Studies on verapamil in the treatment of essential hypertension: a review

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1 Various doses of verapamil, using the conventional and sustained release formulations, have been administered for the treatment of mild or moderate hypertension in different controlled studies for periods of 4–6 weeks, involving a total of 103 patients, and in one long-term trial for 1 year in 12 patients.

2 A double-blind comparison of verapamil and nifedipine showed that the two calcium antagonists had equal antihypertensive action. A significant blood pressure (BP) reduction was achieved with verapamil both at rest and during isometric exercise in the great majority of patients. No significant correlation was found between age and BP reduction, but pretreatment BP and pressure reduction correlated positively. Heart rate (HR) was moderately but significantly reduced by verapamil.

3 The established wide interindividual differences in verapamil pharmacokinetics were confirmed. There was no significant correlation between plasma drug concentrations and BP reduction, but the dosage regimens with the highest mean plasma drug concentrations were associated with the greatest mean reduction in BP. A moderate, but significant, prolongation of AV-conduction was demonstrated. QRS- and QT-intervals were unaffected.

4 Side-effects, with all formulations of verapamil, were generally mild and often transient. No significant haematological or metabolic effects were observed during long-term treatment.

5 It is concluded that the calcium antagonist verapamil is an effective and safe drug. It can be considered as an alternative drug in mild and moderate essential hypertension.

Keywords calcium antagonists verapamil hypertension metabolic effects isometric work

Introduction

Verapamil has been used for many years in a number of cardiovascular disorders, and has proved to be a safe drug (Krikler, 1974; Opie, 1980; Stone *et al.*, 1980). More recently verapamil has been evaluated in hypertension and is now established in this indication (Lewis *et al.*, 1978; Leary & Asmal, 1979; Midtbø & Hals, 1980; Midtbø *et al.*, 1982, 1984; Gould *et al.*, 1984; Fenech *et al.*, 1984; Hulthen *et al.*, 1984a).

The rationale for its use has been based on its direct dilator action on peripheral arterial smooth muscle (Lund-Johansen, 1984; Hulthen *et al.*, 1984b; Singh *et al.*, 1984). The application of verapamil to hypertension seems logical since the predominant haemodynamic disorder in mild/moderate essential hypertension is an increased peripheral vascular resistance (Lund-Johansen, 1980). Moreover, if pathological

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Table 1 Blood pressure and heart rate after 4 weeks of treatment with placebo and after 4 weeks of treatment with verapamil 160 mg three times daily, $n = 23$

	Placebo	Verapamil
Blood pressure sitting (mm Hg)	153 $\pm$ 12 105 $\pm$ 9	139 $\pm$ 11 95 $\pm$ 7
Heart rate sitting (beats min ⁻¹)	68 $\pm$ 8	65 $\pm$ 10

handling of cellular calcium is a mechanism underlying essential hypertension (Aoki *et al.*, 1976; Lederballe Pedersen, 1981), the calcium antagonists may represent a specific approach to the treatment of hypertension. Because of the increased morbidity and mortality associated with hypertension its control is a preventive necessity, and should, as far as possible, be accomplished without impairing the quality of life. In this context verapamil is an interesting drug since, in view of recent observations (MRC report, 1981), there seems to be a need for a new antihypertensive agent of first choice besides thiazides and β -adrenoceptor blockers (Dollery, 1981). The aim of our studies has been to evaluate the efficacy and safety of verapamil in hypertension, and to define its current role in the treatment of this common condition. Some of our recent studies, published and unpublished, are reviewed in this paper.

Double blind comparison of placebo and verapamil (Midtbø & Hals, 1980)

Twenty-three patients with a mean age of 51 years, range 26–62 years, with mild to moderate essential hypertension were studied in a double-blind cross-over trial. After a pretreatment period of 2 weeks, verapamil 160 mg three times daily was compared with placebo for periods of 4 weeks. Verapamil significantly reduced BP and produced a small effect on HR (Table 1). In eight patients plasma concentrations of verapamil and its active metabolite norverapamil were determined after 4 weeks of treatment before the morning dose and 1 h after that dose. There was no significant correlation between BP reduction and plasma drug values. However, the rise in verapamil concentrations following the morning dose correlated significantly with the fall in BP during this hour (Storstein *et al.*, 1981). Serum total cholesterol and triglycerides were not significantly influenced. A slight prolongation of mean PQ-interval in the ECG was observed. No serious side-effects occurred, and in no case was drug withdrawal necessary (Table 2).

Table 2 Side effects with placebo and with verapamil 160 mg three times daily, $n = 23$

Side effects	Placebo	Verapamil
Constipation (mild)	0	8
Exanthema	0	2
Fatigue	2	1
Diarrhoea	1	0
Heartburn	1	0
Palpitation	1	0

Double-blind comparison of verapamil and nifedipine (Midtbø *et al.*, 1982)

In a double-blind cross-over study for 6 weeks in 28 patients, mean age 53 years, with mild or moderate essential hypertension, the hypotensive action of verapamil 160 mg thrice daily was compared with nifedipine 20 mg in a slow release preparation twice daily. Both regimens reduced BP significantly with sustained and slightly increasing effect throughout the periods. Resting HR was significantly decreased by verapamil and insignificantly increased by nifedipine (Table 3). Plasma concentrations of verapamil, norverapamil and nifedipine demonstrated great interindividual variations, and there was no significant correlation between plasma drug values and BP reduction for either drug. Liver function tests, serum creatinine, serum electrolytes (Na^+ , K^+ and Cl^-), serum total cholesterol, HDL-cholesterol and triglycerides were not affected by either agent. AV-conduction time was significantly prolonged by verapamil, and in one patient SA-block occurred. Subjective side-effects were more numerous with nifedipine than with verapamil, but were mainly mild and transient, except for one patient in each group who was withdrawn because of severe adverse reactions (one with SA-block during verapamil, and one with intolerable tiredness during nifedipine) (Table 4). At the end of the trial, most patients had no treatment preference, but six preferred verapamil and one nifedipine.

Table 3 Mean of supine, sitting, and standing blood pressure together, and sitting heart rate, before treatment, after 6 weeks of treatment with verapamil 160 mg three times daily, and after 6 weeks of treatment with nifedipine, 20 mg twice daily, ($n = 26$)

	Pretreatment	Verapamil	Nifedipine
Systolic blood pressure (mm Hg)	149 $\pm$ 13	128 $\pm$ 13	133 $\pm$ 12
Diastolic blood pressure (mm Hg)	107 $\pm$ 5	87 $\pm$ 8	93 $\pm$ 8
Sitting heart rate (beats min ⁻¹)	69 $\pm$ 6	65 $\pm$ 7	71 $\pm$ 8

Table 4 Side effects with nifedipine 20 mg slow release twice daily and with verapamil 160 mg thrice daily, ($n = 28$)

Side effects	Nifedipine	Verapamil
Headache	11	2
Constipation	4	9
Increased micturition	5	3
Flushing	3	2
Fatigue	3	2
Palpitations	2	2
Dizziness	3	0
Urticaria	0	1
Sinoatrial block	0	1

Once and twice daily administration of verapamil two layer sustained release tablets including a dose study of conventional verapamil (Midtbø *et al.* 1984)

A practical draw-back with verapamil has been the supposed need for frequent dosing of the drug. In order to reduce the frequency of administration of verapamil, two slow-release formulations have been developed. We have studied both in the treatment of hypertension. We first studied a two-layer tablet of 240 mg, with an outer layer of 90 mg rapid-release verapamil and a slow release core of the remaining 150 mg. The antihypertensive action of this new preparation, administered once and twice daily, was examined in a randomised controlled study including 28 patients aged 32 to 62 years, mean 50.5 years, with mild to moderate essential hypertension, for periods of 4 weeks. The trial also included two open periods, of 2 weeks each, during which the patients were given conventional verapamil 120 mg twice and thrice daily, respectively. All four regimens significantly reduced BP, the best result being obtained during the 240 mg (two-layer) twice daily period: HR was also significantly decreased (Table 5).

Trough plasma concentrations of verapamil and norverapamil were measured on each dosage regimen and substantial individual variations were observed. We found no significant correla-

tion between plasma verapamil concentration and BP reduction at any dose, but the dosage regimen with the highest mean plasma drug concentration was associated with the greatest mean reduction in BP. Mean PQ-interval (ECG) was prolonged by 240 mg sustained release twice daily ($P < 0.01$) compared with pretreatment values, but failed to reach significance with the other verapamil dosage regimens. In one patient, while on the highest dosage, SA-block occurred. After withdrawal of verapamil he returned to sinus rhythm within a few hours. Mean body weight did not increase during the trial, and no oedema was observed. The predominant side-effect was mild to moderate constipation. Except for the patient with SA-block, no serious untoward reactions occurred (Table 6). Side effects with verapamil are usually dose-related. In this study, however, there were almost as many patients with side-effects with verapamil retard once daily as with twice-daily medication. This may indicate that the single dose of this formulation is too high for some patients, or that this two-layer tablet has pharmaceutical disadvantages. Moreover, this tablet cannot be divided, which is a drawback when dosage titration is needed. The two-layer tablet permitted a simple twice daily dosage regimen, realistic in patients who need higher doses of verapamil. In many individual patients, however, doses of 240 mg retard once daily or 120 mg conventional verapamil twice daily had a significant hypotensive action.

The effect of verapamil on isometric exercise

During the trial with the two-layer 240 mg tablet discussed above an isometric exercise test was included. Twenty-eight patients were studied. At the end of the pretreatment period and at the end of both periods of treatment with verapamil sustained release, an isometric exercise test was performed in the supine position, using a hand-grip dynamometer. Each patient was trained in the procedure and maintained at 50% of maximal voluntary contraction for 90 s. The patients were

Table 5 Sitting blood pressure and heart rates, pre-treatment, after 2 weeks of treatment with 120 mg verapamil thrice daily, after 4 weeks of treatment with verapamil retard 240 mg (bilayer) once daily, after 4 weeks of treatment with verapamil retard 240 mg twice daily, and after 2 weeks of treatment with 120 mg verapamil twice daily. The blood pressure recordings on active treatments are taken in the morning immediately prior to dosing with verapamil, ($n = 26$)

	Pretreatment	120 mg $\times$ 3	Verapamil		120 mg $\times$ 2
			240 mg $\times$ 1	240 mg $\times$ 2	
Sitting blood pressure (mm Hg)	166 $\pm$ 18 109 $\pm$ 9	146 $\pm$ 15 95 $\pm$ 8	148 $\pm$ 14 96 $\pm$ 7	139 $\pm$ 13 89 $\pm$ 7	142 $\pm$ 13 96 $\pm$ 8
Mean heart rates (beats min ⁻¹)	72 $\pm$ 11	68 $\pm$ 10	69 $\pm$ 8	64 $\pm$ 10	66 $\pm$ 11

Table 6 Side effects during various verapamil regimens ($n = 28$)

Side effects	120 mg $\times$ 3	Verapamil		120 mg $\times$ 2
		240 mg $\times$ 1	240 mg $\times$ 2	
Constipation	5	5	5	1
Palpitations		1	4	
Headache		2		
Fatigue		2	1	
Dizziness		2	1	1
Sinoatrial block			1	
Impotence			1	
Number of patients exhibiting side effects	5	6	8	2

instructed to count during the test to avoid the possibility of Valsalva manoeuvre. The results of the study are shown in Table 7. Verapamil blunts the increase of both BP and HR during isometric exercise as all changes are lower after verapamil treatment than at the end of the pretreatment period ($P < 0.001$). Similar changes were seen in the nifedipine/verapamil study referred to earlier where both drugs showed significant differences from placebo.

Verapamil sustained release compared with verapamil instant release

In this trial we studied the second verapamil sustained release tablet which is homogeneously formulated with a sodium alginate matrix to release 240 mg verapamil over 7–8 h.

Patients and methods

Efficacy and safety of this new formulation twice daily were compared with those of conventional verapamil, administered as 80 mg tablets at a dose of 160 mg twice daily. The study was conducted as a single-blind cross-over trial for periods

of 4 weeks, with a placebo treatment period of 2 weeks at the start. Twenty-four patients with a mean age of 51 years (range 33–64) with mild/moderate essential hypertension were studied. BP and HR were measured at the end of the placebo period, after 24 h of treatment, i.e. in the morning of the second day 12 h after the second dose, and then 2 h after that morning dose (the third dose all in all). In the course of the trial, the measurements were performed every 2 weeks throughout the treatment periods in the morning before verapamil 12 h after the previous dose. At the end of the first treatment period (4 weeks), BP and HR were again measured both in the morning prior to dosing and 2 h after the morning dose. Blood samples for plasma drug concentrations were also taken in the morning before the dose and 2 h after 240 mg sustained release or 160 mg conventional release after 1 day of treatment and after 4 weeks.

Results

Twenty-two patients completed the study. BP was significantly lowered by both regimens, vera-

Table 7 Isometric exercise before treatment and after 4 weeks of treatment with verapamil retard 240 mg (bilayer) twice daily ($n = 28$)

	Blood pressure (mm Hg)		Heart rate (beats min ⁻¹)	
	Pretreatment	During treatment	Pretreatment	During treatment
Resting	158 ± 10 98 ± 14	141 ± 13 87 ± 7	74 ± 11	58 ± 9
	$P < 0.001$		$P < 0.001$	
Handgrip 90 s	187 ± 20 124 ± 13	166 ± 16 110 ± 11	93 ± 12	73 ± 9
	$P < 0.001$		$P < 0.001$	

pamil sustained release having a significantly better effect than verapamil instant release in the morning (see Table 8). Most of the reduction was achieved after 24 h of treatment, especially for verapamil sustained release (see Table 9). HR was moderately but significantly decreased during both treatment periods. PQ, QRS- and

QT-intervals in the ECG were unaffected. Once again the plasma drug concentrations varied widely within the patient group, and no correlation was found between pressure reduction and plasma concentrations of verapamil/nor-verapamil. However, as in the previous study, the regimen with the highest mean plasma concen-

Table 8 Blood pressure immediately prior to dosing after 2 weeks with placebo, after 4 weeks with verapamil instant release 160 mg twice daily, and after treatment with verapamil sustained release 240 mg twice daily for 4 weeks ($n = 22$)

	Placebo	Verapamil instant release	Verapamil sustained release
Sitting blood pressure (mm Hg)	161 ± 7 104 ± 5	141 ± 12 90 ± 6	137 ± 11 88 ± 6
	$P < 0.001$		
	$P < 0.001$		
	$P = 0.04$		

Table 9 Blood pressure taken immediately prior to dosing, after 24 h of treatment and after 4 weeks of treatment with verapamil sustained release 240 mg twice daily given as the first treatment ($n = 11$)

	Placebo	Verapamil after 24 h 4 weeks	
Sitting blood pressure (mm Hg)	160 ± 6 104 ± 3	139 ± 10 91 ± 7	137 ± 11 89 ± 7
	$P < 0.001$		
	NS		
	$P < 0.001$		

tration of the drug had the greatest mean reduction in BP at 12 h after the previous tablet. Plasma drug concentrations increased over time. Side effects were few, mild and transient in some cases, except for one patient who was withdrawn because of an itching rash during the second treatment period whilst receiving verapamil (Table 10). A further patient withdrew during the first treatment phase also on verapamil due to hyperventilation which persisted after withdrawal of verapamil and therefore probably had nothing to do with the drug.

Conclusion

The pharmacokinetic data obtained and the smooth BP reduction achieved suggest that this verapamil formulation is suitable as a twice-daily medication in the treatment of hypertension. In contrast to the two-layer tablet, the more recently developed, sustained release tablet can easily be divided, which is an advantage in dosage titration. This verapamil formulation may simplify the dosage regimen in hypertension and improve patient compliance.

Haematological and metabolic studies during long-term treatment with verapamil

Twelve patients with a mean age of 49 years with previously untreated mild essential hypertension have been treated with verapamil instant release for more than 1 year. The mean daily dosage of verapamil was 270 mg (120 mg two or three times daily), and the dosage was titrated to produce a diastolic BP reduction to 85 mm Hg or below. BP, HR, ECG, laboratory tests and body weight were checked before and after 1, 2, 3, 6, 9 and 12

months of treatment. Routine urinalysis, haemoglobin, haematocrit, RBC and WBC count, blood glucose (fasting), BUN, serum creatinine, uric acid, electrolytes (Na^+ , K^+ , Cl^- , Ca^{++} and P^{++}), alkaline phosphatase, ASAT, ALAT, LDH, glutamine transferase, total bilirubin, total serum protein, albumin, serum total cholesterol, HDL-cholesterol and triglycerides were measured. The initial slight prolongation of the PQ-interval did not increase during long-term treatment. No significant change of body weight has occurred. Mild constipation in two patients was reported. None of the laboratory tests changed significantly during the 1 year of treatment, i.e. no negative haematological/metabolic effects have been observed.

Conclusions

The present trials show that verapamil is an effective drug in the treatment of mild/moderate essential hypertension in patients of all age groups. Unlike direct vasodilators, verapamil reduces BP without simultaneously inducing cardiac stimulation. On the contrary, a moderate but significant reduction in HR has been demonstrated in our studies. The recently developed sustained release formulation of verapamil has simplified the dosage regimen and may help to improve patient compliance. However, the daily dosage of verapamil needs to be individually titrated and to be based on the clinical response of the patient, since no significant correlation between plasma drug concentrations and BP reduction can be demonstrated. The various formulations of verapamil are well tolerated by the patients, and no negative haematological/metabolic effects have been observed for treatment periods up to 1 year.

Table 10 Side effects with verapamil sustained release 240 mg twice daily and with verapamil instant release 160 mg twice daily ($n = 22$)

Side effects	Placebo	Verapamil instant release	Verapamil sustained release
Constipation		3	5
Headache	2		
Dizziness		1	
Rash			1
Palpitations	1		
Flushing		1	
Fatigue		1	
Number of patients exhibiting side effects	3	5	6

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