The Newly Developed Calcium Antagonist, Azelnidipine, Increases Drain Volume in Continuous Ambulatory Peritoneal Dialysis Patients

Hiromichi Suzuki, Tsutomu Inoue, Kazuhiro Kobayashi, Junko Shoda, Hidetomo Nakamoto

Many patients undergoing continuous ambulatory peritoneal dialysis (CAPD) receive antihypertensive agents, including calcium antagonists, which produce reflex tachycardia through activation of the sympathetic nervous system. Azelnidipine, a newly developed calcium antagonist, has unique characteristics in that it causes less reflex stimulation of the sympathetic nervous system. In the present study, we used a crossover method to compare the effects of amlodipine (5 – 10 mg daily) and azelnidipine (8 – 16 mg daily) on drain volume and weekly creatinine clearance in 9 CAPD patients (3 women, 6 men; mean age: 64 ± 5 years; mean duration of CAPD: 1.8 ± 0.6 years). Each calcium antagonist was administered for 3 months and then switched for the other. As compared with amlodipine, azelnidipine increased drain volume by 13% ± 2% (p < 0.05) and weekly creatinine clearance by 12% ± 2% (p < 0.05). At the same time, we observed no significant differences in blood pressure and urine volume. The increases in drain volume produced by azelnidipine resulted from less activation of the sympathetic nervous system. We therefore suggest that activation of the sympathetic nervous system induced by calcium antagonists may be important in the regulation of drain volume in CAPD patients.

Key words
Drain volume, calcium antagonist, weekly creatinine clearance, azelnidipine

Introduction
Cardiovascular disease is the leading cause of mortality and morbidity in patients undergoing hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) (1,2). This situation is most likely related to the long-standing hypertension, abnormal lipid profile, ventricular hypertrophy and dysfunction, and high level of sympathetic activation that are characteristic of end-stage renal disease (ESRD) patients (3).

In CAPD, blood pressure control depends on peritoneal ultrafiltration and a decline in fluid retention (4,5). Therapy with antihypertensive drugs is indicated primarily in the few patients in whom hypertension persists despite seemingly adequate volume control. Elevated blood pressure can usually be controlled by most classes of antihypertensive agents. Based on the results of several large-scale clinical studies (6,7), angiotensin converting enzyme (ACE) inhibitors and angiotensin type II receptor blockers (ARBs) are currently in wide use for patients with renal disease. Consequently, a large proportion of the patients undergoing dialysis therapy have already received ACE inhibitors or ARBs at the initiation of dialysis. However, these agents are more effective in reducing blood pressure when volume is depleted or salt is restricted (8,9). In CAPD patients, volume expansion plays an important role in both the development and maintenance of hypertension (3). Thus ACE inhibitors and ARBs are less effective than calcium antagonists, which are very effective and well tolerated in these patients (10).

In Japan, several calcium antagonists that act by blocking T-type (11) or N-type (12) calcium channels are used in clinical practice. In addition, the newly developed calcium antagonist azelnidipine has recently begun to be used for treatment of hypertensive patients. This dihydropyridine calcium antagonist with selectivity for L-type calcium channels has a unique...
property: It has been shown not to produce reflex tachycardia while causing a reduction of blood pressure similar to that of amlodipine (13). With this finding in mind, we conducted a crossover double-blind study to compare the effects of azelnidipine and amlodipine on blood pressure, residual renal function, and weekly creatinine clearance (CCr) in patients undergoing CAPD.

**Patients and methods**

Patients undergoing CAPD complicated with hypertension were eligible for inclusion in this study. All patients were required to have been diagnosed as hypertensive. Eligible patients were fully informed of the aims of the study, and their written informed consent was obtained.

These exclusion criteria were used:

- Myocardial infarction within the preceding 6 months
- Clinically significant valvular disease
- Malignant hypertension
- History of hypertensive encephalopathy or cerebrovascular accident within the preceding 6 months
- Any condition that may have precluded a patient from remaining in the study, such as alcohol or drug abuse, chronic liver disease, malignant disease, or psychiatric disorder

The study protocol was approved by the Ethics Committee of the Saitama Medical School Hospital. This randomized, double-blind crossover trial was performed in accordance with the principles of the World Medical Association Declaration of Helsinki and was conducted in the Kidney Disease Center in Saitama Medical School Hospital, Saitama, Japan.

The 9 enrolled CAPD patients (3 women, 6 men; mean age: 64 ± 5 years; mean duration of CAPD: 1.8 ± 0.6 years) were instructed to maintain a specified diet (30 – 35 kcal/kg daily; 7 g salt; 0.8 g/kg protein daily—diabetic or non diabetic) throughout the study.

The causes of ESRD in the patients were diabetic nephropathy (n = 2), immunoglobulin A nephropathy (n = 3), nephrosclerosis (n = 2), autosomal dominant polycystic kidney disease (n = 1), and unknown (n = 1).

At the start of the study, calcium antagonists were withdrawn if the patients had been taking them. Other antihypertensive drugs were continued. After an initial 2-week period, patients were randomized to receive once-daily amlodipine 5 mg or azelnidipine 8 mg for 3 months. During this 3-month period, target home blood pressure (BP) was 130/80 mmHg or lower. If target home BP was not achieved, the daily dose of amlodipine was increased to 10 mg and of azelnidipine, to 16 mg. After 3 months, amlodipine was switched to azelnidipine and vice versa for the next 3 months.

During the study, home BP measurements were encouraged and checked by trained nurses. The daytime home BP target of 130/80 mmHg or lower was set according to current definitions and criteria defined by Burt and colleagues (14).

For CAPD therapy, patients used 1.5 – 2.5 L of dialysate per exchange for 3 – 5 exchanges daily. The number of 2.5% dextrose exchanges was individually adapted, usually 1 – 2 bags daily, and was continued until the desired dialysis goal was reached.

After randomization, patients were followed monthly. At each clinic visit, serum creatinine, electrolyte concentrations, complete blood count, and other serum chemistries (uric acid, glucose, and liver enzymes) were measured. Residual glomerular filtration rate (GFR) was assessed at 0 and 3 months by 24-hour urine collection. Indices of the adequacy of dialysis, including Kt/V and weekly CCr, were calculated using the Adequest version 2.0 computer program (Baxter Healthcare, Tokyo, Japan) for Windows. Chest radiographs were obtained regularly, and cardiothoracic index was calculated according to established methods.

**Statistical analysis**

Prospective construction of the sample size (α = 0.05 two-sided, β = 0.1) with a clinically significant difference in GFR of 1.5 mL/min required 9 patients in each arm of the study. Continuous data are expressed as mean ± standard error of the mean. The analyses of the effects of calcium antagonists on longitudinal changes in BP, urine volume, serum creatinine, and weekly CCr were performed by repeated-measures analysis of covariance, followed by a Neuman–Keul test for evaluation of significance after combining data obtained from the two portions of the study.

Baseline characteristics were compared between the two randomized groups using the chi-square or Wilcoxon signed tests, as appropriate. A p value less than 0.05 was considered significant.
Results

Clinical characteristics
We observed no significant differences in serum albumin, hemoglobin, calcium, inorganic phosphate, and cardiothoracic ratios between the two groups, as shown in Table I.

Changes in BP during treatment
Oral administration of azelnidipine significantly reduced both systolic [Figure 1(A)] and diastolic BP [Figure 1(B)] to $135.8 \pm 3.6/81.1 \pm 2.1$ mmHg at the end of the study from $154.0 \pm 2.0/84.4 \pm 1.0$ mmHg ($p < 0.001$). In the amlodipine group, systolic and diastolic BP were also both significantly reduced to $130.3 \pm 2.4/77.0 \pm 3.3$ mmHg at the end of the study from $154.0 \pm 2.6/84.5 \pm 1.0$ mmHg ($p < 0.001$). We observed no significant difference between the two groups.

Effects of amlodipine and azelnidipine on urine volume
In the azelnidipine and amlodipine groups alike, urine volume transiently decreased from that measured at the start of the study and then gradually increased toward the end of the study; however, none of the changes were statistically significant (Figure 2). We observed no significant differences between the two groups.

Changes in serum creatinine after the start of treatment
In the treated patients, levels of serum creatinine showed no significant change throughout the study (Figure 3).

Effects of amlodipine and azelnidipine on drain volume
Drain volume increased significantly at 1 month after the start of azelnidipine ($p < 0.01$), and increased drain volume was maintained throughout the study (Figure 4). However, in the amlodipine group, drain volume did not change significantly during the study period. At 1, 2, and 3 months after the start of CAPD, we observed no significant differences between the two groups ($p < 0.01$).

Effects on weekly CCr
The changes in CCr during the study period mirrored the changes in drain volume; however, the degree of

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Comparison of laboratory characteristics between amlodipine and azelnidipine groups</th>
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<tbody>
<tr>
<td></td>
<td>Azelnidipine ($n=16$)</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.6±0.6</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>210±22</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.8±1.2</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>7.9±0.9</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>5.2±1.7</td>
</tr>
<tr>
<td>Cardiothoracic ratio (%)</td>
<td>51.3±6.2</td>
</tr>
</tbody>
</table>
Drain volume increased significantly at 1 month after compared the effects of another long-acting dihydropyridine calcium antagonist—amlodipine—with those of azelnidipine on BP, urine volume, and drain volume. The reductions in both systolic and diastolic BP obtained with amlodipine were similar to those obtained with azelnidipine, in agreement with a previous study carried out in patients with mild-to-moderate hypertension. There are several possible reasons why significant differences in drain volume.
and weekly CCr were found between patients treated with azelnidipine and those treated with amlodipine.

Calcium antagonists are now widely used for treatment of patients with hypertension. Dihydropyridine calcium antagonists have previously been shown to produce sympathetic activation following abrupt BP reduction. However, a long-acting calcium antagonist induces less activation of sympathetic reflexes, and amlodipine in particular is reported to have no effect on sympathetic nerve activation (15). On the other hand, amlodipine treatment has also been shown to significantly increase plasma norepinephrine levels (16). In the present study, we found no significant differences in heart rate after either amlodipine or azelnidipine treatment, although measurements of plasma norepinephrine were not made.

Shokoji et al. (17) demonstrated that amlodipine significantly increased heart rate and integrated renal sympathetic nerve activity in hypertensive animals, but that azelnidipine did not, indicating that azelnidipine might possess sympathoinhibitory effects. In a previous study using a hypertensive animal model with mild renal insufficiency, we reported that administration of amlodipine reduced the diameter of the vessels of the peritoneum responsible for solute transport in peritoneal dialysis therapy (18). From those results, it would be expected that some calcium antagonists constrict these vessels, reducing drain volume. Combining those data, we suggest that azelnidipine, lacking sympathoactivation, might not constrict vessels in the peritoneum when systemic BP is reduced and that this agent might thereby contribute to increases in water transport.

Reactive oxygen species might be involved in the process of increasing solute amounts in the peritoneum. A close relationship between activation of the renin–angiotensin system and production of reactive oxygen species has been described elsewhere (19). We previously reported that administration of ARBs produces an increase in drain volume and weekly CCr in patients undergoing CAPD (20), supporting the idea that the renin–angiotensin system and reactive oxygen species might be linked in the peritoneum of patients undergoing CAPD. Interestingly, Shinomiya et al. (21) showed that azelnidipine exhibited a stronger antioxidative activity in human endothelial cells than did amlodipine or nifedipine. That finding indicates that a similar process might contribute to the increases in drain volume and weekly CCr produced by azelnidipine over those produced by ARBs.

Conclusions
We suggest that the effects of activation of the sympathetic nervous system induced by calcium antagonists may be important in the regulation of drain volume in CAPD patients.

References
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