Felodipine as a replacement for minoxidil in the treatment of severe hypertension

C. G. Wathen, D. MacLeod, L. Tucker and A. L. Muir

Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW, U.K.

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The new calcium antagonist felodipine has been compared with minoxidil in the management of severe hypertension in a group of 17 men. Satisfactory control of blood pressure was achieved in all patients with a combination of beta blocker, loop diuretic and minoxidil after inadequate control on a standard regimen of beta blocker, thiazide and vasodilator. The optimal dose of felodipine was titrated after a placebo phase. In a double blind crossover trial blood pressure on felodipine (150/88 ± 19/8 mmHg, SD) was the same as on minoxidil (148/87 ± 23/11 mmHg, NS) and the postural difference was similar (NS) on both drug regimens. Body weight was lower on the felodipine regimen (P<0-01), as was supine heart rate (P < 0.05). There was a small rise in plasma liver enzymes on felodipine therapy (P<0-01). Felodipine was well tolerated and may be useful in the management of severe hypertension.

Introduction

Despite modern drug therapy the management of true drug resistant hypertension remains a problem in clinical practice. In one comparative study of antihypertensive agents added to treatment when blood pressure remained uncontrolled by a beta blocker plus thiazide diuretic, minoxidil was shown to be the most effective, but was poorly tolerated by the patients[1]. Moreover, hirsutism limits the use of minoxidil to male patients and fluid retention can be a significant problem[3]. It has been our practice to restrict the use of minoxidil to those male patients who have failed to respond to other 'third line vasodilators' such as, hydralazine, prazosin or nifedipine despite good compliance. Recent reports[5-7] have indicated felodipine, a novel dihydropyridine calcium channel antagonist and potent arterial vasodilator might prove useful in severe hypertension.

We have therefore compared felodipine with minoxidil in a group of male patients who had not been controlled on treatment with beta adrenergic antagonists, thiazide diuretics and a vasodilator (prazosin, hydralazine or nifedipine) but were controlled with minoxidil as the third line agent.

Patients and methods

Seventeen hypertensive men (46–67 years of age) who attended our Out-Patient Hypertension Clinic were studied. All suffered from WHO Stage III hypertension with end organ damage in the form of stroke, retinopathy, left ventricular hypertrophy and/or renal failure at presentation. On therapy with atenolol, thiazide diuretic and hydralazine, prazosin or nifedipine, their diastolic blood pressure (Phase V) had remained greater than 115 mmHg and they had eventually been controlled on a combination of atenolol 50–100 mg daily, frusemide in a dose of 40–160 mg or bumetanide 1–3 mg daily and minoxidil 10–45 mg daily (Fig. 1). Because of side effects whilst taking atenolol one patient took labetalol 800 mg daily. Beta blockade was confirmed in all patients, using the rise in heart rate on exercise.

Patients were excluded if they had suffered a myocardial infarction within 3 months prior to the study or had severe angina pectoris, uncompensated heart failure or other severe concomitant disease. Patients were also excluded if they had evidence of poor compliance with treatment or were poor clinic attendees. All patients were told of the nature and purpose of the study and freely consented to take part. The study had the approval of our Institute's Ethics Committee and the Department of Health and Social Security.

MEASUREMENT OF BLOOD PRESSURE

The blood pressure and heart rate was measured...
by a single trained observer using a Hawksley random zero sphygmomanometer. Pressure readings were taken after 5 minutes rest in the supine position and after 1 minute standing. Diastolic pressure was taken at the point of disappearance of sounds (Phase V).

STUDY DESIGN

The optimal dose of minoxidil as antihypertensive therapy had already been established in clinical dose-titration and all patients were considered to have achieved satisfactory control of blood pressure on minoxidil. The mean of three blood pressure recordings taken on three consecutive visits prior to the study were then taken to be the target pressure for the subsequent felodipine dose ranging phase. Minoxidil was then withdrawn and placebo 'felodipine' prescribed. Other therapy was left unchanged. The patient was then observed closely for 2 weeks but if there was a rise in systolic or diastolic blood pressure of 15 mmHg active treatment began (Fig. 1). The patient was then prescribed active felodipine 5 mg twice daily (b.d.) and a dose ranging study commenced with felodipine increased to 10 mg and 20 mg b.d. weekly to achieve the individual's target blood pressure and ascertain the optimal felodipine dosage or until significant side effects appeared. Once optimal readings had been achieved patients were randomized, double blind, to a 6 week treatment period with minoxidil or felodipine at the predetermined optimal doses. The response to therapy was assessed at 3 and 6 weeks. At the end of the 6 week period the alternate drug was administered for a further 6 weeks. All other therapy was kept unchanged.

OBSERVATIONS

In addition to heart rate and blood pressure, body weight was measured at each clinic attendance, as was ankle circumference and evidence of pitting oedema sought. Adverse effects were sought in two ways, firstly by spontaneous comments recorded by the patient at each clinic visit and secondly, by the doctor's enquiries about side effects which was confined to a standard question, 'Since we last met, have you been bothered by any symptoms which are out of the ordinary for you?' at each clinic visit. Prior to entry and at the end of each crossover limb, electrocardiogram, full blood count, serum urea, electrolytes, creatinine and liver function tests were measured. Urinalysis was performed at each clinic visit.

To assess compliance tablets were prescribed in 'blister packs' and tablet counts performed at each clinic visit.

STATISTICAL ANALYSIS

Data are presented as mean ± standard deviation. Statistical analysis was carried out by Wilcoxon rank sum test and values of $P > 0.05$ were considered not significant.

Results

DEATHS AND WITHDRAWALS

One patient died during the initial dose ranging stage. The history and electrocardiogram suggested anterior myocardial infarction and left ventricular failure but autopsy permission was not granted. Blood pressure measured 2 days prior to his death was little different (144/94 mmHg supine) from previous recordings on minoxidil (160/95 mmHg supine). One patient suffered a possible small subendocardial myocardial infarction while on felodipine and was withdrawn. However, 4 months later he still required minoxidil to control his hypertension and he was therefore re-entered into the study. His subsequent progress was uneventful and he remains well on felodipine. One patient withdrew
from the study because he found regular clinical attendance too difficult. There were thus 15 patients who completed both limbs of the study.

The patients were all accustomed to the hirsutism and 2 were able to tell which drug they were on from hair growth. Tiredness and headaches were slightly more common on minoxidil and 'dizziness' on felodipine but the total number of complaints were few.

CLINICAL DATA

The mean supine blood pressure readings on standard triple therapy were 195/118 ± 20/14 (SD) mmHg, on minoxidil 160/94 ± 20/10 mmHg and when placebo was used to substitute for minoxidil 171/108 ± 22/12 mmHg, \( P < 0.01 \) (Fig. 1). In the dose ranging phase of the felodipine treatment 'target' blood pressure was reached in all patients. Five patients required 5 mg b.d. felodipine, eight patients 10 mg b.d. (including the patient who died) and three patients 20 mg twice daily.

In the crossover study there was no significant difference between the supine blood pressure readings on felodipine (150/88 ± 19/8 mmHg) compared with minoxidil (148/87 ± 23/11 mmHg) (Fig. 2). Erect blood pressure readings also showed no significant difference and hence the postural fall in blood pressure was the same on both regimens. Supine heart rate on felodipine was 63 ± 7 bpm whilst on minoxidil it was 69 ± 11 bpm \( (P < 0.05) \) and erect heart rate was also significantly higher on minoxidil \( (P < 0.05) \) Table 1). The mean weight on felodipine was 79.9 ± 13.1 kg whilst on minoxidil was 81.4 ± 13.3 kg \( (P < 0.01) \). Ankle circumference at the end of 6 weeks on minoxidil was 22.1 ± 1.57 cm and was 22.2 ± 1.71 cm after 6 weeks on felodipine (NS).

No significant changes in plasma electrolytes, urate, creatinine or urea concentrations values were observed during the study. There was a small but significant rise in plasma alkaline phosphatase \( (P < 0.01) \) (Table 2) on felodipine and the gamma glutamyl transferase was also higher \( (P < 0.01) \) (Table 2). Bilirubin, alanine aminotransferase, aspartate aminotransferase and plasma proteins were not changed. The random glucose on the minoxidil limb was 5.6 ± 1.5 mmol l\(^{-1}\) and was 5.6 ± 1.8 mmol l\(^{-1}\) (NS) at the end of the felodipine limb.

| Table 1 Measured data |

<table>
<thead>
<tr>
<th></th>
<th>Minoxidil</th>
<th>Felodipine</th>
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<tbody>
<tr>
<td></td>
<td>3 week</td>
<td>6 week</td>
</tr>
<tr>
<td>Supine BP (mmHg)</td>
<td>155/89 ± 25/7</td>
<td>148/87 ± 23/11</td>
</tr>
<tr>
<td>Erect BP (mmHg)</td>
<td>146/89 ± 24/9</td>
<td>142/87 ± 22/11</td>
</tr>
<tr>
<td>Supine HR (bpm)</td>
<td>67.6 ± 13.6</td>
<td>68.9 ± 10.8</td>
</tr>
<tr>
<td>Erect HR (bpm)</td>
<td>69.6 ± 14.6</td>
<td>71.2 ± 9.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.2 ± 13.0</td>
<td>81.4 ± 13.3</td>
</tr>
<tr>
<td>Ankle circumference (cm)</td>
<td>21.9 ± 1.5</td>
<td>22.1 ± 1.6</td>
</tr>
</tbody>
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* \( P < 0.05 \); ** \( P < 0.01 \)
Table 2  Biochemical data

<table>
<thead>
<tr>
<th></th>
<th>Minoxidil</th>
<th>Felodipine</th>
<th>Laboratory normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (µmol 1⁻¹)</td>
<td>116.3 ± 31.78</td>
<td>116.5 ± 30.15</td>
<td>55–150</td>
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<tr>
<td>Random blood glucose (mmol 1⁻¹)</td>
<td>5.6 ± 1.15</td>
<td>5.6 ± 1.80</td>
<td>3.6–11</td>
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<tr>
<td>Plasma potassium (µmol 1⁻¹)</td>
<td>3.9 ± 0.31</td>
<td>3.8 ± 0.29</td>
<td>3.3–4.7</td>
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<td>Plasma bilirubin (µmol 1⁻¹)</td>
<td>9.7 ± 2.44</td>
<td>10.0 ± 3.61</td>
<td>2–17</td>
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<tr>
<td>Plasma ALT (iu 1⁻¹)</td>
<td>24.7 ± 13.28</td>
<td>28.9 ± 16.40</td>
<td>10–40</td>
</tr>
<tr>
<td>Plasma AST (iu 1⁻¹)</td>
<td>23.7 ± 7.11</td>
<td>24.3 ± 9.22</td>
<td>10–35</td>
</tr>
<tr>
<td>Plasma alkaline phosphatase (iu 1⁻¹)</td>
<td>86.6 ± 23.61</td>
<td>101.8 ± 29.23*</td>
<td>40–100</td>
</tr>
<tr>
<td>Plasma gamma glutamyl transferase (iu 1⁻¹)</td>
<td>24.3 ± 10.71</td>
<td>42.3 ± 31.44*</td>
<td>10–55</td>
</tr>
</tbody>
</table>

* P < 0.01

Discussion

A number of studies have shown the effectiveness of minoxidil in management of patients with severe hypertension irrespective of the aetiology and controlled clinical trials have shown it to be more effective than hydralazine and other commonly used 'third line' drugs. However, sodium and water retention, hirsutism, and the occasional occurrence of pericarditis limit its widespread use. In this study all of the patients had failed to have their hypertension controlled by combined therapy with atenolol, thiazide diuretic and either hydralazine, prazosin or nifedipine as a vasodilator. They had eventually been controlled with minoxidil but had required a loop diuretic to minimize fluid retention while continuing their atenolol. The use of potent diuretics had led to gout in 6 patients necessitating the use of allopurinol for its control and also the need for potassium supplements. Hirsutism had been a continuing problem. None of our patients suffered the more serious side effects of pericardial effusion or pericarditis.

The calcium antagonist felodipine has marked arterial vasodilatory properties and as there is little or no venodilation, orthostatic hypotension is unlikely. Furthermore, felodipine seems to have minimal effects on cardiac contractility and even in combination with atenolol negative inotropic effects cannot be demonstrated in man in contrast to the combination of nifedipine and atenolol.

In this study blood pressure rose quickly when placebo tablets were substituted, showing that the minoxidil was exerting significant antihypertensive action, but was as well controlled on felodipine as on minoxidil. The study was designed to show whether felodipine was an effective replacement for minoxidil and indicates that it could be used as an alternative to minoxidil in the management of severe hypertension. A study of this design where felodipine was compared with a standard therapy was considered necessary for ethical reasons.

Ankle circumference was no different on the two drugs but ankle swelling with both drugs may be due to a direct vasodilatory effect on arterioles and hence increases capillary pressure. The significant loss of weight whilst on felodipine suggests that fluid retention is less marked than when on minoxidil. Zins has suggested that minoxidil increased proximal tubular reabsorption of sodium. In contrast preliminary studies with felodipine have suggested a mild diuretic and natriuretic action which has been attributed to an action on the distal nephron. Patients on minoxidil usually require potent diuretics to avoid fluid retention as did our patients but this may be unnecessary with felodipine. The changes in the plasma liver enzymes have been noted previously in one small study of severe hypertension but have not been noted in larger studies in patients with less severe hypertension. From the available data, it is not possible to determine the aetiology of the derangement but the enzyme pattern would suggest mild cholestasis. Calcium antagonist drugs are known to affect gastrointestinal smooth muscle contraction and this may be true of the biliary tree.

In this study felodipine was well tolerated and effective, but longer term trials are required to establish an adverse effects profile and to assess the drug in the management of accelerated phase hypertension.
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References


