitrates and one a diuretic. Following entry into the study, the subjects continued to take propranolol (80 mg twice daily) for 4 weeks. They then followed the protocol described in study 2, except that on the study day a single oral dose of propranolol (80 mg) was taken and an additional blood sample was withdrawn after 12 h. Verapamil (80 mg three times daily) was then added to the treatment and the dose was increased to 120 mg three times daily weeks later providing that no adverse effects had occurred. After a further 4 weeks the same protocol was followed except that single oral doses of both propranolol (80 mg) and verapamil (120 mg) were taken.

Exercise stress tests

In studies 2 and 3 patients underwent exercise stress testing at the end of each 4 week treatment period. The tests were conducted at approximately 6 h after dosing. They were performed under standardised conditions using a motorised treadmill, the work load being increased according to a standard Bruce protocol. The electrocardiogram was monitored continuously; a 12 lead recording was made and systolic blood pressure was measured every 3 min. Testing was stopped at the onset of chest pain, dyspnoea or fatigue.

Drug analysis

Plasma concentrations of verapamil and norverapamil (Harapat & Kates, 1979) and of propranolol (Lo *et al.*, 1982) were measured by high performance liquid chromatography. Coefficients of variation were less than 5% for all of the assays.

Data analysis

The area under the plasma drug concentration-time curve up to the final sample was measured using the linear trapezoidal rule.

Differences in kinetic and dynamic measurements were compared using Student's paired *t*-test and the randomisation test for matched pairs.

Results

Withdrawals

One patient was withdrawn from Study 3 after 5 days of combined propranolol and verapamil (240 mg daily) treatment. He complained of lethargy which was associated with a marked bradycardia. Electrocardiography performed approximately 3.5 h after the last morning dose showed atrioventricular dissociation with a ventricular rate of 37 beats min^{-1}. One hour later sinus bradycardia had returned. Verapamil therapy was stopped immediately. The results from the remaining five patients in Study 3 are presented in Table 2.

Other adverse effects

Two patients developed constipation following the addition of verapamil to their treatment.

Table 1 Pharmacokinetic data for verapamil and norverapamil in Studies 1 and 2. Values are mean ± s.d. V+A, combined treatment with verapamil (120 mg three times daily) and atenolol (50 mg twice daily), V+P, combined treatment with verapamil (120 mg three times daily) and propranolol (80 mg twice daily); V, treatment with verapamil (120 mg three times daily) alone. There were no significant differences between treatment phases

Study	Treatment phase	C_{max} (ng ml^{-1}) Verapamil	C_{max} (ng ml^{-1}) Norverapamil	AUC (ng ml^{-1} h) Verapamil[a]	AUC (ng ml^{-1} h) Norverapamil
1	V+A	372 ± 320	170 ± 34	1985 ± 1660	1175 ± 330
	V+P	491 ± 397	187 ± 29	2075 ± 1524	1172 ± 250
2	V	287 ± 105	219 ± 75	1375 ± 455	1438 ± 496
	V+P	312 ± 55	247 ± 79	1566 ± 486	1615 ± 572

[a]95% confidence intervals for mean difference between treatments: Study 1: 230 to +416 ng ml^{-1} h^{-1}; Study 2: 196 to +523 ng ml^{-1} h.

Their symptoms resolved after the introduction of a high fibre diet. One patient in study 2 complained of hallucinations following propranolol. These disappeared on replacement of propranolol by atenolol at the end of the study.

Pharmacokinetics

Verapamil and norverapamil *Study 1* No statistically significant differences were found between the β-adrenoceptor antagonist treatments in the maximum plasma concentrations (C_{max}) and AUCs of verapamil and norverapamil (Table 1).

Study 2 No differences in C_{max} and AUC were observed during verapamil monotherapy *vs* combined treatment with propranolol (Table 1).

Propranolol (Study 3)

The data for each subject are listed in Table 2 and the mean plasma drug concentration-time profiles are shown in Figure 1. C_{max} values were significantly higher during combined verapamil and propranolol therapy than with propranolol alone. Although all subjects had higher AUC values during combined treatment, this difference just failed to reach statistical significance at the 5% level. There was also no significant difference in the time to reach C_{max} between the two treatment phases.

Pharmacodynamics

The data from the three studies are summarised in Table 3. No statistically significant differences

Table 2 Pharmacokinetic data for propranolol in Study 3. Treatment phases: Propranolol + verapamil, combined treatment with propranolol and verapamil; Propranolol, treatment with propranolol alone. *P* values are for comparison between treatment phases

Subject	C_{max} (ng ml^{-1}) Propranolol	C_{max} (ng ml^{-1}) Propranolol + verapamil	AUC (ng ml^{-1} h) Propranolol	AUC (ng ml^{-1} h) Propranolol + verapamil
1	208	353	1279	1804
2	150	343	1048	2135
3	55	206	516	1481
4	76	109	647	729
5	96	122	694	797
Mean[a]	117	227	837	1389
s.d.	62	117	316	617
P[b]		<0.05		<0.10
P[c]				0.0625

[a]95% confidence interval for mean difference in AUC between treatments = −31 to +1135 ng ml^{-1}h.
[b]Student's *t*-test, propranolol *vs* propranolol + verapamil for C_{max} and AUC.
[c]Randomisation test, propranolol *vs* propranolol + verapamil for AUC.

Table 3 Pharmacodynamic data for studies 1,2 and 3. Values are mean ± s.d. Treatment phases: Verapamil + atenolol, combined treatment with verapamil and atenolol; Verapamil + propranolol, combined treatment with verapamil and propranolol; Verapamil, treatment with verapamil alone; Propranolol, treatment with propranolol alone

Study	*Treatment phase*	*Body weight (kg)*	*Blood pressure (mm Hg) Systolic/Diastolic*	*Number of angina attacks per week*	*Number of GTN tablets taken per week*	*Heart rate (beats min^{-1})* 0h	2h	*PR interval (s)* 0h	2h	*Exercise time (min)*
1	Verapamil + atenolol	75.7 ± 4.3	125 ± 17/72 ± 8	4 ± 4	2 ± 1	54 ± 12	49 ± 9	0.20 ± 0.03	0.22 ± 0.03	—
	Verapamil + propranolol	75.5 ± 4.4	132 ± 18/72 ± 8	4 ± 3	1 ± 1	54 ± 10	46 ± 8	0.20 ± 0.03	0.22 ± 0.04	—
2	Verapamil	73.6 ± 10.5	137.22/77 ± 5	6 ± 5	5 ± 6	58 ± 7	62 ± 14[b]	0.18 ± 0.01[a]	0.20 ± 0.01[a]	6.5 ± 1.1 (n = 3)
	Verapamil + propranolol	73.3 ± 10.5	134 ± 21/72 ± 5	5 ± 5	4 ± 5	52 ± 5	48 ± 9[b]	0.21 ± 0.01[a]	0.23 ± 0.02[a]	7.5 ± 0.8 (n = 3)
3	Propranolol	75.9 ± 14.8	116 ± 6/75 ± 9	10 ± 9	10 ± 9	66 ± 8[c]	54 ± 13[c]	0.17 ± 0.01	0.17 ± 0.01	8.6 ± 2.1 (n = 4)
	Propranolol + verapamil	75.5 ± 14.5	123 ± 18/76 ± 11	6 ± 6	6 ± 6	62 ± 7	49 ± 8	0.17 ± 0.02	0.18 ± 0.03	7.9 ± 3.0 (n = 4)

[a] $P < 0.01$ verapamil *vs* verapamil + propranolol at both 0 and 2 h
[a] $P < 0.05$ 0h *vs* 2 h for both verapamil and verapamil + propranolol
[b] $P < 0.05$ decrease in heart rate at 2 h for verapamil *vs* verapamil + propranolol
[c] $P < 0.01$ 0 *vs* 2 h for propranolol
All other changes were not statistically significant.

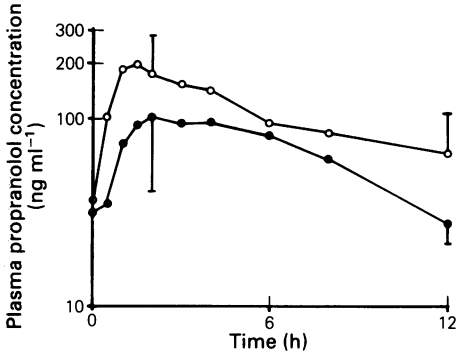

Figure 1 Mean plasma propranolol concentration-time profiles during treatment of five patients with propranolol alone (80 mg twice daily) for 4 weeks (•) and during combined treatment with propranolol (80 mg twice daily) and verapamil (120 mg three times daily) for 4 weeks (○). Bars represent s.d.

in angina frequency, GTN consumption, blood pressure and body weight were observed between the treatment phases in each of the three studies.

Heart rate and PR interval

Study 1 No significant changes in heart rate and PR interval were seen during atenolol compared with propranolol therapy. However, during both treatment periods one patient developed transient, asymptomatic atrio-ventricular dissociation. This occurred 2 h after dosing with return to sinus rhythm 1 h later. This patient had the highest verapamil C_{max} (998 ng ml^{-1}, atenolol phase; 1097 ng ml^{-1}, propranolol phase) and AUC (5096 ng ml^{-1} h, atenolol phase; 4762 ng ml^{-1} h, propranolol phase). After completing the study he remained free of bradyarrhythmias on verapamil (360 mg daily) and a reduced dose of atenolol (50 mg daily) until undergoing coronary artery bypass grafting for severe three-vessel disease.

Study 2 Both immediately before and 2 h after drug ingestion the PR interval was significantly longer during combined treatment with verapamil and propranolol compared with verapamil alone. The PR interval was prolonged significantly at 2 h compared to pre-dose values during both treatment phases. In two patients the 2 h PR interval was 0.24 s during combined therapy. Verapamil treatment was subsequently stopped in one of them because of symptomatic bradycardia (40 beats min^{-1}). However, this patient had the lowest C_{max} and AUC values for verapamil.

The mean reduction in heart rate at 2 h was significantly greater after verapamil and propranolol treatment compared with verapamil alone.

Study 3 Heart rate was significantly lower than pre-dose values 2 h after propranolol dosing. No other significant differences were observed either within or between treatment phases.

Exercise stress tests

One patient in each of Studies 2 and 3 did not satisfactorily complete both exercise tests because of dizziness and pre-existing hemiplegia, respectively. In the remaining patients there was no significant difference in exercise time during combined therapy compared with single drug treatment. The criteria for terminating exercise was identical for both treatment phases in four patients. Exercise was discontinued in one patient because of a 40 mm Hg fall in systolic blood pressure during dual therapy. However, exercise time had increased by 101 s compared with that during verapamil alone when pain was the limiting symptom. Exercise was limited by dyspnoea rather than chest pain in two patients during combined treatment and this was associated with a decrease in exercise time compared with propranolol monotherapy of 26 and 143 s, respectively.

Discussion

As in studies with healthy volunteers (Warrington *et al.*, 1984; MacInnes *et al.*, 1985, 1986) we did not observe significant differences in the pharmacokinetics of verapamil during 1) combined treatment with propranolol compared with that with atenolol or 2) when verapamil was given alone compared with combined treatment with propranolol, in patients with stable angina pectoris. Confidence intervals for these data are wide (Table 1) and proof of no effect of β-adrenoceptor treatment would require a study with larger numbers of subjects. However, a statistically significant degree of inhibition of drug metabolism by propranolol has been observed in studies of similar design and size (Bax *et al.*, 1983; Tucker *et al.*, 1982).

The apparent lack of effect of propranolol on verapamil metabolism may reflect a degree of specificity in the inhibition of individual isozymes

of cytochrome P-450. Thus, propranolol (Schneck & Pritchard, 1981) and lignocaine (Tucker *et al.*, 1982) oxidation are inhibited by propranolol but *N*-dealkylation (one of the major routes of verapamil metabolism (Eichelbaum *et al.*, 1979)) is affected less readily than aromatic hydroxylation. Furthermore, although the metabolism of verapamil is induced by sulphinpyrazone, it is unaffected by cimetidine, a potent inhibitor of the metabolism of many drugs (Wing *et al.*, 1985).

In contrast, verapamil did appear to influence the pharmacokinetics of propranolol during continous therapy. Thus, verapamil caused a mean increase in C_{max} of 94% and in AUC of 66%. These changes were statistically significant for C_{max} but not for AUC at the 5% level. However, they did occur in all five subjects indicating that a larger study is required to confirm these observations. Verapamil may also inhibit the metabolism of metoprolol. In a recent case report a two-fold increase in plasma metoprolol concentrations was observed during the treatment of a patient with verapamil (McLean *et al.*, 1985).

The known capacity of propranolol and verapamil to displace each other from plasma protein binding sites (Yong *et al.*, 1980; Pieper, 1984) may complicate further the interpretation of the present data. Displacement should lead to a decrease in total plasma concentration (with no change in free concentration) after re-equilibration has taken place and so may disguise or lessen the effects of inhibition of metabolism.

The absence of significant differences in the frequency of anginal attacks or exercise time between mono- and combined treatment may be due to the small number of subjects studied, since controlled studies have established the efficacy of concurrent treatment with verapamil and a β-adrenoceptor antagonist (Leon *et al.*, 1981; Subramanian *et al.*, 1982a; Winniford *et al.*, 1985). There are conflicting reports as to whether prolongation of the PR interval is greater with combined treatment compared with verapamil monotherapy (Leon *et al.*, 1981; Subramanian *et al.*, 1982a; Winniford *et al.*, 1985). We found a significant increase in the PR interval during dual therapy in study 2 but not study 3, but the degree of prolongation did not appear to be related to the plasma concentration of verapamil. However, both verapamil and propranolol are administered as racemic mixtures of their enantiomers, one of which in each case possesses most of the pharmacological activity. Since only total drug was measured in the present studies, it was not possible to determine whether there were differences in the pharmacokinetics of the enantiomers between treatment phases. Such a mechanism may contribute to the differences in pharmacodynamics observed in study 2.

No patient developed clinically detectable heart failure but exercise time was decreased because of dyspnoea in two patients during dual therapy suggesting a deleterious effect on cardiac function. Significant bradyarrhythmias occurred in three subjects, two of whom developed atrioventricular dissociation. Although, one of these patients had very high plasma verapamil concentrations the heart block resolved when the dose of β-adrenoceptor antagonist was lowered. The two other subjects experienced a symptomatic bradycardia. In one of these patients plasma verapamil concentrations were lower than in the other subjects of study 2 implying that this adverse reaction arose from the combined effect of both drugs on the atrioventricular node. The observed incidence of bradyarrhythmias (20%) was considerably higher than that reported by others (Subramanian *et al.*, 1982a; Winniford *et al.*, 1985b), possibly reflecting differences in patient selection or the severity of the disease or both.

In summary, we have confirmed that serious adverse reactions may occur in a significant proportion of patient during combined oral treatment with verapamil and propranolol. The occurrence of these effects is related to the time of drug dosing and is probably a consequence of simultaneous, high plasma concentrations of both agents but not of a pharmacokinetic interaction between the two drugs. Hence, when verapamil and β-adrenoceptor antagonists are used together careful titration of the dose of both drugs is necessary. Close supervision of patients is essential and the electrocardiogram should be monitored, ideally at times of peak plasma drug concentrations. Combined treatment should probably be restricted to those patients with symptoms resistant to or unsuitable for other therapy.

We thank Mrs J. Harlow for technical assistance, Professor H. F. Woods for provision of laboratory facilities and ICI and Abbott Pharmaceuticals for financial support. M.S.L. is a Wellcome Trust Lecturer.

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(Received 14 July 1987, accepted 10 November 1987)