Original Article

Azelnidipine and Amlodipine: a Comparison of Their Pharmacokinetics and Effects on Ambulatory Blood Pressure

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We objected: 1) To compare the effects of azelnidipine and amlodipine on 24-h blood pressure; 2) To monitor the plasma concentration vs. the time profile in order to assess the association between pharmacokinetics and hypotensive activity after administration of either drug for 6 weeks. Blood pressure and pulse rate were measured by 24-h monitoring with a portable automatic monitor in a randomized double-blind study of 46 patients with essential hypertension. Azelnidipine 16 mg (23 patients) or amlodipine 5 mg (23 patients) was administered once daily for 6 weeks. Pharmacokinetics were analyzed after the last dose was taken. Both drugs showed similar effects on the office blood pressure and pulse rate. During 24-h monitoring, both drugs caused a decrease in systolic blood pressure of 13 mmHg and had a similar hypotensive profile during the daytime period (07:00–21:30). The pulse rate decreased by 2 beats/min in the azelnidipine group, whereas it significantly increased by 4 beats/min in the amlodipine group. Similar trends in the blood pressure and pulse rate were observed during the nighttime (22:00–6:30) and over 24 h. Excessive blood pressure reduction during the nighttime was not seen in either group. The pharmacokinetic results indicated that the plasma half-life ($t_{1/2}$) of amlodipine was 38.5±19.8 h and that of azelnidipine was 8.68±1.33 h. Despite this difference in pharmacokinetics, the hypotensive effects of amlodipine and azelnidipine were similar throughout the 24-h administration period. (Hypertens Res 2003; 26: 201–208)

Key Words: 24-h blood pressure, pulse rate, pharmacokinetics, azelnidipine, amlodipine

Introduction

Antihypertensive drugs are used to control blood pressure and thereby prevent cerebrovascular and cardiovascular complications. Calcium antagonists are commonly used for the treatment of hypertension because these drugs have a reliable hypotensive effect with few adverse reactions and are particularly effective in preventing stroke (1–5).

However, because it has been reported that short-acting calcium antagonists increase the risk of ischemic heart dis-ease (6, 7), the use of long-acting calcium antagonists is generally recommended (8).

Amlodipine is a calcium antagonist that has a plasma half-life ($t_{1/2}$) of about 39 h. This drug is known to have a slow and persistent hypotensive effect (9, 10). Azelnidipine is a calcium antagonist that was developed by Ube Industries, Ltd. (Yamaguchi, Japan) and Sankyo Co., Ltd. (Tokyo, Japan); its $t_{1/2}$ is about 8 h, which is comparable to that of common dihydropyridine calcium antagonists (11). Because this new calcium antagonist is highly lipid soluble (12), it is retained in the vascular wall after clearance from the blood

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The pharmacokinetics and hypotensive activity of azelnidipine and amlodipine were studied in detail. After administration for 6 weeks, the plasma drug concentration was determined by gas chromatography-mass spectrometry (GC-MS) in compliance with the Good Laboratory Practice by BML Inc. (Tokyo, Japan).

Methods

Inclusion criteria were as follows: 1) blood pressure of ≥140/90 mmHg measured at the outpatient clinic; 2) mean blood pressure of ≥135/85 mmHg recorded with a portable automatic monitor in the daytime (07:00–21:30) during the washout period; and 3) an age of between 20 and 65 years. Patients with severe hypertension (defined as a diastolic blood pressure ≥120 mmHg), advanced liver dysfunction, diabetes mellitus, heart disease, secondary hypertension, impaired atrioventricular conduction (Grade II–III), or atrial fibrillation were excluded from the study. Patients who the physicians considered inappropriate for a variety of other reasons were also excluded. The study protocol was approved by the Institutional Review Board at each of the four participating institutions, and written informed consent was obtained before enrollment for all patients.

Drug assignment was conducted so that differences between the groups could be minimized with respect to the four medical institutions, and the diastolic blood pressure measured using a portable automatic monitor (<90 mmHg, ≥90 and <100 mmHg, and ≥100 mmHg). Ambulatory patients were recruited from December 2000 to March 2001.

After a 2–6-week washout period, the patients were randomized by a double-blind method to one of the two treatment groups and then received 16 mg of azelnidipine or 5 mg of amlodipine once a day after breakfast for 6 weeks. Drug compliance was checked every 2 weeks by clinical research coordinators. The seated blood pressure and pulse rate were measured every 2 weeks. Before and after the 6-week administration period, 24-h monitoring of blood pressure and pulse rate was done with a portable automatic monitor (TM2421; A&D Co., Ltd., Tokyo, Japan), which was programmed to take readings every 30 min. From these 24-h recordings, the blood pressure and pulse rate were calculated for each 1-h interval by averaging the data on the hour and the subsequent 30 min. Daytime was defined as 07:00 to 21:30, and nighttime as 22:00 to 06:30. The mean values for the daytime, nighttime, and 24-h periods were calculated and analyzed. To determine whether there was any excessive fall of blood pressure during the night, the mean blood pressure for each of three consecutive 3-h nocturnal periods (22:00–00:30, 00:30–03:30, and 04:00–06:30) was calculated. On the last day of the 6-week treatment period, blood samples were drawn before and 1, 2, 3, 4, 6, 8, and 24 h after the last administration for a pharmacokinetic assessment. The plasma drug concentration was determined by gas chromatography-mass spectrometry (GC-MS) in compliance with the Good Laboratory Practice by BML Inc. (Tokyo, Japan).

Before and on the last day of the 6-week treatment period, laboratory tests were performed. Symptoms, clinical findings, and adverse events were also monitored during the administration period.

In each group, the systolic and diastolic blood pressures during the washout period and at the end of treatment, as well as the changes from baseline values, were calculated along with the standard deviation and 95% confidence intervals. Similar calculations were done for the pulse rate and pharmacokinetic parameters. The values obtained before treatment were compared with those obtained after treatment by Dunnett’s test and paired Student’s t-test. Values of \( p < 0.05 \) were considered to indicate statistical significance.

Results

Baseline Profile of the Patients

The clinical characteristics of the two treatment groups are presented in Table 1. Both groups were similar with regard to sex, age, weight, and diastolic blood pressure. Systolic blood pressure was higher in the amlodipine group than in the azelnidipine group. Consequently, analysis of covariance was performed during comparison between the two groups. Baseline blood pressures were included in the model as a co-

### Table 1. Clinical Characteristics of the Patients in the Two Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Azelnidipine (( n = 22 ))</th>
<th>Amlodipine (( n = 23 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>13/9</td>
<td>10/13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 7.2</td>
<td>54 ± 6.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.0 ± 9.66</td>
<td>160.2 ± 7.75</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.4 ± 11.02</td>
<td>62.1 ± 9.35</td>
</tr>
<tr>
<td>WHO/ISH stage (I/II/III)</td>
<td>6/16/0</td>
<td>7/16/0</td>
</tr>
<tr>
<td>Seated SBP (mmHg)</td>
<td>153 ± 9.3</td>
<td>155 ± 6.9</td>
</tr>
<tr>
<td>Seated DBP (mmHg)</td>
<td>97 ± 4.3</td>
<td>97 ± 3.6</td>
</tr>
<tr>
<td>Seated pulse rate (beats/min)</td>
<td>71 ± 8.5</td>
<td>70 ± 8.0</td>
</tr>
<tr>
<td>Presence of cardiovascular complication (%)</td>
<td>50.0</td>
<td>39.1</td>
</tr>
<tr>
<td>Presence of prior antihypertensive treatment (%)</td>
<td>59.1</td>
<td>60.9</td>
</tr>
</tbody>
</table>


and continues to elicit a hypotensive effect (13).

In the present study, these two drugs with different physicochemical properties were compared in patients with mild-to-moderate essential hypertension who were treated for 6 weeks. The effects on blood pressure and pulse rate were evaluated by 24-h monitoring with a portable automatic monitor, and the influence on nocturnal blood pressure was studied in detail. After administration for 6 weeks, the plasma concentration vs. time profile was monitored to assess the association between pharmacokinetics and hypotensive activity.
was seen after 4 weeks. There was no difference of the blood
gan to decrease after 2 weeks, and a stable hypotensive effect
against time in Fig. 1. In both groups, the blood pressure be-
the sitting position in patients receiving azelnidipine (·).

Table 2. Changes in Blood Pressure and Pulse Rate in Patients Receiving Azelnidipine or Amlodipine

<table>
<thead>
<tr>
<th></th>
<th>Azelnidipine (n=22)</th>
<th>Amlodipine (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
</tr>
<tr>
<td>24-h average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>141 ± 7.9</td>
<td>129 ± 8.5</td>
</tr>
<tr>
<td>DBP</td>
<td>94 ± 6.1</td>
<td>86 ± 8.8</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>70 ± 9.0</td>
<td>68 ± 8.9</td>
</tr>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>147 ± 8.6</td>
<td>135 ± 9.4</td>
</tr>
<tr>
<td>DBP</td>
<td>98 ± 7.6</td>
<td>90 ± 9.7</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>74 ± 10.1</td>
<td>73 ± 10.3</td>
</tr>
<tr>
<td>Nighttime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>132 ± 9.4</td>
<td>120 ± 8.4</td>
</tr>
<tr>
<td>DBP</td>
<td>88 ± 6.5</td>
<td>80 ± 7.9</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>64 ± 8.2</td>
<td>61 ± 7.1</td>
</tr>
</tbody>
</table>

|                     |          |          |        |         |          |          |        |         |
| CI, 95% confidence interval of pre- and post-dose; SBP, systolic blood pressure; DBP, diastolic blood pressure.

![Fig. 1. Changes of blood pressure and pulse rate measured in the sitting position in patients receiving azelnidipine (n=22) (○) or amlodipine (n=23) (●). Dunnett’s test, *** p<0.001.](image)

variant. All patients had good drug compliance and com-
the trial. In the azelnidipine group, one patient was
cluded from statistical evaluation before code opening due
to his poor physical condition during the final 24-h monitor-
ing period.

Office Blood Pressure and Pulse Rate

The office blood pressure and pulse rate values are plotted
against time in Fig. 1. In both groups, the blood pressure be-
gan to decrease after 2 weeks, and a stable hypotensive effect
was seen after 4 weeks. There was no difference of the blood
pressure vs. time profile between the two groups at any time
during treatment. In addition, the blood pressure did not in-
crease within 24 h after the last dose in either group, indicat-
ing that the hypotensive effect of both drugs was persistent.
There were no changes in pulse rate in either group.

Changes in Blood Pressure and Pulse Rate on 24-h Monitoring

The blood pressure and pulse rate data measured by 24-h mon-
doring during the washout period and at the end of treat-
ment are presented in Fig. 2. The mean±SD of the blood
pressure and pulse rate calculated for 24 h, as well as for the
daytime (07:00–21:30) and nighttime (22:00–06:30) periods
are listed in Table 2. The changes from baseline of the blood
pressure and pulse rate with drug administration were calcu-
ated with and without adjustment for the baseline systolic
blood pressure and are presented in Table 3. Both drugs had
a stable hypotensive effect over 24 h (Fig. 2). In the azelni-
dipine group, the 24-h, daytime, and nighttime mean blood
pressure values (calculated with baseline adjustment) were
reduced by −13/−8 mmHg, −13/−8 mmHg, and −13/−8
mmHg, respectively. The amlodipine group showed de-
creases of −13/−7 mmHg, −13/−7 mmHg, and −12/−7
mmHg, respectively. There were no significant differ-
ences between the two groups. Although the mean pulse rate
for each period was slightly lower than the respective base-
line value in the azelnidipine group (−2 beats/min, −1
beats/min, and −2 beats/min), it was significantly higher in
the amlodipine group (4 beats/min, 4 beats/min, and 4
beats/min) and there was a significant difference between the
two treatment groups (Table 3). The greatest (peak) and
smallest (trough) changes of the mean blood pressure values
were −11 mmHg (17:00) and −7 mmHg (07:00) in the
azelnidipine group vs. −13 mmHg (13:00) and −6 mmHg
(07:00) in the amlodipine group, respectively. The trough/
peak ratios for the azelnidipine and amlodipine groups were 63.6% and 46.2%, respectively.

**Effects on Nighttime Blood Pressure**

Mean blood pressure and pulse rate values before and after treatment were calculated for each of three consecutive 3-h nocturnal periods (Fig. 3). In the two groups, the hypotensive effect was consistent, and the systolic pressure and diastolic pressure reached a nadir between 01:00 and 03:30 both before and after treatment. The lowest blood pressures recorded during the nighttime are listed in Table 4. Both drugs produced similar changes in diastolic blood pressure. With respect to the systolic blood pressure, the lowest post-treat-
Fig. 3. Nighttime systolic and diastolic blood pressure and pulse rate before (●) and after (○) 6 weeks of treatment with azelnidipine (n = 22) or amlodipine (n = 23).

Table 4. Lowest Nighttime Blood Pressure before and after 6 Weeks of Treatment with Azelnidipine or Amlodipine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Treatment</th>
<th>95% confidence</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Min–Max</td>
<td>Mean ± SD</td>
<td>interval</td>
</tr>
<tr>
<td>Azelnidipine</td>
<td>SBP 121 ± 8.9 103 to 143</td>
<td>109 ± 8.1 94 to 124</td>
<td>−16.4 to −7.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>(n = 22)</td>
<td>DBP 80 ± 6.1 66 to 88</td>
<td>71 ± 8.6 58 to 87</td>
<td>−12.4 to −5.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>SBP 127 ± 14.4 96 to 160</td>
<td>115 ± 11.0 94 to 137</td>
<td>−16.4 to −7.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>(n = 23)</td>
<td>DBP 81 ± 10.5 59 to 98</td>
<td>73 ± 7.8 58 to 88</td>
<td>−10.0 to −4.3</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Fig. 4. The plasma drug concentration vs. time profile (○) and average change of mean blood pressure (●) after administration of azelnidipine (n = 22) or amlodipine (n = 23).
Table 5. Pharmacokinetic Parameters in the Two Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Azelnidipine (n = 22)</th>
<th>Amlodipine (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>4.14 ± 1.46</td>
<td>5.35 ± 1.99</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>48.3 ± 19.0</td>
<td>17.1 ± 4.66</td>
</tr>
<tr>
<td>AUC0-24 (ng h/ml)</td>
<td>426 ± 151</td>
<td>332 ± 93.3</td>
</tr>
<tr>
<td>CI/F (ml/h)</td>
<td>42,200 ± 15,400</td>
<td>16,300 ± 4,910</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>8.68 ± 1.33</td>
<td>38.5 ± 19.8</td>
</tr>
</tbody>
</table>

$T_{\text{max}}$, time to peak drug concentration; $C_{\text{max}}$, maximal drug concentration; AUC0-24, area under the time-concentration curve (0–24h); CI/F (ml/h), apparent total body clearance; $t_{1/2}$, plasma half-life.

Plasma Drug Concentration Profile and Mean Blood Pressure

The pharmacokinetics of amlodipine were different from those of azelnidipine. In the azelnidipine group, the blood concentration of the drug peaked at 4 h after administration and the drug was almost completely eliminated from the blood within 24 h. In the amlodipine group, the blood concentration decreased slowly and steadily over 24 h after administration (Fig. 4). The decrease of blood pressure from baseline indicated that both drugs had a stable hypotensive effect that lasted for 24 h after administration. The $T_{1/2}$ of azelnidipine was 8.68 ± 1.33 h and that of amlodipine was 38.5 ± 19.8 h, with the two values being significantly different. The pharmacokinetic parameters for both drugs are listed in Table 5.

Safety

In the amlodipine group, one patient suffered from headache and dizziness on standing, and another patient suffered from an abnormal sensation in the throat. In the azelnidipine group, one patient suffered from soft stools. All of these adverse events were mild. No adverse events related to an excessive decrease of blood pressure were recognized in either group. Regarding laboratory data, an increase of total cholesterol was observed in the azelnidipine group and an elevation of potassium was seen in the amlodipine group, but these abnormalities were mild.

Discussion

Azelnidipine, a new calcium antagonist, differs from amlodipine with respect to its pharmacokinetic profile. In this study, 24-h monitoring of the blood pressure and pulse rate with a portable automatic monitor demonstrated that both drugs had a stable hypotensive effect lasting for at least 24 h after administration. Azelnidipine did not increase the pulse rate, but decreased it slightly, while amlodipine increased it slightly. Neither drug caused an excessive decrease of nocturnal blood pressure.

Recent interventional studies of antihypertensive drugs or meta-analyses of data from such studies have shown that calcium antagonists are comparable to diuretics and $\beta$-blockers with respect to prevention of cardiovascular complications, and superior in preventing stroke (14–18). Among Asians such as Japanese and Chinese, the incidence of stroke is 4 to 8 times higher than that of myocardial infarction (1, 3, 17). Consequently, calcium antagonists are expected to remain important as antihypertensive agents for the foreseeable future. However, meta-analyses have shown that calcium antagonists are less effective for preventing myocardial infarction and heart failure and that even long-acting calcium antagonists show limited efficacy in the prevention of cardiac complications in patients with hypertension (19, 20). Because calcium antagonists cause reflex sympathetic stimulation in association with a decrease of blood pressure and increase the load on the heart secondary to an increase of the pulse rate, an increased cardiac workload may account for their limited preventive effect against cardiac complications (6, 7).

Some calcium antagonists have been reported to act on types of calcium channels other than the L-type channel, and such calcium antagonists may suppress sympathetic stimulation (N-type) or atrial conduction (T-type) (21, 22). Cilnidipine, which has been reported to suppress the N-type calcium channel in a clinical pharmacological study (23), did not decrease the pulse rate during 24-h monitoring (24). Amlodipine has been reported to block N-type as well as L-type calcium channels (25), while preclinical studies have shown that azelnidipine does not act on either the N-type or T-type calcium channel (Azelnidipine Investigator’s Brochure 2002: unpublished).

The pulse rate decreased by 2 beats/min in the azelnidipine group, while it significantly increased by 4 beats/min in the amlodipine group by 24-h monitoring. The office pulse rate was unchanged in both groups. The pulse rate during 24-h monitoring may reflect the diurnal condition of the patient more accurately than the office pulse rate. Mengden et al. and Eguchi et al. reported that the pulse rate increased significantly after amlodipine treatment in patients with hypertension (26, 27), but the pulse rate was unchanged in many clinical trials with amlodipine (28, 29). In the present study, differences in the baseline 24-h blood pressure values be-
between groups may have accounted for the different results.

Other clinical studies of azelnidipine have also demonstrated that this drug does not increase the pulse rate (30, 31). The lack of an increase in pulse rate suggests that azelnidipine does not cause reflex sympathetic stimulation. Consequently, this drug may avoid the disadvantages of conventional calcium antagonists and their untoward effects on the heart.

An excessive decrease of nocturnal blood pressure may increase the risk of cerebral infarction, so it is important to investigate the effects of antihypertensive drugs on nocturnal blood pressure (32). In the present study, both drugs had a stable hypotensive effect, with no excessive fall in blood pressure during the night. When the mean blood pressure for each 3-h nocturnal period was calculated, the hypotensive effect of both drugs was stable throughout the night.

After the patients had been treated for 6 weeks, a pharmacokinetic investigation was also performed. As in previous reports, the plasma amlodipine level either varied minimally over the course of the day or decreased slowly. In contrast, azelnidipine had a plasma half-life of about 8 h and it disappeared from the blood within 24 h of administration, showing no accumulation. These results are consistent with data reported previously (11).

Azelnidipine and amlodipine showed a similar 24-h hypotensive effect, but were significantly different regarding the plasma concentration profile and the 24-h pulse rate. The plasma level of amlodipine showed only a very slight decline over the 24 h after administration, which may have contributed to the stability of its hypotensive effect over a period of at least 24 h. In contrast, the plasma profile cannot explain the stable hypotensive effect of azelnidipine. Azelnidipine is highly lipophilic, and thus is retained in the vascular wall. A preclinical study showed that azelnidipine could not be removed from the blood vessels, even by washing (12).

Consequently, azelnidipine probably elicits a persistent effect because it is retained in the vascular wall and shows hypotensive activity even after disappearance from the blood. At present, it is difficult to explain the difference in the effects of the two drugs on the pulse rate. Further studies will be needed to determine whether these differences are related to a difference in the affinity for calcium channels or a difference of drug levels in the vessel wall due to differences in lipophilicity or water solubility.

References


