Comparison of nisoldipine and nifedipine as additional treatment in hypertension inadequately controlled by atenolol


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Summary: Twenty-eight patients (11 Caucasian, 17 black) whose blood pressure was more than 160/96 mmHg after 4 weeks on placebo added to atenolol 100 mg/day were randomly given, in addition, nisoldipine 10 mg or nifedipine 20 mg each twice a day for 8 weeks in a double-blind cross-over study. There was a statistically significant \((P < 0.001)\) fall in blood pressure with no change in heart rate, both supine and erect, on both drugs. There were no significant differences between nisoldipine and nifedipine. Adverse effects were recorded in 15%, 17% and 35% of the patients available for safety comparison for placebo, nisoldipine and nifedipine, respectively. There were no significant differences between the black and Caucasian patients in blood pressure responses, although the study had only a low power to detect these. However, the fasting serum triglyceride levels at the end of both calcium antagonist treatment periods were highly significantly lower in the black patients compared with the Caucasian patients. Nisoldipine, which has a higher coronary vascular selectivity and less negative inotropism than nifedipine, is as effective and as well tolerated as nifedipine in patients whose hypertension is inadequately controlled on atenolol. It may have a special role in hypertensive patients with impaired left ventricular function.

Introduction

Nisoldipine is a second-generation dihydropyridine calcium channel blocking drug which has been shown to be a more potent vasodilator with higher coronary vascular selectivity and less negative inotropism than nifedipine.\(^1\)\(^-\)\(^3\) Nisoldipine is as effective and well tolerated as nifedipine for monotherapy of mild to moderate hypertension.\(^4\)\(^-\)\(^5\) It is twice as effective as nifedipine weight for weight and longer acting.\(^6\) Although the combination of nifedipine and atenolol is of proven value in hypertension,\(^7\) the only previous study of nisoldipine combined with atenolol suggested that there was a rapid development of tolerance to the calcium blocker.\(^8\) We have conducted a randomized double-blind cross-over study comparing nisoldipine and nifedipine as second-line agents in black and Caucasian patients whose hypertension was inadequately controlled on atenolol 100 mg a day.

Patients and methods

Patients recruited were attending the hypertension clinics at either the Whittington or Royal Northern Hospitals and had blood pressure (BP) that was not adequately controlled on atenolol 100 mg daily. They returned 2 weeks later when those whose BP had risen above 200/120 mmHg started active treatment (as at week 4). Those not on active treatment returned at week 4, when, if the BP was less than 160/95 mmHg, the patient was withdrawn as a placebo responder. Those patients still satisfying the entry criteria were assigned to one of two treatment sequence groups using a predetermined randomization scheme stratified for black and Caucasian patients. The treatments were nisoldipine 10 mg twice daily plus nifedipine placebo, and nifedipine 20 mg twice daily plus nisoldipine placebo each for 8 weeks, after which the patients crossed over to receive the alternative treatment, the dose of atenolol remaining unchanged throughout. Patients returned after 4 weeks of active treatment for measurement of BP and heart
rate, compliance check and assessment of adverse events. At the end of the run-in period and of each 8 week treatment period, the patients returned fasting for fractionated serum lipid estimation by standard laboratory techniques in addition to the other observations. BP was measured using a random-zero sphygmomanometer (phase V) and the means of two readings lying supine for 3 minutes and standing for 1 minute were used for analysis.

The efficacy data (BP, heart rate and lipids) at the end of each treatment period were analysed using ANOVA with race, sequence group (nisoldipine or nifedipine as first treatment), period (first or second 8 week treatment period) and treatment effects taken into account. The changes over each active treatment period were compared using paired t-tests.

Statistical analysis was performed using SAS/PC version 6.04. It was calculated that to detect a difference between nisoldipine and nifedipine of 10 mmHg in SBP and 5 mmHg in DBP at the 5% significance level with 80% power required 17 and 27 patients, respectively. The study was approved by the Islington District Ethics committee and each patient gave written informed consent.

### Results

Fifty-two patients entered the study, of whom four withdrew during the placebo period. Twenty patients were valid for safety analysis but not for efficacy (six showed poor compliance, four had BP measurements made outside the range of 1–4 hours post-medication and 10 did not complete both treatment periods). Twenty-eight patients were valid for both efficacy and safety. The demography of the groups of patients analysed for efficacy and for safety respectively are shown in Table I.

Statistically significant ($P \leq 0.001$) mean changes from end of placebo run-in to the end of each treatment period was observed for both SBP and DBP supine and standing for both treatments and both races. There were no statistically significant effects of race, treatment sequence, period or the active treatments for any of the blood pressures or heart rates. Table II shows the results of the treatment groups combined.

There were no statistically significant differences in fasting fractionated lipids between nisoldipine and nifedipine treatment or between Caucasians and blacks for these variables, except for triglycerides. The black patients had a higher mean value

### Table I Demographic data

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Safety</th>
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<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>Mean age (s.d.) (years)</td>
<td>55.6 (9.7)</td>
<td>54.4 (8.8)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/21</td>
<td>14/34</td>
</tr>
<tr>
<td>Mean weight (s.d.) (kg)</td>
<td>84.0 (19.5)</td>
<td>82.6 (18.7)</td>
</tr>
<tr>
<td>Caucasian/black</td>
<td>11/17</td>
<td>18/30</td>
</tr>
<tr>
<td>Mean duration of hypertension (range) (years)</td>
<td>7.0 (2.3–13.8)</td>
<td>6.5 (2–11.6)</td>
</tr>
<tr>
<td>Abnormal electrocardiogram</td>
<td>14</td>
<td>23</td>
</tr>
</tbody>
</table>

### Table II Blood pressure and heart rate response

<table>
<thead>
<tr>
<th></th>
<th>Entry Week 0</th>
<th>Run-in Week 4</th>
<th>Nisoldipine 4 weeks</th>
<th>Nisoldipine 8 weeks</th>
<th>Nifedipine 4 weeks</th>
<th>Nifedipine 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP supine (mmHg)</td>
<td>28</td>
<td>184.3 (16.3)*</td>
<td>181.0 (17.0)</td>
<td>153.8 (18.4)</td>
<td>147.1 (18.4)</td>
<td>151.8 (18.6)</td>
</tr>
<tr>
<td>SBP standing (mmHg)</td>
<td>28</td>
<td>180.6 (16.7)</td>
<td>178.3 (18.0)</td>
<td>148.0 (21.5)</td>
<td>143.5 (18.8)</td>
<td>149.0 (19.5)</td>
</tr>
<tr>
<td>DBP supine (mmHg)</td>
<td>28</td>
<td>111.0 (8.6)</td>
<td>110.4 (9.1)</td>
<td>92.3 (9.9)</td>
<td>88.5 (10.8)</td>
<td>94.7 (12.3)</td>
</tr>
<tr>
<td>DBP standing (mmHg)</td>
<td>28</td>
<td>112.8 (11.1)</td>
<td>112.6 (12.4)</td>
<td>95.0 (11.3)</td>
<td>91.8 (10.8)</td>
<td>96.6 (12.8)</td>
</tr>
<tr>
<td>HR supine (bpm)</td>
<td>28</td>
<td>70.2 (8.3)</td>
<td>68.6 (6.9)</td>
<td>69.0 (10.9)</td>
<td>70.8 (13.1)</td>
<td>71.7 (10.7)</td>
</tr>
<tr>
<td>HR standing (bpm)</td>
<td>28</td>
<td>71.8 (8.2)†</td>
<td>69.2 (7.2)</td>
<td>71.6 (9.4)</td>
<td>73.0 (12.9)</td>
<td>72.6 (11.1)</td>
</tr>
</tbody>
</table>

*n = 27; †mean (s.d.). HR = heart rate.
for high density lipoprotein (HDL) cholesterol and lower mean values of total cholesterol, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol and triglycerides than Caucasians after both active treatments (Table III). There was a statistically significant ($P = 0.013$) race effect for triglycerides, the mean levels being lower in black patients after both nisoldipine and nifedipine. The race effect showed a greater statistically significant difference ($P = 0.0012$) when the data were analysed after log transformation. There was also a significant ($P < 0.05$) decrease in mean triglycerides on nifedipine in the black patients (placebo 1.51 mmol/l; nifedipine 1.24 mmol/l).

Adverse events were experienced by seven (15%) of the 48 patients valid for safety analysis during the placebo run-in period, eight (17%) of 48 patients on nisoldipine and 15 (35%) of the 43 patients assessed on nifedipine. The most frequently reported adverse event was headache on nisoldipine (seven vs three on nifedipine) and peripheral oedema on nifedipine (four vs two on nisoldipine).

Discussion

Nisoldipine 10 mg twice a day proved to be as effective and well tolerated as nifedipine 20 mg twice a day in patients whose hypertension is not adequately controlled on atenolol 100 mg/day. In contrast to the findings of Ramsay and Waller\textsuperscript{2} in a smaller study, and in agreement with a chronic study of nisoldipine as monotherapy,\textsuperscript{9} there was no evidence of the development of tolerance to the hypotensive effect of nisoldipine. The mean SBP and DBP was lower after 8 than after 4 weeks treatment. There was also no evidence of a different response of black and Caucasian patients to the calcium blocker drugs in agreement with other studies.\textsuperscript{10} The statistical power of the present investigation was, however, low in this respect.

As this was an exploratory study and no allowance was made statistically for multiple comparisons, the finding of an apparent race effect for triglyceride lowering on the calcium blocker drugs is of uncertain biological significance. Moreover the data refer to only some of the total group of patients and we have no record of possible weight changes. But nonetheless the differences noted were statistically highly significant. The calcium antagonist drugs are generally thought to be neutral in terms of effects on carbohydrate tolerance and blood lipids,\textsuperscript{11} although reductions in triglyceride levels have been recorded previously.\textsuperscript{12,13} We know of no studies of the effects of calcium antagonist drugs on $\beta$ blocker-induced raised triglyceride levels\textsuperscript{14} and no evidence for a racial difference in response.

The effects of calcium blocking drugs in patients with impaired left ventricular function seem to relate largely to a balance between the vasodilator and negative inotropic properties of the individual drug. The major net influence of currently available calcium antagonists seems to be adverse for patients with more than only mildly impaired cardiac function.\textsuperscript{15} Nisoldipine has, however, been shown to be effective and well tolerated in congestive cardiac failure,\textsuperscript{16,17} probably due to its dominant vasodilator characteristics. It is also, like other calcium antagonist drugs, anti-anginal.\textsuperscript{18} Nisoldipine may therefore come to be of value in hypertensive patients with seriously impaired left ventricular function and coronary artery disease.

Acknowledgements

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References


