ANTIHYPERTENSIVE DRUG THERAPY
IN CONSIDERATION OF CIRCADIAN
BLOOD PRESSURE VARIATION*

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Abstract: J-MUBA was a large-scale clinical study which, for the first time in the world, evaluated the effects of an antihypertensive drug on circadian BP variation in more than 600 patients with hypertension. Although ACE inhibitors reportedly exert equal 24-hour antihypertensive effects on daytime and nighttime BP, α- and β-blockers are reported to have weaker effects on nighttime BP than on daytime BP. However, clinical studies that have investigated the effects of these drugs on circadian BP variation have included only 20–30 subjects and have offered no detailed analyses of circadian BP variation, unlike J-MUBA. An outline of antihypertensive drug therapy in consideration of circadian BP variation has been given in this paper, including the results of J-MUBA. ABPM can provide additional useful information on BP that cannot be obtained by measurement of casual office BP. Increased clinical application of this technique based on further accumulation of study data is expected.

Key words: Circadian blood pressure variation; 24-hour blood pressure; Ambulatory blood pressure monitoring (ABPM); Antihypertensive drug therapy

Introduction

The diagnosis and treatment of hypertension have long been based on casual blood pressure (BP) measurements obtained at outpatient clinics. In contrast, 24-hour ambulatory monitoring of BP, a technique that has become available in recent years, has revealed the time-course of variation in BP and the presence of a circadian rhythm, in that BP is high during the daylight waking hours and low during nighttime sleep.

Thus, it has become apparent that a single BP measurement obtained during a visit to an outpatient clinic does not represent the patient’s true BP, a concept that is not tenable since BP is variable. Therefore, it is now generally recom-
mended that diagnosis and treatment policy be based a comprehensive evaluation of casual BP measurements obtained at multiple visits to an outpatient clinic.

It has been reported that the mean 24-hour BP is more helpful in determining the prognosis of patients with hypertension than casual BP measured at an outpatient clinic. Additional data analysis from the Syst-Eur (Systolic Hypertension in Europe) trial reported in *JAMA* in 1999 indicated that nighttime BP is a better prognostic factor for the likelihood of developing of cardiovascular disease.

In this paper, in connection with discussing antihypertensive drug therapy in consideration of circadian BP variation, the author describes the usefulness and clinical significance of 24-hour ambulatory BP monitoring (ABPM), and introduces the results of a large-scale Japanese clinical study focused on ABPM, the Japanese Multicenter Study on Barnidipine with ABPM (J-MUBA).

**Clinical Significance of ABPM**

ABPM is useful for evaluating the circadian BP pattern, particularly for determining nighttime and morning BP, for identifying white-coat hypertension, and for evaluating response to antihypertensive drugs.

1. **Nighttime blood pressure**

Many normotensives and mild or moderate essential hypertensives have nighttime BP 10–20% lower than their daytime BP. Individuals who have this distinct circadian BP profile are called dippers. On the other hand, elderly people or patients who have hypertensive vascular organ damage or complications in the brain, heart, or kidney show lesser or no decreases in nighttime BP. These individuals who have no distinct circadian BP variation are called non-dippers.

A number of studies have documented that in non-dippers it is important to control high nighttime BP as well as daytime BP to obtain a better prognosis. To this end, medication with long-acting antihypertensive drugs that permit 24-hour control of BP is necessary.

In contrast, in dippers it is necessary to control daytime BP, whereas over-reduction of nighttime BP may induce ischemic complications. Therefore, the use of strong antihypertensive drugs that may cause excessive decreases in nighttime BP should be avoided. In particular, recent studies have shown a group of extreme-dippers who have a wide variation in diurnal BP characterized by a large reduction in nighttime BP of 20% or more compared with daytime BP. In these patients, it is recommended that only daytime BP be lowered, while causing no further reduce in their already low nighttime BP.

2. **Morning blood pressure**

As research on ABPM advanced, it became apparent that BP increases in the early morning and that the increase, called a morning surge, is particularly steep in certain individuals. It is suspected that hypertension in the early morning or morning surge is involved in complications such as myocardial infarction and cerebral hemorrhage occurring immediately after rising from bed, and much attention is being paid to the investigation of the actual status and treatment of morning
hypertension. In particular, when determining the dosing method for antihypertensive drugs, once-daily administration is used for drugs whose antihypertensive effects last until the early morning of the following day (sustained action), based on measurements of ABPM before and after administration, whereas twice- or three-times-daily administration may be necessary as a natural consequence for drugs that have shorter antihypertensive effects that do not last until the following morning. The definitions of morning hypertension and morning surge and their treatment will be described in greater detail later, in the context of outlining the results of J-MUBA.

3. White-coat hypertension

Some people repeatedly show hypertension when BP is measured at an outpatient clinic, although their BP is normal when measured outside the hospital. This condition, called white-coat hypertension, is a pressor reaction to the doctor’s elevated status as represented by his or her white coat, and is considered to be a problem involved in the evaluation of casual BP measured at outpatient clinics. Although the white-coat phenomenon is found in not a few normotensives and general hypertensives, it often diminishes and disappears as they accommodate to visiting the hospital. In contrast, in a certain group of patients, the white-coat phenomenon persists indefinitely. Although white-coat hypertension has been studied extensively, its pathogenesis remains unclarified.

The prognosis of white-coat hypertension, which has been attracting particular attention, is considered to be better than that of true hypertensives and similar to that of normotensives. However, the possibility that white-coat hypertension frequently develops into true hypertension at a later stage has been suggested, and periodic observation is therefore necessary.

Measurement of casual BP at an outpatient clinic does not permit differentiation between white-coat hypertension and true hypertension. White-coat hypertension generally requires no antihypertensive drug therapy. In particular, since the use of potent antihypertensive drugs carries the risk of inducing excessive BP reduction, it is necessary to distinguish true hypertension from white-coat hypertension by ABPM or measurement of BP at home. Whereas it may be difficult for practicing clinicians to employ ABPM for hypertensive patients seen in their daily practice, adequate measurement of BP at home facilitates differentiation between white-coat hypertension and true hypertension.

Automatic cuff-oscillometric devices currently are widely used for home BP measurement in Japan. The reproducibility of the results of ABPM varies according to the pattern of activity on the day of monitoring. In contrast, home BP measurements are highly reproducible; data are consistent and reliable if the BP is measured before breakfast with the patient in the sitting position after gotten up and urinated. It is, however, important to teach the patient how to measure BP correctly. Measuring at the same hour under the same conditions every day is important, and measurement in a cold or hot environment or immediately after eating, drinking alcohol, or smoking should be avoided. Although some of the currently available automatic cuff-oscillometric devices measure BP at the wrist or finger, rather than at the upper arm, these types are more susceptible to error. The
use of automatic devices that measure BP at the upper arm should be encouraged.

Outline of the Results of J-MUBA

A large-scale clinical study, J-MUBA, in which 121 facilities in various parts of Japan participated is described below. This clinical study was designed mainly to study the effects of a long-acting Ca antagonist, barnidipine (Hypoca®) (once-daily administration), on circadian BP variation in Japanese hypertensive patients, using ABPM. All leading ABPM researchers in Japan participated in this clinical study.

1. Purposes and methods of J-MUBA

The purposes of the study were to (1) investigate the influences of patient characteristics on ABPM pattern; (2) compare the clinical significance of ABPM data, home BP measurements, and casual BP data from clinics; (3) examine the action of the antihypertensive drug on white-coat hypertension; (4) determine the action of the drug on nighttime BP, and (5) examine the action of the drug on morning hypertension or morning surge.

The subjects were hypertensive patients aged 30 years or older who had a mean systolic BP of 160 mmHg or more, and/or a mean diastolic BP of 95 mmHg or more in casual office measurements obtained during the observation period. Details of the study were explained to potential participants, and consent to participate was obtained from each patient before the start of treatment.

After obtaining ABPM data during the observation period, a dose of 10–15 mg of the long-acting Ca antagonist barnidipine was given to each patient once daily after breakfast for at least 6 months, and ABPM data obtained during the treatment period were compared with corresponding data obtained during the observation period.

In J-MUBA, the definitions of the terminology of circadian BP variation and processing procedures of ABPM data and their criteria were specifically established prior to data analysis, on the basis of the results of previous clinical studies. These definitions and criteria provide possible standards for future clinical studies on circadian BP variation.

2. Characteristics of registered patients

A total of 612 patients from 121 facilities in various parts of Japan were registered, and 99% of them had essential hypertension (WHO stage I in 45% and stage II in 49%). Most patients were mild hypertensive, without accompanying target organ impairment, with only 4.1%, 2.7%, and 2.2% of patients having impairment in the brain, heart and kidney, respectively. Most subjects were in the age of 40–69 yrs.

Overall, patients’ mean 24-hour systolic and diastolic BP were about 20 mmHg and 10 mmHg lower than the mean casual office systolic and diastolic BP, respectively. When the difference between daytime BP and nighttime BP was examined, according to the definitions of daytime BP as BP obtained between 9:00 am and 9:00 pm and nighttime BP as those obtained between 0:00 am and
5:00am, the mean nighttime systolic and diastolic BP were generally about 20mmHg and 10mmHg lower, respectively, than the corresponding daytime BP.

### 3. Summary of results

The long-acting Ca antagonist exerted steady antihypertensive effect for 24 hours, regardless of daytime or nighttime, on 24-hour BP in all hypertensive patients, but had no influence on pulse rate. The drug caused a significant decrease in casual office BP, but caused hardly any reduction in 24-hour BP in patients with white-coat hypertension who had high casual office BP and normal 24-hour BP. When circadian BP variation was examined in 398 patients with true hypertension who had both high 24-hour and casual office BP, dippers, in whom nighttime BP was at least 10% lower than daytime BP, accounted for about 60%, with extreme-dippers, in whom nighttime BP was at least 20% lower than daytime BP, accounting for 16%. Non-dippers, who had only slight nighttime decreases, accounted for about 40%, and a little more than 10% of all patients were inverted-dippers, in whom nighttime BP was at least 20% lower than daytime BP, accounting for 16%. Non-dippers, who had only slight nighttime decreases, accounted for about 40%, and a little more than 10% of all patients were inverted-dippers, in whom nighttime BP were higher than daytime BP (Table). Whereas non-dippers accounted for a large subgroup (60–70%) among patients of advanced age or with cerebrovascular disorders, 30–40% of younger patients with mild hypertension (30–40 years of age) were also found to have a non-dipper pattern. This is a noteworthy finding that had not been described prior to J-MUBA.

True hypertensive patients were divided into dippers and non-dippers according to circadian BP pattern, and the antihypertensive effects of the long-acting Ca antagonist in these two groups were compared. In non-dippers, who had high BP levels in both day- and nighttime, the drug caused an adequate reduction in nighttime BP as well as in daytime BP, achieving steady 24-hour control. On the other hand, in dippers, who had a nighttime BP decrease, the long-acting Ca antagonist resulted in a sufficient decrease in the high daytime BP, but exerted hardly any effect on the low nighttime BP. In particular, there was no effect on nighttime BP in extreme-dippers, who had normal nighttime BP levels (Fig. 1). Thus, the results

| Table | Number of Patients and BP Values (mean ± SD) by the Circadian BP Pattern in J-MUBA |
|-------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|       | All | Lower-range hypertensives | Higher-range hypertensives | inverted-dippers | non-dippers | dippers | extreme-dippers |
|       | (%) | (n) | (mmHg) | (21) | (79) | (13) | (29) | (42) | (16) |
| 24-hour BP | SBP | 148 ± 15 | 128 ± 6 | 153 ± 12 | 156 ± 12 | 155 ± 13 | 152 ± 12 | 148 ± 10 | 89 ± 9 |
|       | DBP | 89 ± 11 | 79 ± 8 | 91 ± 10 | 89 ± 9 | 90 ± 12 | 93 ± 10 | 163 ± 11 | 98 ± 10 |
| Daytime BP | SBP | 154 ± 15 | 136 ± 8 | 159 ± 13 | 153 ± 12 | 158 ± 9 | 160 ± 12 | 160 ± 12 | 98 ± 10 |
|       | DBP | 93 ± 12 | 84 ± 9 | 95 ± 11 | 89 ± 10 | 93 ± 12 | 98 ± 10 | 163 ± 11 | 98 ± 10 |
| Nighttime BP | SBP | 136 ± 19 | 114 ± 10 | 142 ± 17 | 162 ± 15 | 150 ± 14 | 137 ± 11 | 122 ± 10 | 73 ± 7 |
|       | DBP | 80 ± 12 | 70 ± 8 | 83 ± 11 | 88 ± 9 | 86 ± 12 | 83 ± 9 | 73 ± 7 | 73 ± 7 |
| Casual office BP | SBP | 169 ± 15 | 163 ± 13 | 171 ± 15 | 176 ± 17 | 172 ± 16 | 170 ± 14 | 169 ± 14 | 101 ± 9 |
|       | DBP | 99 ± 10 | 98 ± 8 | 100 ± 10 | 98 ± 12 | 98 ± 10 | 101 ± 9 | 101 ± 9 | 101 ± 9 |
of J-MUBA showed that the long-acting Ca antagonist achieved good 24-hour control of high BP, while it did not reduce low BP, causing no excessive reduction in nighttime BP.

To examine morning hypertension and morning surge, J-MUBA included an analysis of systolic BP over 3 hours before and after awakening. Morning hypertension was defined by at least one measurement of 170 mmHg BP 3 hours after awakening, and under this definition, 37% of all patients had morning hypertension. Morning surge was defined by an abrupt 30 mmHg or higher elevation of mean systolic BP during the 3-hour period after awakening compared with that during the 3-hour period prior to awakening. Twenty-nine percent of patients with morning hypertension exhibited morning surge.

The long-acting Ca antagonist achieved significant control of morning BP in
all patients during the 3 hours before awakening. In particular, in patients with sustained-type morning hypertension, i.e., those who had high BP even before awakening, the drug decreased the high BP before and after awakening by about 20 mmHg for systolic BP and about 10 mmHg for diastolic BP. In patients with morning surge, the drug exerted a potent reduction on the high BP that occurred after awakening, suppressing the abrupt morning elevation of BP by about 50% (Fig. 2).

These results indicate that the long-acting Ca antagonist was able to achieve good 24-hour control of BP. The trough-peak ratio (T/P ratio) is a known index for evaluating the sustained action of antihypertensive drugs. Although this index was also examined in J-MUBA, it was associated with a number of problems, including the method of calculation. This index is therefore considered to require further refinement before it can be of practical use.

REFERENCES

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