**Amlodipine lowers blood pressure without affecting cerebral blood flow as measured by single photon emission computed tomography in elderly hypertensive subjects**

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Abstract

**Aim:** to evaluate the effect of amlodipine on blood pressure and cerebral blood flow in elderly subjects with mild to moderate hypertension.

**Methods:** a double-blind, parallel group study of 26 patients. After a 4-week placebo run-in period, amlodipine (5–10 mg) or matching placebo was given once daily for 8 weeks.

**Results:** amlodipine significantly reduced blood pressure compared with baseline. Diastolic blood pressure was significantly reduced by amlodipine compared with placebo ($P < 0.02$ to $P < 0.01$). Ambulatory blood pressure monitoring showed that blood pressure control was sustained over the 24-h dosing interval. Relative regional cerebral blood flow, assessed using single photon emission computed tomography, was not significantly affected by amlodipine. Three placebo patients, but no amlodipine patients, withdrew because of adverse events.

**Conclusion:** amlodipine was a well-tolerated and effective antihypertensive agent, and did not reduce regional cerebral blood flow in elderly hypertensive patients.

**Keywords:** ambulatory blood pressure, amlodipine, cerebral blood flow, elderly, hypertension, single photon emission computed tomography

Introduction

Adequate control of high blood pressure (BP) is important to reduce cardiovascular morbidity and mortality [1, 2]. Twenty-four-hour control of BP may prevent excessive BP falls during the night, and minimize the BP rise that occurs early in the morning, when the risk of stroke, transient ischaemic attacks and myocardial infarction is greatest [3–5].

In normal subjects, $\alpha$-adrenergic innervation, activation of the renin–angiotensin system, and endothelial-derived relaxing and constricting factors contribute to autoregulation of cerebral blood flow [6]. Patients with long-standing hypertension frequently do not tolerate a sudden lowering of BP because of impaired cerebrovascular autoregulation, characterized by sluggish and incomplete autoregulatory responses [6, 7]. Pathogenic cerebrovascular changes such as atherosclerosis may render this impairment difficult to reverse, and antihypertensive treatment should not impair cerebral blood flow further.

Calcium channel blockers induce beneficial peripheral haemodynamic effects in elderly patients [8–10] and do not appear to reduce cerebral perfusion [11–14]. Amlodipine is a calcium channel blocker which provides sustained antihypertensive activity over 24 h [15, 16], in elderly subjects as well as younger groups [17–20]. We have examined the effects of amlodipine on BP and regional cerebral blood flow, using single photon emission computed tomography (SPECT), in elderly subjects with mild to moderate hypertension. This is the first report of the use of SPECT to...
measure cerebral blood flow in elderly hypertensive subjects.

**Patients and methods**

This was a double-blind, placebo-controlled, parallel group study, conducted according to the guidelines of the Declaration of Helsinki. The protocol was approved by the Lewisham and North Southwark committee on ethical practice. Written informed consent of all patients was obtained.

**Patients**

Patients of either sex aged ≥ 60 years had supine diastolic BP ≥ 95 mmHg, with upper limits of 105, 110 and 115 mmHg in patients aged 60–74, 75–84 and ≥ 85 years, respectively. Exclusion criteria included: concurrent antihypertensive or vasodilator drugs; malignant hypertension; intolerance to calcium channel blockers; and stroke or myocardial infarction during the preceding 3 months.

**Treatment**

Patients were allocated to treatment groups by minimization [21] based on age, sex, body weight, smoking habit and supine diastolic BP. After a 4-week placebo run-in, patients received 5 mg amlodipine or placebo once daily in the morning for 8 weeks, doubled to 10 mg after 4 weeks if supine diastolic BP remained > 90 mmHg (subject to toleration).

**Assessment of BP**

BP and heart rate were measured at each visit in the morning, approximately 24 h after the previous dose, with a random-zero sphygmomanometer, by the same examiner using the same arm. Measurements were made to the nearest 2 mmHg under quiet conditions after 5 min supine and 2 min standing. The mean of two measurements was recorded.

Twenty-four-hour ambulatory BP and heart rate were recorded at baseline and after treatment, using a Spacelabs 90207 recorder. Recordings began before the daily dose of study treatment. Mean BP was calculated for each hour, and mean BP values for the daytime (start of recording until 2200 h), night-time (2300–0600 h) and 24-h period were derived.

**Cerebral blood flow**

Cerebral blood flow was measured before and after treatment using SPECT [22]. Doses of 339–632 MBq [99mTc]hexamethylpropylene amine oxime ([99mTc]-HM-PAO; Ceretec, Amersham International) were injected intravenously and SPECT measurements were made 10–30 min later under quiet conditions using a head scan γ-camera. HM-PAO distribution was quantified in predefined regions of interest.

Absolute regional uptake was calculated for the frontal, temporo-sylvian, parietal, occipital, basal ganglia and cerebellar [23, 24] areas. Absolute regional uptake was expressed as the photon count per pixel per MBq of injected [99mTc]-HM-PAO (counts/MBq) and calculated with a decay correction factor based upon the half-life of 99mTc. The regional to mean index (%) and regional to occipital index (%) were selected as regional perfusion indices: the latter has been shown to be the most sensitive index in detecting changes in regional cerebral blood flow [22].

**Safety**

During each clinic visit, adverse events were elicited by the investigator using open questions such as ‘how do you feel?’, and were classified as mild, moderate or severe. Their relationship to study medication was noted.

**Statistical methods**

A linear-model repeated measures analysis of variance was used. All tests were two-tailed and the level of significance was taken as \( P < 0.05 \). Statistical analyses were performed by an independent statistics house.

It was estimated that, using an \( \alpha \) level of 0.05, inclusion of 24 patients (12 per group) would show significant differences between groups in cerebral blood flow with a power of 0.80.

**Results**

Of 26 patients enrolled, 23 completed the study. In the placebo group, two patients discontinued because of adverse events, one patient died of a myocardial infarction, three patients stopped taking study medication too early or too late, ambulatory BP measurements were started too late at the final visit for three patients, and cerebral blood flow was not measured for one patient. In the amlodipine group, ambulatory BP measurements and cerebral blood flow measurements were not recorded for two patients. These patients were excluded from the analysis.

The treatment groups were well matched for demographic details (Table 1). A history of stroke was not recorded for any patient during the physical examination before the study. The mean maintenance daily dose of amlodipine was 7.3 mg, with seven patients remaining on 5 mg and six increasing the dose to 10 mg. The corresponding mean dose for placebo patients was 8.85 mg.

**Clinic BP and heart rate**

All mean BP values after 8 weeks of treatment were significantly lower than at baseline in the amlodipine group (\( P < 0.0082 \)), whereas there was little change in
BP after placebo treatment (Table 2 and Figure 1). The difference between groups reached statistical significance for both supine and standing diastolic BP ($P < 0.02$ and $P < 0.01$, respectively). Supine and standing heart rate did not differ significantly between groups.

Ambulatory BP monitoring

Amlodipine, but not placebo, induced clinically important BP reductions during the daytime, nighttime, and full 24-h periods (Figures 2 and 3). The effects of amlodipine were statistically significant relative to placebo for daytime systolic and diastolic BP, nighttime systolic BP, and 24-h systolic and diastolic BP (Table 2 and Figure 3). Heart rate changes were slight and clinically unimportant.

Table 1. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amlodipine ($n = 13$)</th>
<th>Placebo ($n = 13$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>1/12</td>
<td>2/11</td>
</tr>
<tr>
<td>Age (years) Median</td>
<td>79.0</td>
<td>78.0</td>
</tr>
<tr>
<td>Age (years) Range</td>
<td>68–91</td>
<td>66–82</td>
</tr>
<tr>
<td>Body weight (kg) Median</td>
<td>63.0</td>
<td>66.0</td>
</tr>
<tr>
<td>Body weight (kg) Range</td>
<td>53–82</td>
<td>52–87</td>
</tr>
<tr>
<td>Height (cm) Median</td>
<td>157.0</td>
<td>160.0</td>
</tr>
<tr>
<td>Height (cm) Range</td>
<td>152–163</td>
<td>152–175</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Smoker</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mean supine blood pressure (mmHg)</td>
<td>185/104</td>
<td>189/104</td>
</tr>
</tbody>
</table>

Table 2. Clinic and ambulatory blood pressures before and after 8 weeks of treatment with amlodipine or placebo

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean blood pressure (and SD), mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amlodipine ($n = 13$)</td>
</tr>
<tr>
<td>Clinic</td>
<td>Baseline</td>
</tr>
<tr>
<td>Supine</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
<tr>
<td>Standing</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>Baseline</td>
</tr>
<tr>
<td>Daytime</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
<tr>
<td>Night-time</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
<tr>
<td>24-h</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
</tbody>
</table>

Values of clinic BP were determined approximately 24 h after the previous dose. All mean measurements of clinic BP after treatment in the amlodipine group were significantly lower than baseline measurements ($P < 0.0082$). There were no significant differences between baseline and after treatment measurements within the placebo group. Significance of changes in blood pressure measured by ambulatory monitoring: $^aP < 0.05$; $^bP < 0.01$; $^cP < 0.001$. 

Figure 1. Change in mean value of blood pressure following 8 weeks of treatment with amlodipine (■) or placebo (□). $^*P < 0.02$; $^{**}P < 0.01$ for the change with amlodipine versus the change with placebo.
Cerebral blood flow

The overall mean absolute regional uptake was not significantly different between the amlodipine and placebo groups, and relatively small, but statistically significant differences between the two groups were observed in only three of the 12 individual measurements (Table 3). Relative regional blood flow in the temporo-sylvian and frontal regions of the right and left hemisphere were not significantly changed after treatment relative to baseline or placebo (Table 4).

Adverse events

No adverse events were reported in patients treated with amlodipine. Three placebo-treated patients experienced five adverse events which led to treatment withdrawal. A myocardial infarction in a patient receiving placebo was unrelated to treatment.

Discussion

This study confirms that amlodipine effectively reduces BP in elderly patients with mild to moderate hypertension.
hypertension. BP was lowered throughout the 24-h dosing interval—including the night and early morning hours. The antihypertensive activity of amlodipine is therefore consistent with previous studies in younger and older patients [17–19, 25].

Ambulatory BP measurement during normal activities [26] avoids the influence of ‘white coat hypertension’. In our study, amlodipine induced a significantly greater BP reductions than placebo during the daytime and night-time periods, and the magnitudes of BP lowering were of clinical importance. These results highlight the theoretical protection of the patients during the critical early-morning phase, when the risk of myocardial infarction and stroke is at its greatest. This pattern of response on ambulatory monitoring with amlodipine has not previously been described in elderly subjects.

The confirmation of a reduction in BP after amlodipine treatment was essential to allow proper interpretation of the concomitant cerebral blood flow measurements made using SPECT. This method is well documented and reproducible, and keeps operator-dependent steps to a minimum. Absolute regional uptake may be used to demonstrate changes in regional cerebral blood flow [22]. It does not require an internal standard. However, its value is limited by variations in the radiopharmaceutical dose administered and variations between subjects in tracer clearance, cardiac output and cerebral blood flow [23].

The regional to mean and regional to occipital indices are more reliable indicators of regional blood flow and by the difficulty of interpreting regional differences which interact with the mean and each other. The regional to occipital index appears to be the most reliable method: although studies in hypertensive patients are lacking, the occipital cortex in dementia has been shown to be relatively free of pathology [22], and the blood flow in the occipital cortex is unaffected by ageing [27].

The ability of the present study to detect small changes in cerebral perfusion was limited by the unexpectedly high rate of treatment withdrawals. However, despite the lowering of BP by amlodipine, the drug did not have a clinically important effect on cerebral blood flow, although small but statistically significant reductions in absolute regional uptake occurred in three out of 12 regions of interest. The lack of significant effect of amlodipine on relative indices of cerebral blood flow in the frontal area suggests that the reduction in frontal absolute regional uptake may have been a statistical artefact. Alternatively, as regional to occipital index and regional to mean index values for the parietal areas were not available, the possibility of a slight effect on blood flow in these areas cannot be excluded, and further investigation is required.

Some calcium channel blockers display greater selectivity towards cerebral vessels than coronary or mesenteric vessels in vitro [27, 28]. Functionally, however, cerebrovascular blood flow may not be adversely affected by calcium channel blockers so long as the cerebral autoregulatory capacity is maintained. Previous clinical studies with dihydropyridine calcium channel blockers in hypertensive [11, 12] or normotensive [13] patients have not demonstrated reductions in cerebral blood flow. The results of

### Table 4. Relative regional cerebral blood flow in frontal and temporo-sylvian regions before and after 8 weeks of treatment with amlodipine and placebo, expressed as regional to mean (R/M) and regional to occipital (R/O) indices (%) for the right and left hemispheres

<table>
<thead>
<tr>
<th>Region</th>
<th>Index</th>
<th>Side</th>
<th>Mean relative cerebral blood flow (and SD), %</th>
<th>Amlodipine</th>
<th>Placebo</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline (n = 10)</td>
<td>8 weeks (n = 11)</td>
<td>Baseline (n = 6)</td>
<td>8 weeks (n = 6)</td>
</tr>
<tr>
<td>Frontal</td>
<td>R/M</td>
<td>Right</td>
<td>91 (4)</td>
<td>91 (4)</td>
<td>91 (4)</td>
<td>93 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left</td>
<td>90 (4)</td>
<td>91 (4)</td>
<td>90 (4)</td>
<td>91 (2)</td>
</tr>
<tr>
<td></td>
<td>R/O</td>
<td>Right</td>
<td>88 (7)</td>
<td>89 (7)</td>
<td>90 (5)</td>
<td>92 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left</td>
<td>87 (8)</td>
<td>89 (7)</td>
<td>89 (4)</td>
<td>90 (2)</td>
</tr>
<tr>
<td>Temporo-sylvian</td>
<td>R/M</td>
<td>Right</td>
<td>97 (3)</td>
<td>97 (4)</td>
<td>97 (7)</td>
<td>98 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left</td>
<td>99 (3)</td>
<td>98 (3)</td>
<td>100 (5)</td>
<td>98 (3)</td>
</tr>
<tr>
<td></td>
<td>R/O</td>
<td>Right</td>
<td>94 (6)</td>
<td>94 (6)</td>
<td>98 (9)</td>
<td>97 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left</td>
<td>96 (8)</td>
<td>95 (4)</td>
<td>98 (7)</td>
<td>97 (4)</td>
</tr>
</tbody>
</table>

<sup>a</sup>For the difference between change following treatment for the amlodipine versus placebo groups.
our study are therefore in agreement with previous clinical evaluations of the effects of calcium channel blockers.

None of the amlodipine-treated patients experienced adverse events and all completed the 8-week treatment period. The good safety profile of amlodipine in the elderly patients of this study is in agreement with other amlodipine studies that have found an overall low incidence of adverse events and few differences between younger and older hypertensive patients [17].

In conclusion, this study provides further evidence that amlodipine, 5–10 mg once daily, reduces BP and is well tolerated in elderly hypertensive patients. The BP lowering activity was sustained for the full 24-h period between amlodipine doses and protected patients against the early-morning rise in BP that commonly occurs in untreated patients. Relative indices of cerebral blood flow in these patients were not reduced during amlodipine administration.

Key points
- Once-daily amlodipine reduces blood pressure in elderly hypertensive patients.
- The antihypertensive effect was maintained throughout the 24-h dosing interval.
- Relative indices of cerebral blood flow were not significantly affected by amlodipine.
- Amlodipine was well tolerated in this elderly population.

Acknowledgement
This study was supported by a grant from Pfizer Ltd.

References


Received 23 April 1997; accepted in revised form 28 October 1998