Controlled-Release Nifedipine Effectively Inhibits Morning Hypertension: A Cross-Over Study with Doxazosin

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To examine the effect of controlled-release nifedipine (nifedipine CR) given at bedtime on morning hypertension and to compare its effect with that of \( \alpha \)-adrenergic blocker, doxazosin, given at bedtime, we performed a cross-over study in ten (5 males, 5 females) hypertensive patients with morning hypertension. After control measurements, the patients were assigned to either nifedipine CR (20-40 mg) first or doxazosin (1-2 mg) first. After 4 weeks of the treatment, measurements were repeated and medication was switched to another drug for another 4 weeks. Systolic and diastolic blood pressure (BP) and heart rate were measured using a 24-hour ambulatory BP monitoring system. While BP at evening and early nighttime (16:00-3:00) were the same in the three conditions (control, nifedipine CR, and doxazosin), nifedipine CR significantly suppressed BP at the latest nighttime (5:00-6:00) (systolic BP/diastolic BP: control 128.4±12.0/85.1±10.6 mmHg, doxazosin 124.5±11.6/81.4±10.7 mmHg, nifedipine CR 111.2±16.0/77.7±11.2 mmHg, \( p < 0.01 \) control vs nifedipine CR, \( p < 0.05 \) doxazosin vs nifedipine CR). Nifedipine CR also suppressed BP at the morning (6:30-9:30) (control 144.2±11.2/92.2±12.2 mmHg, doxazosin 137.2±8.4/87.1±11.1 mmHg, nifedipine CR 123.9±10.8/83.1±12.1 mmHg, \( p < 0.02 \) control vs nifedipine CR, \( p < 0.01 \) nifedipine CR vs doxazosin). There was a significant increase in heart rate only in the doxazosin group during sleep time (control 64.7±5.2/min, doxazosin 68.5±8.8/min, nifedipine 64.5±5.7/min, \( p < 0.05 \) doxazosin vs nifedipine). These results indicate that the dose of nifedipine CR that does not affect BP from evening through early morning, administered before sleep, is effective in the treatment of morning hypertension.

Key words: controlled-release nifedipine, doxazosin, morning hypertension

Introduction

Recently, morning hypertension has attracted more attention due to its close linkage to the increase in risk of cerebrovascular and cardiovascular disease. Most of physicians treating hypertensive patients have noticed that to suppress high blood pressure (BP) in the morning is a challenge. To date, a standard treatment of morning hypertension is to prescribe \( \alpha \)-adrenergic blocker before sleep because the morning surge is closely related to the increase in sympathetic nervous activity. Doxazosin mesilate is one of the most widely used \( \alpha \)-adrenergic blockers, which is usually given at night in addition to other drug(s) in the daytime. Previous studies have shown the efficacy of this method in suppressing morning hypertension. Nifedipine is one of the most widely used calcium channel blockers in the treatment of hypertension. Recently, a newly designed control released nifedipine (nifedipine CR) was developed, which has the inner core under the outer drug to maintain a serum concentration of the drug above the effective minimal level during 24 hours. As the result of this design change, drug release has double peaks: the first peak comes at 2.5-5 hours after the intake and the second peak or shoulder at 6-12 hours after

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the intake. Because of the delayed second peak, we considered that nifedipine CR should be effective in suppressing the morning hypertension. Therefore, we examined the effectiveness of nifedipine CR in the treatment of morning hypertension and we compared its efficacy with that of doxazosin.

**Methods**

We selected 10 patients with essential hypertension who had morning hypertension and accepted to participate in the cross-over drug study in the morning hypertension. Blood pressure was measured in the outpatient clinic three times in the sitting position in the morning. The averaged systolic BP of the participants was 170±20 mmHg and diastolic BP was 94±8.5 mmHg (Table 1). The patients underwent 24 hours ambulatory BP monitoring using an ABPM monitoring system (FM-200, Fukuda Denshi, Tokyo, Japan). Morning hypertension was defined as the averaged morning (6:30-9:30) systolic BP exceeded the averaged sleep time (22:30-6:00) systolic BP by >20 mmHg. The BP measurements with ABPM were done every 30 minutes during 7:00 to 22:00 and every 60 minutes thereafter. The protocol was approved by the local ethics committee and written informed consent was obtained from all the participants.

The demographic data of the participants are shown in Table 1. The average age was 60.9±7.6 years, and the number of male and female was 5 each. Twenty four-hour averaged blood pressure was 137.8±8.8/85.8±10.6 mmHg and sleep time (22:30-6:00) and morning (6:30-9:30) blood pressure were 121.7±9.8/80.1±9.7 mmHg and 144.8±10.5/90.7±12.4 mmHg, respectively. Four patients were on other antihypertensive medications other than nifedipine CR or doxazosin at the inclusion and these medication were continued throughout the study period. Nifedipine CR and doxazosin were allocated as follows. If the day of inclusion was an even numbered day, the patient was assigned to group A, in which doxazosin was started first (n=7), and if the day was an odd numbered day, the patient was assigned to group B, in which nifedipine CR was started first (n=3). Both drugs were administered at bedtime. At inclusion, the blood sample was collected as the baseline data. The patients in group A were started on doxazosin (1 mg) and continued for 2-4 weeks unless side effects appeared. If the antihypertensive effect was unsatisfactory, the dose was doubled to 2 mg after 2 to 4 weeks. For the patients in group B, 20 mg of nifedipine CR was started and titrated up to 40 mg as needed. After 4 weeks of each treatment, ABPM was repeated and the blood sample was collected. Then, the drug was switched to the other one. In the same manner as the first medication, each drug was titrated up to 2 mg of doxazosin or 40 mg of nifedipine CR. At the end of the 4th week of the second medication, ABPM along with the blood sampling was done. Because one patient in group A complained of palpitation one day after nifedipine CR administration and did not wish to continue the medication, this patient completed.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients characteristics (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.9±7.6</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>5/5</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>62.0±10.6</td>
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<tr>
<td>Height (cm)</td>
<td>160±9.4</td>
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<tr>
<td>Body mass index</td>
<td>23.9±2.0</td>
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<tr>
<td>BP at outpatient clinic (systolic/diastolic : mmHg)</td>
<td>170.2±19.7/94.4±8.5</td>
</tr>
<tr>
<td>Twenty four-hour averaged BP (systolic/diastolic : mmHg)</td>
<td>137.8±8.8/85.8±10.6</td>
</tr>
<tr>
<td>Sleep time (22:30-6:00) averaged BP (systolic/diastolic : mmHg)</td>
<td>121.7±9.8/80.1±9.7</td>
</tr>
<tr>
<td>Morning (6:30-9:30) averaged BP (systolic/diastolic : mmHg)</td>
<td>144.8±10.5/90.7±12.4</td>
</tr>
<tr>
<td>Other antihypertensive medications</td>
<td>Telmisartan 40 mg in 2 patients, Valsartan 20 mg in 1 patient, Trichlormethiazide 2 mg in 1 patient</td>
</tr>
</tbody>
</table>
only the doxazosin treatment and was excluded from further analysis. No patient experienced symptomatic orthostatic hypotension.

**Statistical analysis**

The data of blood pressure and heart rate from ABPM were compared among control, doxazosin, and nifedipine using paired-t test at each time. The whole day data were first subdivided into 2 parts: those during awake time (6:30–22:00) and those during the sleep time (22:30–6:00) and the averaged data in each daytime and the sleep time were used for the analysis. Secondly, the awake time and the sleep time were further subdivided into three parts respectively: awake time was divided into morning (6:30–9:30), daytime (10:00–15:30), and evening (16:00–22:00), sleep time was divided into nighttime 1 (22:30–1:00), nighttime 2 (2:00–4:00), and nighttime 3 (5:00–6:00). The averaged data were compared using Wilcoxon’s matched-pairs test. Other clinical data were also compared among the three conditions using Wilcoxon’s matched-pairs test. A value <0.05 was considered statistically significant.

**Results**

The final dose of each drug used in the study is presented in Table 2. Six patients continued to take 1 mg of doxazosin and 20 mg of nifedipine. No significant change indicating any side effect was noted in the blood chemistries during the treatment of either drug except for a tendency for plasma renin activity to increase after nifedipine as compared with control (control 1.16±0.89 ng/mL/hr, doxazosin 1.38±0.94 ng/mL/hr, nifedipine 2.60±2.15 ng/mL/hr, *p* = 0.07 control vs nifedipine).

The time courses of systolic and diastolic BP and heart rate (HR) at control and during the treatment with doxazosin and nifedipine in 9 partici-

**Table 2** Final dose of the medication

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Doxazosin (mg)</th>
<th>Nifedipine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Drop out</td>
</tr>
</tbody>
</table>

![Fig. 1](image)

*Fig. 1* Time course of blood pressure and heart rate in three groups

Data at every time is shown.

* : *p* < 0.05, ** : *p* < 0.01 doxazosin vs nifedipine
pmons are summarized in Figure 1. Neither systolic nor diastolic BP during the period from bedtime to 4 am were different among the three conditions. At 5 and 9 am, nifedipine significantly suppressed both systolic and diastolic BP compared with doxazosin. HR at 1 and 2 am under doxazosin treatment was significantly higher than that under nifedipine.

When the averaged data of the whole day were compared among the three conditions, only systolic BP under nifedipine was slightly but significantly lower than that under control condition (control 138.3±9.2 mmHg, nifedipine 127.8±11.0 mmHg, p<0.05, Fig. 2, left). HR under doxazosin was significantly higher than that under nifedipine (control 72.4±2.3/min, doxazosin 75.6±5.8/min, nifedipine 72.9±5.4/min, p<0.01 doxazosin vs nifedipine). When the whole day data were divided into the awake time (6:30-22:00) and the sleep time (22:30-6:00), a significant difference in both systolic and diastolic BP was present between control and nifedipine only during the awake time (SBP : control 146.0±9.7 mmHg, doxazosin 140.1±6.8 mmHg, nifedipine 132.8±10.9 mmHg, p<0.05 nifedipine vs control, and nifedipine vs doxazosin, DBP : control 90.3±10.1 mmHg, nifedipine 85.2±7.7 mmHg, p<0.05 nifedipine vs control, Fig. 2, middle). On the other hand, a significant difference in HR was recognized between doxazosin and nifedipine only during the sleep time (doxazosin 68.5±8.8/min, nifedipine 64.5±5.7/min, p<0.05, Fig. 2, right). Nifedipine did not affect HR at any time during the whole day.

To examine the effect of each medication on the morning BP, we further subdivided the awake time data into 3 divisions: morning, daytime, and evening. We found that nifedipine significantly reduced both systolic and diastolic BP compared with both control and doxazosin in the morning (control 144.2±11.0/92.2±12.2 mmHg, doxazosin 137.2±8.4/87.1±11.0 mmHg, nifedipine 123.9±10.8/83.1±12.1 mmHg, p<0.05, Fig. 3, left). Though nifedipine significantly reduced SBP compared with control in the daytime, there was no significant difference in BP between nifedipine and doxazosin both during the daytime and evening. The doxazosin-induced increase in HR was only significant in the evening (Fig. 3, right).

The nighttime was also divided into three time groups to further elucidate the precise effect of the medication. There was a significant reduction in
systolic and diastolic BP (control 130.2±11.5/86.1±10.5 mmHg, doxazosin 126.0±12.5/83.2±10.4 mmHg, nifedipine 111.7±16.0/76.8±12.2 mmHg, \( p < 0.05 \) nifedipine vs control and doxazosin) only in nighttime 3, namely, just before awaking. HR increased significantly under doxazosin treatment only in the nighttime 1 compared with both control and doxazosin (control 67.3±7.0/min, doxazosin 75.3±12.5/min, nifedipine 66.1±6.2/min, \( p < 0.01 \) doxazosin vs nifedipine, \( p < 0.05 \) control vs doxazosin).

**Discussion**

The present study indicated that nifedipine CR effectively suppressed the morning BP elevation without affecting sleep time BP in hypertensive patients with a rise in BP in the morning by 20 mmHg as compared to that at the sleep time. This effect was superior to that of 1-2 mg of doxazosin, which has been utilized as a standard regimen for the treatment of morning hypertension\(^\text{16,19}\). Our data also showed that this reduction in BP by nifedipine was not accompanied by reflex tachycardia. On the other hand, doxazosin showed a significant increase in HR in nighttime 1 (Fig. 4), which might come from the reflex tachycardia but the exact mechanism of this tachycardia is unclear. Our findings that the differences in BP reduction among the three conditions were noted between 5:00 and 9:30 are consistent with the findings that the second peak of the BP reduction by nifedipine CR comes about 10 hours after administration of the drug\(^\text{39}\), because patients had taken this drug around 22 o’clock.

Another interesting finding was that patients showed the trough of BP at 2 am in the control condition and under doxazosin, but nifedipine administration shifted this trough toward early morning without additional BP reduction in nighttime 1 and 2 (Fig. 1 and 4). It is wellknown that the trough of BP comes in the late night (around 3 am) in normal subjects\(^\text{39}\). The shift of the trough of BP in the patients with hypertension toward the earlier time and morning hypertension may indicate abnormal diurnal BP control in this type of patient. Nifedipine CR effectively shifted the trough of BP toward morning and suppressed the increase in BP even after awaking. Thus, the administration of nifedipine CR at bedtime successfully controlled early morning hypertension.
The recently increased attention to morning hypertension comes from the findings that a close relationship exists between morning hypertension and the increase in the risk of cardiovascular accident. Kario et al reported that asymptomatic lacuna infarction as well as symptomatic cerebral infarction in the follow-up period of 40 months were associated with morning hypertension\(^\text{10}\). It is also known that cardiovascular events occur mainly in the morning\(^\text{9}\). With these findings, many researchers in the field of hypertension attempted to find the mechanism of morning hypertension and tried to decrease the BP in the morning. If suppression of high blood pressure brings a better prognosis for patients with morning hypertension, this regimen may a promising treatment.

Morning hypertension is closely linked to an abrupt surge of sympathetic nervous activity in the morning\(^\text{9}\). After the report of the HALT study, in which 1-16 mg of doxazosin administered at bedtime effectively controlled morning hypertension\(^\text{34}\), alpha-adrenergic blocking agents became a standard drug for the control of morning hypertension.

Newly designed nifedipine has a unique characteristic in the time course of the antihypertensive effect due to its double structure\(^\text{10}\). In particular, the second peak of the effect manifests at 6-12 hours after administration and this should be effective in the control of morning hypertension. Indeed, our study showed that morning hypertension was almost completely normalized 4 weeks after the start of nifedipine CR. The antihypertensive effect of 20-40 mg of nifedipine CR against morning hypertension was superior to that of 1-2 mg of alpha-adrenergic blocking agent doxazosin.

Because alpha-adrenergic agents have a well-known side effect of orthostatic hypotension, especially in aged patients, the administration of doxazosin may be hazardous at a high dose in aged patients, especially in Japan. It has been shown that orthostatic hypotension was observed in 8% of patients treated with 2 mg of doxazosin given twice a day and the incidence of orthostatic hypotension increased as the dose increased\(^\text{10}\). It is also shown that doxazosin at the dose of 1 mg decreased systolic BP by 26 mmHg and diastolic BP by 12

Fig. 4  Data during sleep time was subdivided into three parts: nighttime 1 (22:30-1:00), nighttime 2 (2:00-4:00) and nighttime 3 (5:00-6:00). A significant decrease in BP was noted in night time 3 only with nifedipine therapy (right).

\(*: p < 0.05, **: p < 0.01, \square: \text{doxazosin vs nifedipine} \)
mmHg in hypertensive patients\(^{10}\). We, therefore, chose 1 mg as the starting dose and titrated up to 2 mg to suppress morning hypertension with minimal side effects. However, because our dose of doxazosin could not attain significant BP reduction in the morning and no orthostatic hypotension was documented, the dose of doxazosin should have been doubled. Compared with alpha-adrenergic blocking agents, calcium channel blockers are relatively safe as to orthostatic hypotension. In our results, BP in the morning as well as just before wake-up (nighttime 3) was effectively suppressed by nifedipine CR (Fig. 3 and 4). The rise in BP during nighttime is also shown to be associated with an adverse prognosis\(^{22}\). Our results indicate that nifedipine CR may be useful not only in the treatment of morning hypertension but also in the patients whose BP is abnormally high just before wake-up. Because our dose of nifedipine did not affect BP from evening through 4 o'clock, this regimen can be easily added to the standard antihypertensive therapy.

One of the limitations of the present study may be the order effect of the drugs. Because the number of study subjects is small and the order was eventually distributed unevenly, the possibility that the effect of the second drug appeared stronger than the first drug due to the order effect can not be denied. We, therefore, calculated the average systolic BP in the group where the first drug was nifedipine. In this group, the value was 134 ± 4 mmHg, 126 ± 6 mmHg, 129 ± 2 mmHg under control, nifedipine, and doxazosin, which did not contradict the result of the present study. This point should be further evaluated in a larger study.

In summary, our study revealed that treatment using nifedipine CR at the dose of 20-40 mg given at bedtime effectively suppressed a rise in BP from the late night through the early morning in hypertensive patients with morning hypertension. This effect exceeded that of doxazosin at the dose of 1-2 mg, which is widely used for the treatment of morning hypertension.

References