Control of hypertension in elderly patients with felodipine and metoprolol: a double-blind, placebo-controlled clinical trial

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1 Forty-nine patients aged 65–80 years, whose Phase V diastolic blood pressure (dBP) was above 95 mmHg after 4 weeks open treatment with metoprolol 50 mg twice daily were randomized to receive, double-blind, the calcium antagonist felodipine ($n = 32$) 2.5 mg twice daily or placebo ($n = 17$) in addition to metoprolol for 2 weeks. If the dBP remained > 95 mmHg, the dose of felodipine or placebo was doubled for a further 2 weeks; if the dBP was still > 95 mmHg, the dose of felodipine was doubled again to 10 mg twice daily or the corresponding placebo dose given. The duration of the double-blind period was 6 weeks, all patients receiving metoprolol 50 mg twice daily throughout.

2 At the end of the double-blind period, the seated dBP was reduced from 103 ± 5 (mean $\pm$ s.d.) to 88 ± 7 mmHg ($P < 0.001$) by felodipine and from 105 ± 7 to 100 ± 11 mmHg (NS) by placebo. The differences between these reductions ($P < 0.01$) and between the final dBPs ($P < 0.001$) were significant. Eighty-nine per cent of patients receiving felodipine and 33% of those receiving placebo ($P < 0.001$) had controlled (dBP ≤ 95 mmHg) BPs. Half (14/27 completing) of the patients receiving felodipine required 2.5 mg throughout; 9/27 needed 5 mg and 4/27 10 mg twice daily. Adverse events occurred with equal frequency in the two groups, but the profile was different.

3 In this group of patients aged 65–80 years, felodipine 2.5–10 mg twice daily is an effective and safe antihypertensive agent when added to metoprolol 50 mg twice daily. Larger numbers of patients and longer periods of therapy are, however, needed for further evaluation.

Keywords hypertension elderly patients felodipine calcium antagonist metoprolol

Introduction

There is increasing evidence that hypertension in the elderly should be detected and treated (O'Malley & O'Brien, 1980; Australian Mild Hypertension Trial, 1981), in order to reduce the risk of stroke (Shekelle *et al.*, 1974) and cardiovascular mortality and morbidity (Amery *et al.*, 1985). Indeed, the identification of elderly hypertensive patients as a group at high risk of cerebrovascular accidents has led to the suggestion that in this group there is clear reason to treat their hypertension (Anon, 1985).

What is less clear than the need for antihypertensive therapy in elderly patients is the appropriate choice of drugs. The EWPHE trial (Amery *et al.*, 1985) has shown that in elderly hypertensives, diuretics are relatively safe and probably could be given in smaller doses than hitherto recommended. Newer drugs such as ACE inhibitors and calcium antagonists have also been shown to be effective and claimed to have fewer side effects but further experience is indicated in order to assess their long term efficacy.

Since β -adrenoceptor blockers are effective anti-hypertensive agents in the majority of patients, it seemed reasonable to assess the efficacy of a Ca^{2+} antagonist plus a β -adrenoceptor blocker (metoprolol and felodipine) since they appear to complement one another haemodynamically. Consequently they may be effective in lower doses than would be required for monotherapy with either drug.

Methods

Elderly patients in need of antihypertensive therapy were identified by screening or case-finding in seven General practices; in some cases previous therapy was withdrawn prior to the run-in.

The inclusion criteria for the metoprolol monotherapy run-in were: (1) aged 65–79 years, (2) seated phase V diastolic pressure (dBP)

100 mmHg or above, untreated, on each of 3 occasions. Exclusion criteria were: (1) systolic phase I pressure (sBP) < 160 or > 240 mmHg, (2) dBP > 125 mmHg, (3) immobility, (4) severe renal, hepatic or haematological disorders, (5) potentially poor compliance, (6) insulin-dependent or unstable diabetes, (7) angina requiring medication other than sublingual GTN and/or metoprolol 50 mg twice daily, (8) second or third degree A–V conduction defects or bundle branch block, (9) cardiac failure, cerebrovascular accident or myocardial infarction in the past 3 months, (10) clinical need for, or known intolerance to, β -adrenoceptor blockers or calcium antagonists, (11) symptomatic or treated peripheral oedema, and (12) unwillingness of the patient or GP. Of these only (10) and (11) are regarded as being specifically related to the trial medication. The design of the trial is shown in Figure 1.

Visit	1	2	3	4	5	6	7
Weeks	0	2	4	8	10	12	14
BP+HR	+	+	+	+	+	+	+
Weight	+	+	+	+	+	+	+
Height	+						
Lab tests/ECG		+					+
Side-effects			+	+	+	+	+
Physical examination	+						+

Figure 1 Trial design M metoprolol, F felodipine, P placebo (a, b or c to match felodipine), c controlled (dBP 95 mmHg or less), nc not controlled (dBP over 95 mmHg), R randomization. All doses are in mg twice daily.

Phase I (sBP) and V (dBP) arterial pressure was recorded using a random-zero sphygmomanometer (Hawksley) and appropriate sized arm cuff, both seated (after 5 min rest) and standing (after 1 min); heart rate (HR) was counted over 30s from the radial pulse after each BP measurement. Measurements were scheduled 12 h after tablet ingestion.

Seated dBP was used for all trial decisions and to define BP 'control'. A seated diastolic blood pressure of 95 mmHg or below was prospectively defined as 'controlled'.

Potential participants, untreated for hypertension, were invited to attend a blood pressure clinic at the GP's surgery (Visit 1) and if their dBP was 100 mmHg or more, they returned in 2 weeks (Visit 2). If the dBP was ≥ 100 mmHg at Visit 2 they had a standard blood and urine laboratory screen, physical examination, and 12-lead ECG to confirm eligibility. They returned in a further 2 weeks (Visit 3) and if the dBP was still ≥ 100 mmHg received metoprolol 50 mg (Betaloc, Astra) twice daily openly for 4 weeks. They were then randomised to one group, which received felodipine 2.5 mg twice daily and another group receiving placebo in addition to 50 mg metoprolol twice daily, provided that their dBP was > 95 mmHg. Thereafter the patients attended at 2-weekly intervals. If their dBP was > 95 mmHg, the dose of felodipine was doubled, until dBP reached 95 mmHg or less. To conform to usual practice in GP clinics, patients were allowed to attend at any time during the day.

Possible adverse drug experiences were elicited by active questioning using a standard 35 point questionnaire at every visit.

Statistics

The main analysis is an on treatment analysis including data for all patients available at each Visit. A second 'pragmatic' analysis includes only measurements made arbitrarily 7–17 h post-ingestion of tablets in an attempt to assess the minimum antihypertensive effects. The data were examined for centre effects and there were no qualitative differences between felodipine and placebo effects between centres. Student's *t*-test was used except for dichotomous variables (Chi-square test) and laboratory data (analysis of variance of ranks; Mann-Whitney).

Data are expressed as means $\pm$ s.d., *P* values of 0.05 or greater are regarded as non-significant (NS).

Ethics

The trial was conducted in accordance with the

Declaration of Helsinki, and was approved by Ethics Committees responsible for Wandsworth, South Glamorgan, Mid-Glamorgan and Oxfordshire. Written informed consent was obtained from each participant.

Results

Diagnosis and run-in

Eighty eight patients were considered potentially eligible at Visit 1 of whom 78 were confirmed to be eligible at Visit 3 (dBP ≥ 100 mmHg). After metoprolol 50 mg twice daily for 4 weeks, 29 (37%) had a 'controlled' BP (dBP ≤ 95 mmHg) leaving 49 'not controlled' who entered the double-blind comparison.

Randomization (Table 1)

Randomization yielded two comparable groups of patients.

Changes in BP and HR over the trial period (Figure 2)

Seated dBP was reduced from 103 ± 5 to 88 ± 7 mmHg ($P < 0.001$) by felodipine after dose titration in the range 2.5–10 mg and from 105 ± 7 to 100 ± 11 mmHg (NS) by placebo (Figure 2) after 6 weeks. The difference between the reduction in dBP due to felodipine (15 ± 7 mmHg) and that due to placebo (5 ± 11 mmHg) was statistically significant ($P < 0.01$). The difference between the seated dBPs at Visit 7 (88 ± 7 mmHg in the felodipine group and 100 ± 11 mmHg in the placebo group) was also significant ($P < 0.001$).

Seated sBP was reduced by 18 ± 21 mmHg in the felodipine group ($P < 0.001$) and 8 ± 15 mmHg (NS) in the placebo group, the difference between the changes in the two groups just failing to achieve significance ($P = 0.06$).

Standing dBP was reduced by 13 ± 9 mmHg ($P < 0.001$) in the group receiving felodipine for 6 weeks compared with 6 ± 9 mmHg ($P < 0.05$) in the placebo group. The difference between these reductions was statistically significant ($P < 0.05$), as was the difference between the standing dBP at Visit 7 (94 ± 9 mmHg in the felodipine and 104 ± 12 mmHg in the placebo group: $P < 0.01$).

Standing sBP fell by 18 ± 22 mmHg ($P < 0.001$) and 4 ± 13 mmHg (NS) in the groups of patients receiving felodipine and placebo respectively, a significantly ($P < 0.05$) greater reduction in sBP with felodipine compared with placebo.

Table 1 Patient characteristics at randomization

	Felodipine	Placebo
Number randomized	32	17
Sex (M:F)	12:20	8:9
Age (years)	72 ± 4	72 ± 5
WHO stage (I: II: III)	30:1:1	16:1:0
Metoprolol therapy (days)	33 ± 11	30 ± 9
Weight (kg)	71 ± 13	73 ± 12
Seated BP (mmHg)	178 ± 18/103 ± 5	181 ± 21/106 ± 7
HR (beats min ⁻¹)	74 ± 14	72 ± 17
Standing BP (mmHg)	177 ± 21/107 ± 9	176 ± 18/111 ± 11
HR (beats min ⁻¹)	75 ± 14	74 ± 15

Data are expressed as mean ± s.d.

Figure 2 Changes in blood pressure after 2 (Visit 5) and 6 (Visit 7) weeks on felodipine plus metoprolol or placebo plus metoprolol compared with metoprolol monotherapy (Visit 4). *n* = number of patients. Stars within bars show significance of changes from Visit 4; lower bars show significance of difference in antihypertensive effects. * *P* < 0.05, ** *P* < 0.01, *** *P* < 0.001. Horizontal broken line = 95 mm Hg.

There was no tendency to faintness on standing and no significant difference between seated and standing pressures in either group at any visit.

There were no significant changes in body weight in either the felodipine or the placebo groups between Visits 4 and 7. The median

intervals from tablet ingestion to BP measurement at Visit 7 were 12 h in the felodipine group and 9 h in the placebo group. Omission of the results where BP was measured outside the range 7 to 17 h after tablet intake reduced the statistical power of the study but did not alter the pattern of results (Figure 2).

Control of BP (Table 2)

At Visit 7, significantly ($P < 0.001$) more patients receiving felodipine than placebo had controlled blood pressures. At the end of the trial, 89% of patients receiving metoprolol plus felodipine had controlled blood pressure (Table 2).

Adverse events

Adverse 'events' occurred with equal frequency but the profile of adverse reactions differed in the two groups (Table 3). They were not dose related. In the felodipine group the main complaints were dyspepsia, dizziness, headaches and peripheral oedema; in the placebo group dyspnoea, fatigue and wheezing. One patient withdrew from felodipine because of ankle oedema. Non-drug related withdrawals were because of a fall (which was unrelated to felodipine therapy), non-compliance (placebo) and withdrawal of consent (three felodipine and one placebo).

In the felodipine group there was a small but significant decrease in haematocrit, Hb concentration and red cell count.

Discussion

This study was designed to fit in, as far as possible, with the usual treatment of systemic hypertension in elderly patients in the U.K. The group of patients, who were ultimately entered into the trial were highly selected but this in accord with the results of other anti-hypertensive trials (MRC and EWPHE) which indicate the need for better selection of patients. The proportion of patients whose BP was controlled on metoprolol monotherapy (37%) was smaller than expected. This might be due to the fact that a full β -adrenoceptor blocking dose of metoprolol was not used because of combination therapy. After the run-in period two well matched groups resulted.

Felodipine produced greater reductions in sBP and dBP, and controlled the dBP of a significantly greater proportion of patients than placebo

after 6 weeks treatment: 89% of the patients receiving felodipine compared with 33% of those receiving placebo in addition to metoprolol had a 'controlled' blood pressure. Symptoms recorded were roughly equally-distributed between the two treatment groups, but there was a slight excess of ankle oedema and dyspepsia in the group receiving felodipine.

The timing of BP measurements needs to be considered: patients were excluded from the pragmatic analysis if their blood pressures were measured at times substantially different from the protocol requirement of 12 h after taking the tablets. However, in the 'on treatment' analysis, despite variability in the timing of BP measurements, the median times at Visits 5, 6 and 7 approximate well to this 12 h interval and there was no difference between the groups with respect to timing of measurements, or between the results obtained with the two methods of analysis. It is probable that the time intervals in the 'on treatment' analysis correspond with those that would occur in General Practice and the results suggest that a twice daily regimen is adequate for daily BP control and that BP readings need not be taken at rigidly prescribed times in relation to felodipine administration.

In elderly patients treated in General Practice in whom metoprolol 50 mg twice daily is not an adequate antihypertensive regimen, felodipine has been shown to be a safe and effective second-line drug. Although the lower dose (2.5 mg twice daily) was not shown statistically to have an unequivocally better effect than placebo after 2 weeks, in about half of the patients receiving felodipine, the lowest dose was adequate, and few patients needed the highest dose, 10 mg twice daily. On the basis of this study it may be appropriate to recommend a starting dose of 5–10 mg daily in elderly patients requiring additional antihypertensive medication to β -adrenoceptor blocker monotherapy, with adjustments of the felodipine dose on the basis of clinical need.

There was a small but significant fall in Hb, haematocrit and RBCs. This has occurred in other trials with felodipine but, in each patient,

Table 2 Proportions of patients with controlled BP at the end of the trial

Visit	Felodipine doses (mg)*			All felodipine	All placebo
	2.5	5	10		
7	13/14	8/9	3/4	24/27 (89%)	5/15 (33%) $P < 0.001$

* (number controlled)/(number in group).

Table 3 Adverse events. The proportion of patients reporting any of the most common adverse events during the trial

	% of patients reporting adverse event	
	Visit 4 (metoprolol monotherapy)	Visits 5, 6 and 7 (metoprolol plus placebo or felodipine)
Placebo group (n = 17)		
Dyspnoea	23	15
Fatigue	23	13
Constipation	12	4
Dizziness	12	6
Insomnia	12	4
Rhinitis	12	6
Somnolence	12	4
Flatulence	6	6
Headache	6	6
Wheezing	6	8
Felodipine group (n = 32)		
Dyspepsia	13	19
Dyspnoea	13	10
Dizziness	3	3
Tinnitus	6	8
Fatigue	6	14
Headache	6	10
Insomnia	13	5
Rhinitis	3	5
Chest pain	3	5
Flatulence	3	8
Sweating	3	5
Peripheral oedema	0	9

the lower values of their laboratory tests remained within normal limits. The cause of these changes is unknown, but they are not progressive.

Others (Amery *et al.*, 1985) have shown that it is desirable and worthwhile to treat hypertension in elderly people; we have shown that the combination of low doses of metoprolol and the dihydropyridine calcium antagonist felodipine is an effective and safe antihypertensive treatment in this age group.

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(Received 29 January 1987,
accepted 14 May 1987)