Timing for Administration of an Antihypertensive Drug in the Treatment of Essential Hypertension

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Abstract To find the best timing for administration of long-acting antihypertensive drugs, we gave nitrendipine, a calcium antagonist of the dihydropyridine group, once a day to six hospitalized and drug-free patients with essential hypertension, changing the time of administration and studying the effects on the circadian rhythm of blood pressure. After control values of 24-hour blood pressure variations were taken with patients on placebo, a 10-mg tablet of nitrendipine was given for 3 days on three occasions—at 6 AM on awakening, at 8:30 AM after breakfast, and at 6 PM after supper; 24-hour blood pressure values for each period were recorded on the third day. The 24-hour blood pressure values during the control period showed a biphasic circadian rhythm, with higher values during wakefulness and lower values during sleep. The control period was also characterized by a rapid rise in blood pressure on awakening, the so-called morning surge of blood pressure, and a gradual decline during sleep at night. Although the morning surge was not completely suppressed by nitrendipine given after breakfast, it was diminished by the drug given on awakening or after supper; the latter brought a deeper decline in blood pressure during sleep compared with other times. The average of 24-hour blood pressure values obtained by nitrendipine given on awakening was the lowest among the three occasions. Thus, administration of long-acting calcium antagonists with a rapid onset of action on awakening in the early morning seems to be a more rational and beneficial alternative than the conventional administration after breakfast. The earlier administration may prevent dangerous cardiovascular catastrophes, including stroke, myocardial infarction, and sudden death, known to occur often during the morning surge of blood pressure.

Key Words • antihypertensive agents • nitrendipine • circadian rhythm • hypertension, essential • blood pressure

Circadian rhythm of blood pressure is known to be biphasic, with blood pressure higher during wakefulness and lower during sleep than the average 24-hour blood pressure value. Especially in patients with essential hypertension, an abrupt rise in blood pressure after awakening in the early morning is commonly observed; this is called the “morning surge” of blood pressure and has been suggested to be a dangerous trigger of cardiovascular catastrophes. Occurrences of stroke, myocardial infarction, and sudden death have been shown to increase between the hours of 6 and 9 AM compared with the rest of the day. A number of precipitating factors may be involved in these early morning catastrophes, but the marked rise in blood pressure almost certainly is a major factor, perhaps by causing a rupture of atherosclerotic plaques whereby thrombus is formed.

Antihypertensive drugs that are given once a day have come into common use in the treatment of essential hypertension. Nitrendipine is one of the long-acting calcium antagonists of the dihydropyridine group whose clinical usefulness in the treatment of essential hypertension has been established either as monotherapy or in combination with β-blockers. Nitrendipine has a rapid onset of action and is usually given once or twice a day. Pharmacokinetic studies on dihydropyridine calcium antagonists performed in hypertensive patients have also found a relatively straight correlation between the logarithmic value of the plasma drug concentration and the antihypertensive effect, suggesting that a higher plasma level will bring a more profound antihypertensive effect. We therefore sought to find out the best timing for administration of such drugs, especially in those patients who suffer from remarkable morning surges of blood pressure even when they are taking antihypertensive drugs.

In the present study, we used automatic noninvasive blood pressure monitoring and performed chronopharmacologic evaluation on the timing of administration of a long-acting antihypertensive drug.

Methods

Six patients with essential hypertension (World Health Organization stages I or II) including three men and three women aged 32 to 58 years were involved in this study. They were admitted for further examinations of hypertension with blood pressures greater than 160/95 mm Hg on at least two consecutive visits in the outpatient clinic. After admission, any medication including antihypertensive drugs was discontinued and a standard hospital diet was given. During the first 2 weeks, patients underwent clinical evaluations to exclude any identifiable cause of hypertension and were diagnosed as having essential hypertension. Details of the present study were explained, and informed consent was obtained.

Patients were trained for 24-hour ambulatory blood pressure monitoring with an automatic sphygmomanometer (ABPM-203NP, Nippon Colin, Tokyo, Japan) in which the
data on systolic, diastolic, and mean blood pressures (MBP) and heart rate were stored in a memory block and printed out through an analyzer when required. Calibration was made against a mercury sphygmomanometer before each recording. Accuracy of this device has been validated when it is used on the left arm to allow two microphones within the cuff to differentiate between Korotkoff sounds and extraneous noises. Left forearm readings were taken every 30 minutes over 24 hours using a standard-sized cuff with CO₂ gas inflation. All patients kept a diary of the times they awoke, took nitrendipine or placebo tablets, ate, and went to sleep at night.

During a run-in period of 3 days, a placebo tablet was given at 8:30 AM (after breakfast), and 24-hour blood pressure variations were recorded on the third day as control values. During the therapeutic period of 9 days, a 10-mg tablet of nitrendipine was given at 6 AM on awakening for 3 days, after breakfast (8:30 AM) for 3 days, and after supper (6:30 PM) for 3 days. The order of changing the time of nitrendipine administration was randomized among patients.

The MBP of each hour was obtained from the mean of two readings taken every 30 minutes. Data are expressed as mean±SEM. Differences among the four occasions of placebo and drug administrations were evaluated by two-way ANOVA and Tukey's multiple comparison test. The relation between the percent reduction in the morning MBP and that in the 24-hour MBP was examined by correlation analysis and regression analysis. Values of P<.05 were defined as significant.

Results

Hourly blood pressure during the placebo run-in period fell progressively from the onset of sleep to its lowest level of 101.7±4.2 mm Hg at 2 hours before awakening. When patients awoke at 6 AM, MBP elevated slightly to 108.4±5.2 mm Hg and markedly to 117.6±7.2 mm Hg at 7 AM, which was the highest of the day, and then declined rapidly to 107.5±4.5 mm Hg at 8 AM (Fig 1). This abrupt rise of blood pressure, with a sharp peak seen in the early morning, is the morning surge.

When nitrendipine was given on awakening at 6 AM, the peak height of this morning surge was markedly suppressed from 117.6±7.2 mm Hg during placebo to 98.2±4.9 mm Hg (P<.0001). It was also suppressed significantly to 105.2±7.0 mm Hg (P<.01) by nitrendipine given after supper at 6 PM, and the time of the early morning peak in blood pressure was delayed 1 hour. When nitrendipine was given after breakfast at 8:30 AM, however, the peak height of the morning surge at 7 AM was 103.0±12.4 mm Hg, which was not significantly lower than that during placebo. While patients were awake, few blood pressure variations were observed in both the run-in and therapeutic periods, with a few small peaks at noon, 3, and 6 PM. After the onset of sleep, the fall in blood pressure was more profound on the occasions when nitrendipine was given on awakening and after supper compared with that after breakfast or placebo. The lowest value in MBP during sleep at night was 87.6±5.4 mm Hg when nitrendipine was given after supper.

Twenty-four-hour MBP in the run-in period was 108.8±3.1 mm Hg, which was markedly lowered to 95.0±2.5 mm Hg with administration of nitrendipine on awakening (P<.01) and to 97.5±2.7 mm Hg with administration after supper (P<.05) but not significantly lowered to 100.9±2.8 mm Hg with administration after breakfast (Fig 2). When the mean of early morning blood pressures calculated from six readings during the 3 hours from 6 to 9 AM was compared among the four occasions including placebo and the three different timings of nitrendipine administration, the value when nitrendipine was given on awakening or after supper was significantly lower than that during placebo (95.1±3.2 [P<.001] or 101.0±3.2 mm Hg [P<.05] versus 109.7±2.8 mm Hg, respectively). Similarly, mean waking blood pressures from 9 AM to 10 PM and mean sleeping blood pressures from 10 PM to 6 AM, were lowered significantly when nitrendipine was given on awakening in the early morning (P<.05). The mean of sleeping blood pressures during nitrendipine administration after supper was 89.4±3.8 mm Hg, which was the lowest among the four occasions. Furthermore, a significant correlation was found between the percent...
Thus, sudden increased firing in the sympathetic nervous system seems to be a dangerous trigger of cardiovascular catastrophes, including stroke, myocardial infarction, ischemic heart attack, and sudden death. Although a number of precipitating factors may be involved in these early morning catastrophes, the marked rise in blood pressure is one of the major factors, causing the rupture of atherosclerotic plaques whereby thrombus is formed. Accordingly, attenuation of the morning surge of blood pressure may be one of the most important targets in the treatment of essential hypertension.

In this decade, a major part of antihypertensive therapy has been changed from the use of relatively short-acting drugs usually given two or three times a day to the long-acting drugs given once a day; nevertheless, the mechanism of action is variable. The purpose of this change might be to improve patient compliance with therapy and/or achieve a more stable control of 24-hour blood pressure variations. However, little attention has been paid on the timing of administration of long-acting drugs, because in principle, the antihypertensive effects of such drugs have been proved to last for 24 hours. Currently, patients usually are advised to take long-acting drugs after breakfast, without any particular considerations, perhaps because of simple convention or an expectation of better absorption from the intestine. This also might be true in most clinical trials on long-acting antihypertensive drugs, because any particular description of the timing of drug administration has not been found.

Nitrendipine is one of the long-acting calcium antagonists whose antihypertensive effect is characterized by a rapid onset of action similar to that of other dihydropyridine calcium antagonists including nifedipine, nisoldipine, and manidipine. Although the clinical usefulness of nitrendipine in the treatment of essential hypertension has been widely accepted when it is given once a day, Maclean et al pointed out that the duration of its antihypertensive effect is less than 24 hours and recommended twice-a-day administration. In fact, some patients receiving nitrendipine once a day and measuring their home blood pressures often complain of insufficient control of blood pressure in the early morning. Especially in the cold season, their early morning blood pressures are extremely high even when they are taking the drug every day after breakfast. This is somewhat reasonable because plasma concentrations of the drug might be near minimum at that time. There is a relatively straight correlation between the antihypertensive effect of calcium antagonists and logarithmic value of plasma concentrations, so antihypertensive effects in the early morning should be at a minimum when such drugs are taken after breakfast.

The chronic pharmacologic aspect of the present study clearly demonstrated that the morning surge in blood pressure can be attenuated by administration of antihypertensive drugs on awakening instead of after breakfast. Another alternative for attenuating the early morning surge in blood pressure is the administration of drugs after supper. However, this seems to be somewhat problematic, because blood pressures can become too low during sleep, which can be unfavorable especially in patients with atherosclerotic changes on the cerebral arteries because of induction of thrombosis. However, evidence that cerebral infarction is a nocturnal illness is not convincing. In this context, an abrupt rise in blood pressure in the early morning may be more harmful than blood pressures that are too low during sleep.
It is difficult to explain why the most profound depressor effect on 24-hour blood pressure was observed by administration of nitrendipine on awakening compared with the other two occasions (see Fig 2). An extraneous factor such as an order effect is not likely because the order of the three occasions was randomly assigned. One can speculate that the more appropriately controlled morning blood pressure may bring better control of 24-hour blood pressure because extraordinary stimuli during the morning surge may activate the sympathetic nervous system, the renin-angiotensin system, or other pressor mechanisms—all factors that can affect blood pressure variation during 24 hours. This hypothesis may be supported by the finding in this study that there was a significant correlation between the percent reduction in morning MBP and in 24-hour MBP during nitrendipine administration.

In conclusion, administration of dihydropyridine calcium antagonists with a rapid onset of action on awakening in the early morning instead of after breakfast can reduce not only morning blood pressure but also 24-hour MBP. It is also worth noting that patients taking such drugs on awakening appear to show a better compliance with treatment and fewer symptoms of flushing and palpitation, especially during daytime working hours, compared with patients taking such drugs after breakfast. These observations require further chronopharmacologic studies on other long-acting antihypertensive drugs to find the best timing of administration while considering effectiveness or even lifestyle of each patient. Further large studies are necessary to answer the most important question of whether these approaches can prevent cardiovascular catastrophes in patients with essential hypertension.

References
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