Prevention of Morning Surge of Hypertension by the Evening Administration of Carvedilol

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Abstract

Object To test the clinical usefulness of chronotherapy with a β-blocker, evening carvedilol administration was added to first-line antihypertensive therapy in patients with essential hypertension showing a morning blood pressure surge.

Methods Patients with hypertension (12 men and 5 women) were treated with first-line antihypertensive drugs for 4 weeks and then underwent 24-hr ambulatory blood pressure monitoring. Patients (6 men and 3 women) who still had high blood pressure exceeding 140/90mmHg in the morning were given carvedilol (10mg/day) as a single dose in the morning or evening in a randomized, crossover open-label protocol. After 4 weeks, ambulatory systolic blood pressure, diastolic blood pressure, and pulse rate were reassessed by 24-hr monitoring.

Results Evening carvedilol administration significantly suppressed the morning surge, while morning administration lacked an significant anti-surge effect. The 24-hr mean systolic pressure was also significantly reduced by evening carvedilol administration. Evening administration significantly decreased the early morning, but not the nocturnal, pulse rate.

Conclusions Evening carvedilol administration significantly suppressed the morning increases in systolic pressure and pulse rate. The addition of chronotherapy with carvedilol may be an effective way to suppress morning surges of hypertension.

Key words Hypertension, β-blocker, Chronotherapy, Circadian rhythm, Morning surge, Carvedilol

Introduction

Since ambulatory blood pressure monitoring has become common, certain patterns of circadian variation in blood pressure have been closely linked with the risk of hypertensive organ damage.1–3 In particular, an early morning blood pressure surge appears to be associated with an increased risk of cerebrovascular and cardiovascular events.4–5 Controlling 24-hr variation in blood pressure as well as pressure measured casually at office visits has become an important aim of antihypertensive therapy. Pharmacotherapy that targets such specific circadian blood pressure changes is increasingly recognized as an important strategy. Clinical research concerning the management of hypertension has traditionally focused on the choice of antihypertensive drugs, while more recently, chronotherapy — timing of administration based on a chronobiologic approach — has attracted attention.6 Incorporating the concept of chronotherapy into routine antihypertensive strategies will be a major challenge for clinicians.

Newly introduced antihypertensive drugs with differing mechanisms of action have greatly facilitated blood pressure control in patients with hypertension. The choice of first-line antihypertensive treatment is not usually difficult, being based on national and international guidelines.7,8 However, more variability is introduced upon
selecting a second-line antihypertensive drug when the first-line drug has failed to achieve good 24-hr blood pressure control. When first-line therapy fails to prevent a morning surge in blood pressure, the dose of the first-line drug can be increased; the drug can be replaced by a mechanically similar drug with a longer half-life; or the first drug can be combined with another drug having a different mechanism of action. The greatest advantage of adding another drug with a different mechanism of action is the likelihood of antihypertensive synergism between the two treatments without an increase in toxicity such as might occur after simply increasing the dose of the original drug. However, little has been determined about the optimum timing of second-line treatment to suppress a morning surge after the failure of the first-line drug to do so.

For the management of hypertension, β-blockers have been recommended by various national and international guidelines; unless contraindicated, they are considered the drugs of first choice for lowering high blood pressure in patients with increased sympathetic tone. Since β-blockers specifically block the sympathetic drive, they may be particularly effective for suppressing the morning blood pressure surge, which occurs when sympathetic activity exceeds parasympathetic activity in the course of the circadian rhythm of autonomic regulation. However, adequate evidence of the effectiveness of this strategy has not been obtained.

In the present study, patients with essential hypertension who still showed a morning blood pressure surge despite first-line therapy were additionally given carvedilol, a long-acting β-blocker, as second-line therapy to determine whether this addition could suppress the morning surge. The antihypertensive effect of carvedilol was compared between two different once-daily dosing schedules: adding morning administration at the same time as the first-line drug, and adding evening administration instead, to clarify the chronopharmacodynamic profile of the drug.

Methods

Seventeen untreated patients (12 men and 5 women) initiating ambulatory treatment at our University Hospital for moderate essential hypertension diagnosed according to the criteria specified in the sixth report of the Joint National Committee gave informed consent to participate in the study. They received first-line treatment with a long-acting calcium antagonist (n = 9) or an angiotensin-converting enzyme inhibitor (n = 8) once in the morning every day. Patients with heart failure, asthma, arteriosclerosis obliterans, severe bradycardia, severe hepatic dysfunction, and severe diabetes mellitus were excluded from the study.

After 4 weeks of first-line treatment, each patient underwent monitoring of blood pressure for 25 hr using an ambulatory blood pressure monitor (ES-H-531; Terumo, Tokyo). Systolic blood pressure, diastolic blood pressure, pulse pressure, and pulse rate was measured at hourly intervals. The data obtained from the second hour onward were processed by a specifically configured analyzer (ES-A531; Terumo, Tokyo). The 24-hr mean value was calculated, as well as the mean values for early morning (6 to 10 AM), waking hours (6 AM to 10 PM), and nighttime (10 PM to 6 AM).

After 4 weeks of first-line treatment, nine patients (five treated with a calcium antagonist, four treated with an angiotensin-converting enzyme inhibitor) showed an early morning (6 to 10 AM) mean systolic pressure over 140 mmHg or a diastolic pressure over 90 mmHg. The nine patients were then treated further with the addition of carvedilol (10 mg once daily). This group included six men and three women; their ages ranged from 51 to 78 years (65 ± 3). They were assigned randomly to one of two groups. Five took the additional drug in the morning for 4 weeks, followed by 25-hr ambulatory blood pressure monitoring, and then in the evening for 4 weeks followed by monitoring (Group I). The two treatments were given in reverse order in Group II (n = 4). This crossover design was used to compare the two dosing schedules.

For each hemodynamic parameter, changes at the end of the morning or evening administration of carvedilol from the values observed at various times of day at the end of the first-line treatment were tested for significance using multivariate analysis of variance. For the same parameters, differences in mean values in early morning, waking hours, nighttime, and 24-hr periods between the first-line and post-supplemental treatment were tested for significance using a paired t-test. In all analyses, significance was defined as a P value below 0.05.
Results

The concomitant morning administration of carvedilol did not alter the circadian rhythms of systolic and diastolic pressure from those observed during first-line antihypertensive treatment alone. In contrast, the administration of carvedilol at the same daily dose in the evening accomplished a significant reduction in systolic pressure at 6:00, 7:00, and 8:00 the next morning. The evening administration of carvedilol also caused a significant reduction in diastolic pressure at 6:00 and 7:00 the next morning compared with the values recorded at the end of the first-line treatment period (Fig. 1). Irrespective of the timing of administration, carvedilol caused no significant changes in pulse pressure or its circadian rhythm.

The evening administration of carvedilol caused the mean systolic pressure in early morning (6 to 10 AM) to decrease significantly, from 148±17 to 134±14 mmHg (P<0.01). After the morning administration of carvedilol, the early morning mean systolic pressure was 147±17 mmHg, which remained similar to the value observed at the end of the first-line treatment. Compared with the first-line value (85±9 mmHg), the early morning mean diastolic pressure was significantly reduced to 82±8 mmHg (P<0.05) by the morning administration of carvedilol, and to 77±8 mmHg (P<0.01) by the evening administration. The 24-hr mean systolic pressure was significantly reduced from 144±14 mmHg at initial measurement to 134±12 mmHg (P<0.05) by the evening administration of carvedilol. Both the morning and evening administration of carvedilol significantly reduced the 24-hr mean diastolic pressure, from 82±7 mmHg at initial measurement to 78±9 and 76±9 mmHg, respectively (P<0.01; Fig. 2).

The first-line 24-hr mean pulse rate was 67±11/min; this was significantly reduced to 63±12/min by morning carvedilol and to 64±11/min by evening carvedilol. The decrease in pulse rate induced by carvedilol was significant during waking hours, but not at night. The mean pulse rate in the early morning was significantly
reduced by the evening but not the morning administration of carvedilol (Fig. 3).

**Discussion**

Cardiovascular events in patients with hypertension, including myocardial infarction and stroke, are well known to occur predominantly during the morning.\(^{11,12}\) Data concerning circadian variation in blood pressure indicate that a morning blood pressure surge is involved in the etiology of these cardiovascular events.\(^{13}\) Hematohemellogic studies have also shown that a morning increase in platelet aggregability may trigger ischemic events.\(^{14}\) The increase in both blood pressure and platelet aggregability has been linked to a morning increase in sympathetic tone.\(^{15,16}\) We demonstrated that the evening administration of a \(\beta\)-blocker, carvedilol, significantly suppressed the morning blood pressure surge. Suppression of sympathetic hypertonia might therefore be effective in suppressing the surge.

A number of biologic functions maintain their individual circadian rhythms. Data obtained by ambulatory monitoring have elucidated the circadian rhythm of blood pressure.\(^{17-20}\) Patients with hypertension show various patterns classified as “nondipper,” “dipper,” and “extreme-dipper,” defined by the extent of the nocturnal fall in blood pressure compared with daytime pressure, specifically as less than 10%, 10% to 20%, and more than 20% for these respective groups of patients.\(^{21}\) A study of hypertensive patients with coronary disease showed that antihypertensive therapy led to an increase in the risk of nocturnal myocardial ischemia in subjects showing an extremedipper pattern.\(^{22-25}\) Therefore, the risk of an excessive fall in nocturnal blood pressure should be avoided. In the present study, no excessive decrease in nocturnal blood pressure occurred after the evening administration of carvedilol, while the morning surge was suppressed effectively. Since nocturnal autonomic regulation is characterized by the predominance of parasympathetic activity, sympathetic blockade by carvedilol might be less effective at that time.

The negative chronotropic effect of \(\beta\)-blockers is another concern with evening administration, considering the reported risk of an excessive decrease in nocturnal pulse rate.\(^{26}\) We actually found less reduction in nocturnal pulse rate with the evening than the morning dosage. The negative chronotropic effect of carvedilol appeared to be weak, although the reliability of this finding was limited by the small sample size.

The benefit of chronotherapy in suppressing
the morning blood pressure surge has been investigated by the nighttime administration of doxazosin, an α₁-blocker, but few studies have assessed the benefit of chronotherapy with a β-blocker. Carvedilol has some α₁-blocking activity, but this is far less potent than its β-blocking activity (about one-eighth). Suppression of the morning surge by carvedilol was considered to have resulted from β-blocking activity.

Chronotherapy is an approach to treatment based on the observed circadian rhythms of various parameters. The development of long-acting antihypertensive drugs ordinarily permits the maintenance of normal blood pressure by taking the drug(s) once in the morning. When the morning surge can be controlled by a single dose of an antihypertensive drug in first-line treatment, there may be little benefit from additional consideration of chronotherapy, which instead appears to be an effective option in patients who need second-line antihypertensive therapy. Our findings indicate that the morning and evening addition of carvedilol to a first-line antihypertensive drug has different effects upon the circadian rhythm of blood pressure. This suggests that adding a second-line drug at a different time may yield an adequate response with no change in the dose of the first drug, avoiding dose-related adverse reactions.

The 24-hr mean blood pressure profile has been reported to show good correlation with the severity of hypertensive organ damage and to predict the prevention or reversal of hypertensive damage by long-term treatment. Our data indicate that the addition of chronotherapy with carvedilol where needed may also help to prevent or reverse hypertensive organ damage by improved management of the 24-hr mean blood pressure. However, further studies are needed to evaluate the long-term efficacy of chronotherapy with carvedilol in a larger patient population showing a morning surge after first-line therapy with morning drug administration.

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