Symposium

Clinical Trial of Arotinolol in the Treatment of Hypertension: Dippers vs. Non-Dippers

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To compare the effects of an α, β blocker, arotinolol, in the treatment of essential hypertension between patients with a dipper and those with a non-dipper profile by means of 24-h ambulatory blood pressure monitoring (ABPM), a multicenter single blind parallel trial was carried out in five clinical centers. After a one-week single blind placebo run-in period, the patients underwent ABPM if their clinic diastolic blood pressure (DBP) ranged from 90–109 mmHg and their clinic systolic blood pressure (SBP) was <180 mmHg. They were divided into two groups according to the absence (non-dipper group, 24 cases) or presence (dipper group, 23 cases) of nocturnal BP reduction ≥10% of daytime BP. ABPM was measured again at the end of the active treatment phase. All patients were given Arotinolol 10–20 mg twice daily for 4 weeks. Twenty four-hour systolic and diastolic average BPs (MSBP, MDBP), 24-h systolic and diastolic blood pressure load (LS BP, LDBP), daytime systolic and diastolic average BPs (dMSBP, dMDBP), daytime systolic and diastolic blood pressure load (dLSBP, dLDBP), nighttime systolic and diastolic average BPs (nMSBP, nMDBP) and nighttime systolic and diastolic blood pressure load (nLSBP, nLDBP) were calculated. Arotinolol was effective in 78.2% of dippers and 54.2% of non-dippers, but the difference in effectiveness between these groups was not statistically significant. After treatment, SBP and DBP-including 24-h, daytime and nighttime systolic and diastolic BPs- were significantly reduced in both groups. During the daytime period, the systolic and diastolic blood pressures were significantly reduced in both dippers and non-dippers, while nighttime systolic and diastolic blood pressures were significantly reduced only in the non-dipper group. No significant changes were found in the dipper group over this period. In conclusion, Arotinolol, which can be dosed twice daily, is an effective antihypertensive agent which effectively lowers blood pressure during the day while reducing nighttime blood pressure more in non-dippers than in dippers, without excessive lowering blood pressure in the latter. *(Hypertens Res 2001; 24: 605–610)

Key Words: ambulatory blood pressure monitoring, hypertension, arotinolol

Introduction

Blood pressure has been universally accepted as one of the most important risk factors of cardiovascular morbidity and mortality. In Eastern countries such as China and Japan, the association between blood pressure and stroke seems stronger than in Western populations, whereas cholesterol concentration seems to be less important in Eastern than in Western countries (1).

Epidemiologic studies have demonstrated that abnormal patterns of circadian blood pressure variations carry a high risk of cardiovascular complications. Since the introduction of ambulatory blood pressure monitoring (ABPM) in the
evaluation of blood pressure rhythm, many studies on the relationship between end-organ damage and ABPM have been carried out.

A wide range of definitions is used to distinguish hypertensives with a blunted circadian pattern of blood pressure, or non-dippers, from those presenting with a normal fall in night blood pressure, or dippers. Consequently, the prevalence of the non-dipping phenomenon is quite uncertain: anywhere from 6% to 10% of hypertensive subjects have been estimated to be non-dippers. The mechanisms of the fall in night blood pressure remain unclear, but the autonomic nervous system has been shown to be involved to some degree (1). The non-dipper profile appears to be of prognostic significance because it is associated with increased target-organ damage and a worsened cardiovascular outcome. Some cross-sectional studies have indicated that end-organ damage was greater in patients whose blood pressure showed a non-dipper profile (2–4).

Although there are some discrepancies concerning the definition of and reproducibility of results regarding dippers and non-dippers (5, 6), any method of reducing nighttime blood pressure in non-dippers to within a normal range without excessively reducing the nighttime blood pressure of dippers would be of great interest.

Recently, an α, β blocker, arinolol, was found to be effective in the treatment of hypertension — and particularly in severe hypertension and hypertensive complications when used either alone or in combination with other antihypertensive agents (7–9). The aim of this study was to compare the effects of arinolol in the treatment of essential hypertension between patients with a dipper and those with a non-dipper profile by means of 24-h ABPM. The trial was designed to see whether this agent could effectively lower the nighttime high blood pressure level in non-dipper patients without excessively lowering the nocturnal blood pressure in dippers.

**Methods**

**Patient Selection**

Outpatients aged 18 to 75 years old (49.6±7.8 years) with established primary hypertension of grade 1 or 2 (1999 WHO/ISH Hypertension Management Guideline and 1999 Chinese Hypertension Guideline) were enrolled in this study.

Exclusion criteria included the following: malignant and severe hypertension, secondary hypertension, atrial fibrillation, II-III AVB, sinus bradycardia (HR < 60 bpm), congestive heart failure, allergic asthma, obstructive pulmonary disease, severe liver or renal diseases, stroke within the previous 6 months, myocardial infarction within the previous 6 months, patients taking concomitant medications known to affect BP, patients who worked during the night and slept during the day, and patients who were considered uncooperative.

The protocol was approved by the ethics committee of each participating center and was carried out in accordance with the Declaration of Helsinki (1964) and the Guidelines of Good Clinical Practice of the Ministry of Health of China. All patients gave their informed consent before entering the study.

**Study Protocol**

The study was a multicenter single blind parallel trial carried out in 5 clinical centers of Beijing, China. All the patients ceased to take antihypertensive agents prior to the study. After a one week single blind placebo run-in period, the patients underwent ABPM if their clinic diastolic blood pressure (DBP) ranged from 90–109 mmHg and their clinic systolic blood pressure (SBP) was < 180 mmHg. They were divided into two groups according to the absence (non-dipper group, 24 cases) or presence (dipper group, 23 cases) of nocturnal BP reduction ≥ 10% of daytime BP. ABPM was measured again at the end of the active treatment phase, during which all patients were given arinolol 10–20 mg twice daily for 4 weeks. Throughout the study, all patients were encouraged to take their medication as closely as possible to 8:00 and 20:00. The patients were visited once weekly in the morning before dosing. At each visit, clinic blood pressure (CBP) was measured using a standard mercury sphygmomanometer after at least 15 min of rest in the sitting position and was determined by the average of three consecutive measurements. Heart rate was measured for at least 30 s. ABPM was measured by a noninvasive portable recorder (Spacelabs 90207; Redmond, Washington, USA) set up to measure blood pressure automatically at 20 min intervals throughout the day (6:00–22:00) and 30-min intervals during the night (22:00–6:00). The following quality control criteria were established as standards for acceptability for each ABPM report: 1) a minimum of 24 h of data postdose;
Table 1. Baseline Characteristics of Patients in the Dipper and Non-Dipper Groups

<table>
<thead>
<tr>
<th></th>
<th>Dipper</th>
<th>Non-dipper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.3±7.7</td>
<td>48.8±7.9</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Course (years)</td>
<td>5.1±3.7</td>
<td>6.7±5.9</td>
</tr>
<tr>
<td>BP (mmHg): SBP</td>
<td>150.6±14.6</td>
<td>149.1±14.1</td>
</tr>
<tr>
<td>DBP</td>
<td>100.4±3.8</td>
<td>100.3±4.0</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>78.3±7.6</td>
<td>78.1±8.4</td>
</tr>
</tbody>
</table>

*p >0.05. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

2) a minimum validity of at least 80% of total readings; 3) a minimum of one valid reading during each hour of the monitoring period; and 4) a minimum of 22 total valid reading hours. When quality control criteria were not fitted, the ABPM was repeated between 2 and 5 days after the failed monitoring.

To compare the antihypertensive effect between the dipper and non-dipper groups, the following indices were calculated: 24-h systolic and diastolic average BP (MSBP, MDBP), 24-h systolic and diastolic blood pressure load (LSBP, LDBP), daytime systolic and diastolic average BP (dMSBP, dMDBP), daytime systolic and diastolic blood pressure load (dlSBP, dlDBP), nighttime systolic and diastolic average BP (nMSBP, nMDBP), and nighttime systolic and diastolic blood pressure load (nLSBP, nLDBP). Systolic and diastolic blood pressure loads were determined by calculating the percentage of systolic and diastolic BP above 140/90 mmHg among the daytime measurements and above 120/80 mmHg among the nighttime readings.

The criteria for evaluation of effectiveness of antihypertensive treatment were as follows: 1) Markedly effective: DBP reduction ≥ 10 mmHg and DBP < 90 mmHg or DBP reduction ≥ 20 mmHg; 2) Effective: DBP reduction < 10 mmHg and DBP < 90 mmHg or DBP reduction 10–19 mmHg; 3) Not effective: DBP >90 mmHg and DBP reduction <10 mmHg.

Since the dosing interval was 12 h, the peak effect was taken as the largest reduction of SBP/DBP at 2–6 h after drug intake compared with the baseline value for the same period, and the trough changes were calculated by averaging the differences between pre- and after-treatment blood pressure values over the last 2 h of the next dosing (12 h after the first dosing).

Statistical Analysis

The analysis was performed on an intent-to-treat basis using the last available visit or endpoint, defined as the last visit at which a patient contributed data. Data obtained after one week placebo treatment were designated as baseline. An independent t-test was applied for continuous variables. Comparisons of response rates were performed using an χ² test. Values are given as the mean±SD. All statistical comparisons were two-tailed. P values < 0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS 10.0 software (SPSS Inc., Chicago, USA).

Results

Baseline Characteristics

Forty-seven age- and sex-matched hypertensive patients were recruited for this study and divided into two groups based on their nighttime blood pressure reduction: a dipper (n = 23) and a non-dipper (n = 24) group. The demographics

Table 2. Rate of Effectiveness of Arotinolol in the Dipper and Non-Dipper Groups after Treated with Arotinolol

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Not effective</th>
<th>Total effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dippers</td>
<td>23</td>
<td>8 (34.8%)</td>
<td>9 (39.1%)</td>
<td>6 (26.1%)</td>
<td>17 (78.2%)</td>
</tr>
<tr>
<td>Non-dippers</td>
<td>24</td>
<td>4 (16.7%)</td>
<td>9 (37.5%)</td>
<td>11 (45.8%)</td>
<td>13 (54.2%)</td>
</tr>
</tbody>
</table>

*p >0.05.

Table 3. Office Blood Pressure and Heart Rate during the Treatment Period

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP Dippers</td>
<td>150.7±14.6</td>
<td>139.6±11.8*</td>
<td>139.0±11.2*</td>
<td>133.0±12.3*</td>
<td>132.9±11.7*</td>
</tr>
<tr>
<td>Non-dippers</td>
<td>149.1±14.1</td>
<td>138.3±12.5*</td>
<td>135.5±12.7*</td>
<td>131.6±10.8*</td>
<td>131.7±8.7*</td>
</tr>
<tr>
<td>DBP Dippers</td>
<td>100.4±3.8</td>
<td>92.4±8.7*</td>
<td>89.4±7.5*</td>
<td>85.7±5.7*</td>
<td>85.7±5.7*</td>
</tr>
<tr>
<td>Non-dippers</td>
<td>100.3±4.0</td>
<td>92.4±7.3*</td>
<td>90.0±6.9*</td>
<td>87.2±7.7*</td>
<td>87.2±7.7*</td>
</tr>
<tr>
<td>HR Dippers</td>
<td>78.3±7.6</td>
<td>70.8±8.0*</td>
<td>68.9±7.7*</td>
<td>68.0±7.8*</td>
<td>68.0±7.8*</td>
</tr>
<tr>
<td>Non-dippers</td>
<td>78.1±8.4</td>
<td>71.8±8.0*</td>
<td>69.4±7.0*</td>
<td>69.3±6.4</td>
<td>69.3±6.4</td>
</tr>
</tbody>
</table>

*p <0.01 compared with Week 0. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
and clinical characteristics of the 47 patients in two groups are outlined in Table 1 by group; there were no significant differences between the two groups with respect to age, sex, course of hypertension, baseline CBP or heart rate.

**Effects on Clinic Blood Pressure**

CBP and heart rate were all significantly reduced after 1 week of treatment and antihypertensive response became maximal after 4 weeks of treatment. The effectiveness rate was 78.2% in the dipper group and 54.2% in the non-dipper group, but the difference between groups was not statistically significant (Table 2, 3).

**Effects on Ambulatory Blood Pressure**

After 1 week of placebo treatment, the baseline indices of the blood pressure component of daytime (dMSBP, dMDBP, dLSBP, dLDBP) and MDBP, LDBP were comparable between the two groups (all \( p > 0.05 \)), but those of nighttime (nMSBP, nMDBP, nLSBP, nLDBP, \( p < 0.01 \)) and MSBP, LSBP, LDBP (\( p < 0.05 \)) were significantly higher in non-dippers than in dippers (Table 4, 5).

Figure 1 provides the mean reductions in ambulatory systolic and diastolic blood pressures from baseline to the end of the study in all 47 patients. After treatment, SBP and DBP, including 24-h, daytime and nighttime systolic and diastolic BP, were significantly reduced in all these patients. During the daytime period, the systolic and diastolic blood pressures were significantly reduced in both the dipper and non-dipper groups, while at nighttime the systolic and diastolic blood pressures were significantly reduced only in non-dippers. No significant changes were found in the dipper group during the same period (Fig. 2, 3).

**Calculation of Trough:Peak Ratio**

Arotinolol was administered twice daily, and the trough:peak ratio of this agent was calculated for both the daytime and nighttime. Daytime trough:peak ratios for systolic and diastolic pressure were 68.2% and 83.2%, and those of the nighttime were 58.4% and 63.6%, respectively.
Discussion

Hypertensive patients with a non-dipper profile have a higher than normal pressure load that adversely affects the cardiovascular system. It is desirable to restore this abnormal blood pressure to within a normal range. Previous studies have reported that non-dipper hypertensive patients show decreased parasympathetic activities, which may be one of the reasons for their blunted nocturnal fall in blood pressure (10).

Uzu et al. found that enhanced sodium sensitivity is an independent determinant for the diminished nocturnal fall in essential hypertension and that sodium restriction could restore the nocturnal decline, especially in patients with enhanced sodium sensitivity whose nocturnal decline was diminished. Reduced renal sodium excretory capability may be one of the mechanisms involved in non-dipping (11).

Haemodynamically, the combination of α- and β-adrenoceptor antagonists is a logical one. The α-adrenoceptor blockade causes vasodilatation and hence counteracts elevated peripheral vascular resistance, the most consistent haemodynamic derangement in established essential hypertension. Beta-blockers, which lower elevated blood pressure by a different mechanism, suppress the reflex tachycardia triggered by vasodilatation. The combination of α- and β-adrenoceptor blockade can be obtained by simultaneous administration of both types of adrenoceptor antagonists, as well as by administering drugs that possess α- and β-adrenoceptor antagonistic activity in the same molecule (12).

Arotinolol, an α,β-blocker with a 1:8 effect on the blocking action of α1-receptor and β-receptor, reaches a peak concentration at 2 h after dosing and has a half life of 11.2 h. In previous studies, it was found that arotinolol could improve the balance between the sympathetic and parasympathetic nervous systems (13, 14).

Morimoto et al. found that the potent blocking effects of arotinolol and its metabolite on the increased renin release in response to β-adrenoceptor stimulation may contribute to the antihypertensive effect of this agent. These blocking effects inhibited isopropanol-induced enhancement of renin release in a concentration-dependent manner. Similar results were observed with propranolol or labetalol, although the inhibitory potencies of these agents were considerably lower than that of arotinolol (15).

This study indicates that arotinolol, given at a dose of 10–20 mg twice daily, has a significant effect in the treatment of hypertension in patients with either dipper or non-dipper profiles. Heart rate was also reduced in both groups. Although the difference was not statistically significant, the finding that the total effective rate of antihypertensive treatment was slightly higher in the dipper group than in the non-dipper group may account for the higher nighttime blood pressure in those subjects of the latter in whom the autonomous tension was high.

Interestingly, the nighttime blood pressure in the non-dipper group returned to a level similar to that in the dipper group, while there was no excessive reduction in the latter. Some investigators have reported that there is a critical blood pressure level at which the antihypertensive effect disappears. The critical blood pressure level for each drug is in normal blood pressure range but not in the hypotensive range. Therefore, an antihypertensive regimen would be safe even in extreme-dipper hypertension without excessive nocturnal hypotension, and might even be beneficial because of the decreasing amplitude and speed of the nocturnal BP decline. Thus an antihypertensive drug regimen should control BP throughout a 24-h period regardless of circadian BP variation (16).

The antihypertensive effect of arotinolol, which was able to change the circadian rhythm of non-dippers, may not be a unique property of this agent; many other antihypertensive agents with long acting effects may have similar properties.

In conclusion, it is important to note that arotinolol, which can be dosed twice daily, is an effective antihypertensive agent that effectively lower blood pressure during the day while reducing nighttime blood pressure more in non-dippers than in dippers, without excessive lowering blood pressure in the latter. The long term benefits of this agent in the management of hypertension should be elucidated by large-scale outcome studies.
References