NIFEDIPINE IN THE TREATMENT OF HYPERTENSION: REPORT OF A DOUBLE-BLIND CONTROLLED TRIAL

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- 1 The effect of oral nifedipine has been examined in patients with hypertension in whom arterial pressure was not adequately controlled by the combination of a β -adrenoceptor antagonist (or α -methyl dopa) and a diuretic.
- 2 In 42 patients, nifedipine (10 mg capsules) was added to the existing therapy in a final dose of 20–60 mg daily. Six patients had to stop the drug on account of side-effects. In the 36 patients who continued treatment, arterial pressure fell by an average of 24/9 mmHg supine and 26/10 mmHg standing.
- 3 In 11 of these patients who subsequently completed a double-blind, cross-over, placebo controlled trial, nifedipine (30–60 mg daily) was found to reduce arterial pressure by an average of 19/11 mmHg supine and 21/12 mmHg standing.
- 4 In all 11 patients who were changed to a sustained release preparation of nifedipine, control of arterial pressure was at least as good as it had been when taking the capsules.

Introduction

Drugs acting directly or indirectly to dilate resistance vessels are widely used in the treatment of those patients with hypertension in whom the combination of a β -adrenoceptor antagonist and a diuretic has failed to reduce arterial pressure to an acceptable level. None of the currently available dilator agents is entirely satisfactory: some, such as prazosin and hydralazine, are not consistently effective, and most give rise to unwanted effects of sufficient severity to significantly limit their usefulness. Nifedipine is a smooth muscle relaxant that is believed to work by inhibiting the inward flux of calcium through potential operated channels (Grün & Fleckenstein, 1972); in consequence of this mode of action, nifedipine is a selective dilator of resistance vessels with little or no effect on capacitance vessels (Robinson *et al.*, 1980). This pattern of action, which resembles that of hydralazine and diazoxide, suggested that nifedipine might be effective in the treatment of hypertension, and the wide experience that has been gained with the drug in angina pectoris indicates that it is relatively free from serious unwanted effects in long term treatment. We therefore undertook to study the effect of nifedipine in patients with hypertension in whom arterial pressure was not adequately controlled by the combination of a β -adrenoceptor antagonist (or α -methyl dopa) and a diuretic and in whom the addition of a dilator agent was indicated.

Methods

Open trial

A total of 42 patients was studied; 22 were men and 20 women and they ranged in age from 38 to 68 years (mean 53 years). All patients had been assessed by full clinical examination and all had been investigated by chest X-ray, electrocardiography and estimation of plasma electrolytes, urea and creatinine; in 40 patients, hypertension appeared to be primary in origin, but in two it was secondary to chronic renal disease. All patients had hypertension that was not adequately controlled by standard drugs other than dilator agents. Nifedipine was added to the existing regime in a dose of 10 mg three times daily increasing as necessary to a maximum of 20 mg three times daily, and the effect on arterial pressure was recorded at routine clinic visits. Arterial pressure was measured with a standard sphygmomanometer and the diastolic was recorded at phase four of the Korotkoff sounds.

Double-blind placebo controlled trial

Twelve patients (6 men and 6 women) who had appeared to respond to nifedipine in the open study agreed to take part in a controlled trial. Each patient gave their consent after full explanation of the procedure, and permission for the trial was given by the Ethics Committee of St George's Hospital. During

the trial, arterial pressure was measured at each attendance by the same observer with a random zero sphygmomanometer and unwanted effects were enquired for by a second observer. Each patient was seen twice before entering the blind phase of the trial which consisted of two 2-week periods during each of which the patient took 10 mg nifedipine capsules or matching placebo capsules for 1 week each in random order. All other treatment remained unchanged.

Assessment of sustained release preparation

The effectiveness of a sustained release preparation in the form of tablets containing 20 mg of nifedipine was assessed in 11 patients previously stabilised on the standard 10 mg capsules. Informed consent was again obtained from each patient and permission for the trial was given by the Ethical Committee of St George's Hospital. Those patients receiving a daily total of 30 mg of nifedipine in capsule form (7) and the single patient receiving 40 mg daily were given one 20 mg tablet twice daily; those receiving 60 mg daily (3) were given two 20 mg tablets in the morning and one in the evening. The dosage of all other drugs remained unchanged. Arterial pressure was measured using a random zero sphygmomanometer; it was recorded at a morning clinic on one occasion before the changeover and on at least two occasions over a 6-week period while taking the sustained release preparation. In five patients, arterial pressure was also assessed on one occasion during the afternoon.

Results

Open trial

In 6 of the 42 patients in whom treatment with nifedipine was initiated, the drug was discontinued before its effect could be assessed; 3 patients stopped the drug themselves within a few days with complaints of drowsiness and depression (1), flashing lights (1) and vague malaise (1); in 3 patients the drug was withdrawn because of deterioration of intermittent claudication (1) or aggravation of previously unrecognised angina (2); in each case the symptoms cleared rapidly when the drug was stopped.

Of the 36 patients who continued with the drug, 31 were receiving a β -adrenoceptor antagonist and 5 α -methyldopa; 33 were taking a diuretic and 1 bethanidine; 3 patients were taking hydralazine which had been partially effective. In the 4 patients who had been taking hydralazine or bethanidine, these drugs were successfully withdrawn after stabilisation on nifedipine. When the optimal dose of nifedipine had been achieved (20 mg daily in 1 patient, 30 mg daily in 30 patients, 40 mg daily in 2, and 60 mg

daily in 3 patients), arterial pressure was reduced on average by 24/9 mmHg supine and 26/10 mmHg standing (Table 1). Unwanted effects were reported by 13 of the 36 patients, but in only two did these limit the dose that could be given; subjective effects included light headedness (5), headache with a sensation of flushing (5) and burning legs (1); 3 patients developed ankle oedema without evidence of cardiac failure. One patient who had responded to an initial 20 mg dose of nifedipine with a fall in arterial pressure from 210/110 to 138/80 mmHg showed no response during long term treatment. All patients who maintained their response over the first week or so, however, continued to respond over the ensuing months; in a small number, the dose of nifedipine was increased after the first few months, usually in relation to the elimination of other drugs from the regime. The first patients to be included in this series have now been maintained on nifedipine for more than 4 years with continuing control of arterial pressure.

Double-blind trial

Of the 12 patients included in the double-blind trial, one man withdrew during the first week with complaints of side effects while taking placebo. In the remaining 11 patients, all of whom were taking a β -adrenoceptor antagonist together with a diuretic, the dose of nifedipine was 10 mg three times daily in 4, 20 mg twice daily in 1 and 20 mg three times daily in 6. The results confirmed the findings of the open study with an average reduction of arterial pressure while taking nifedipine of 19/11 mmHg supine and 21/12 mmHg standing (Table 1); heart rate in the supine position averaged 63 beats/min while taking nifedipine and 60 beats/min while on placebo (difference not significant). Body weight showed no significant difference between the periods on active drug and the periods on placebo which suggests that under the conditions of this study no retention of salt and water occurred. Nevertheless, one patient had ankle swelling while taking the active drug which disappeared when taking placebo; no other unwanted effect showed a consistent relationship to treatment with nifedipine.

Sustained release preparation

In the four patients who remained on the same total dose of nifedipine after the changeover from the capsule to the slow release tablet, there was no significant change in arterial pressure. In the remaining seven patients in whom the change of preparation necessitated an increase of 10 mg in the total daily dose, arterial pressure fell after transfer to the slow release tablet so that there was a significant reduction in pressure in the group as a whole (Table 2). In the five patients in whom observations were made at different

Table 1 Effect of nifedipine on arterial pressure. Values show mean $\pm$ s.e. mean. Statistical significance of differences has been tested by paired *t*-test.

	Arterial pressure (mmHg)				Weight (kg)
	Lying Systolic	Lying Diastolic	Standing Systolic	Standing Diastolic	
<i>Open study</i>					
(<i>n</i> = 36)					
Before nifedipine	165 ± 5	106 ± 3	178 ± 4	109 ± 2	
Nifedipine	141 ± 3	97 ± 2	152 ± 4	99 ± 2	
Significance	<i>P</i> < 0.001	<i>P</i> < 0.005	<i>P</i> < 0.001	<i>P</i> < 0.001	
<i>Double-blind trial</i>					
(<i>n</i> = 11)					
Placebo	157 ± 6	99 ± 3	148 ± 6	103 ± 3	70.0 ± 2.9
Nifedipine	138 ± 5	88 ± 4	127 ± 5	91 ± 3	69.8 ± 2.9
Significance	<i>P</i> < 0.01	<i>P</i> < 0.025	<i>P</i> < 0.05	<i>P</i> < 0.005	NS

times of day, there was no significant change in pressure between the morning and afternoon: supine arterial pressure was $142 \pm 7/89 \pm 7$ mmHg in the morning and $134 \pm 9/88 \pm 1$ mmHg in the afternoon; standing pressure was $139 \pm 7/93 \pm 6$ mmHg in the morning and $135 \pm 10/89 \pm 2$ mmHg in the afternoon. No patient receiving the sustained release preparation reported any adverse effects, and all 11 patients remarked on the convenience of the twice daily regime.

Discussion

The results of the open trial suggest that nifedipine induces a useful additional fall in arterial pressure when given to patients who have not responded fully to standard therapy. This impression was confirmed by the results of the double-blind cross-over trial. The present study has thus confirmed, under more rigorous conditions than those of previous investigations that nifedipine is an effective agent for the treatment of raised arterial pressure. Nifedipine has previously been demonstrated to have a potent hypotensive action when given acutely to patients with severe hypertension (Guazzi *et al.*, 1977) and it has also been reported to be effective in more prolonged

therapy when given either alone or in combination with α -methyldopa (Olivari *et al.*, 1979; Guazzi *et al.*, 1980). When given alone, nifedipine induces a greater proportional reduction in arterial pressure in patients with hypertension than it does in normal subjects (MacGregor *et al.*, 1981). This property, which is not shared by other antihypertensive drugs, may be related, at least in part, to the observation that the forearm resistance vessels of patients with hypertension show a response to the pharmacologically related compound, verapamil, that is significantly greater than that of normotensive controls (Robinson *et al.*, 1982). This alteration in responsiveness of the resistance vessels may reflect a specific functional abnormality of the vascular smooth muscle and suggests that calcium channel blockers may be particularly suited to use as arteriolar dilators in patients with hypertension.

Nifedipine was not effective in every patient, and in one a large initial effect was not maintained in long-term treatment. In the majority who did respond, however, the fall in arterial pressure that was achieved was comparable to that reported with hydralazine (Zacest & Koch-Weser, 1972) and one patient who was almost entirely resistant to hydralazine responded well to nifedipine. The direct pharmacological effects of nifedipine are of relatively

Table 2 Effect of sustained release preparation of nifedipine compared to that of standard capsules. Values shown are mean $\pm$ s.e. mean (*n* = 11). Statistical significance has been tested by paired *t*-test.

	Arterial pressure (mmHg)			
	Lying Systolic	Lying Diastolic	Standing Systolic	Standing Diastolic
Nifedipine capsules	147 $\pm$ 5	91 $\pm$ 4	140 $\pm$ 5	94 $\pm$ 3
Nifedipine sustained release preparation				
2 weeks of therapy	129 $\pm$ 4	84 $\pm$ 3	125 $\pm$ 4	86 $\pm$ 2
Significance	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001
6 weeks of therapy	139 $\pm$ 5	84 $\pm$ 5	133 $\pm$ 5	85 $\pm$ 4
Significance	<i>P</i> < 0.001	<i>P</i> < 0.01	<i>P</i> < 0.001	<i>P</i> < 0.001

short duration when the drug is given in capsule form, but the effect on arterial pressure has been reported to persist for 8 to 12 h so that satisfactory control of hypertension can be obtained with a three times daily regime (Guazzi *et al.*, 1980). In the present trial, measurements of arterial pressure were made 2 to 3 h after the morning dose of capsules and no information on the duration of action is available. In the investigation of the sustained release preparation, however, it was found that control of arterial pressure after an early morning dose was at least as good in the afternoon as it had been in the morning. The sustained release preparation was preferred by the patients and may prove to be the most convenient way of administering the drug in the treatment of hypertension.

Unwanted effects were mostly of a subjective nature and not intrinsically serious. Two patients, however, reported aggravation of angina, an effect that has been noted by others in occasional patients (Jariwalla & Anderson, 1978). Another patient reported aggravation of intermittent claudication, but

placebo controlled studies would be required before concluding that this effect resulted from the action of nifedipine. Nifedipine induces a rise in plasma renin activity (MacGregor *et al.*, 1981), but unlike many dilator drugs, it shows little tendency to cause sodium retention. This might relate, at least in part, to the observation that nifedipine attenuates the aldosterone response to angiotensin II (Millar *et al.*, 1981). The occasional appearance of ankle oedema appears unrelated to any general sodium retention or cardiac failure and probably reflects selective dilatation of the precapillary resistance vessels with consequent elevation of filtration pressure.

The results of the present investigation indicate that nifedipine is an effective agent for the treatment of hypertension when used in conjunction with a β -adrenoceptor antagonist (or α -methyldopa) and a diuretic. It is at least as effective as hydralazine and offers advantages over other peripheral dilators currently in use clinically. Further evaluation of its place in the management of hypertension appears warranted.

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