# Morning Versus Evening Administration of a Calcium Channel Blocker in Combination Therapy for Essential Hypertension by Ambulatory Blood Pressure Monitoring Analysis

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**SUMMARY**

Patients with moderate to severe hypertension may need more than two antihypertensive drugs in combination to achieve ideal blood pressure (BP) control. The purpose of this study was to compare the efficacy and safety of administering the antihypertensive agents either all together in the morning or separately with two agents in the morning and one calcium channel blocker (CCB) in the evening. Twenty-four-hour ambulatory BP monitoring (ABPM) was performed among 15 patients (mean, 59 years) with moderate to severe essential hypertension. All patients received at least 3 antihypertensive drugs for ideal BP control. Two treatment regimens were given to each patient: Regimen 1: All antihypertensive agents were given once a day in the morning; Regimen 2: All antihypertensive agents were given in the morning, except the CCB which was given at 4:00 pm. After receiving regimen 1 for 4 weeks, each patient underwent 24-hour ABPM to analyze the BP control. After the first ABPM, each patient was switched to regimen 2. After 4 weeks of treatment with regimen 2, each patient underwent the second ABPM measurement. The pretreatment mean systolic and diastolic BP were 179.6 ± 21.7 and 107.4 ± 19.9 mmHg, respectively. Between the two regimens, there was no significant difference in the mean 24-hour BP (126.1 ± 5.8/73.3 ± 3.8 versus 130.2 ± 6.2/75.1 ± 4.7 mmHg), daytime BP (128.2 ± 6.5/75.3 ± 3.8 versus 132.4 ± 5.8/77.2 ± 4.4 mmHg), nighttime BP (125.2 ± 4.9/72.4 ± 3.3 versus 130.9 ± 6.2/73.8 ± 4.1 mmHg), and 24-hour heart rate (65.1 ± 3.8 versus 64.2 ± 3.4 bpm). The circadian BP and heart rate profiles were almost identical between regimen 1 and regimen 2. We conclude that in patients with moderate to severe hypertension treated with at least 3 antihypertensive agents, administering a CCB simultaneously with other antihypertensive agents in the morning or separately in the evening did not affect the 24-hour BP control. (Int Heart J 2005; 46: 433-442)

**Key words:** Hypertension, Ambulatory blood pressure monitoring, Calcium channel blocker

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THE development of noninvasive 24-hour ambulatory blood pressure monitoring (ABPM) devices marked a significant advancement for clinical hypertension research.[1-2] The long-term reproducibility of ABPM is superior to office measurement,[3] especially in patients with white coat hypertension.[4-5] In hypertensive patients, the pattern of the manifestation of the 24-hour blood pressure (BP) recording has proved to be able to predict the long-term cardiovascular prognosis[6-7] and degree of target organ damage.[8-10] ABPM also is an ideal tool for evaluating the efficacy of antihypertensive agents.[11]

Previous reports have shown that most patients with hypertension may need more than one antihypertensive drug in combination to achieve ideal BP control.[12-16] It is convenient and an acceptable rule for patients with moderate to severe hypertension to take more than one long-acting antihypertensive drug simultaneously once a day, usually in the morning. However, it remains unclear whether there is a potential risk for the over-reduction of BP during the day, caused by drug interactions among the different antihypertensive agents. Another option for combination therapy may be administering the antihypertensive agents separately with 1 or 2 agents in the morning and the other agent in the evening. However, the efficacy of therapy involving divided administration of antihypertensive agents on the 24 hour BP control remains unknown. There are still no data available to compare the antihypertensive effects of the same combination of antihypertensive agents which were administered at different times during the day and it is still not clear which regimen of drug administration is better for BP control in patients with moderate to severe hypertension. In the present study, for patients who need more than two antihypertensive agents for their BP control, we investigated and compared the efficacy and safety of administering the antihypertensive agents either all together in the morning or separately with two agents in the morning and one agent in the evening using 24 hour ABPM.

## METHODS

**Study population:** This matched-paired, cross-over study was performed in our cardiovascular outpatient clinic from September 2000 to July 2001. A total of 15 patients were enrolled in this study, and they all visited the cardiovascular outpatient clinic monthly. Exclusion criteria included a history of unstable angina or prior myocardial infarction, renal failure (creatinine > 2.0 mg/dL), chronic liver disease, and gastrointestinal disease that might have interfered with drug absorption. The antihypertensive agents were titrated monthly according to the patient's own home BP records and BP measurements taken during clinic visits. All 15 patients needed at least 3 antihypertensive agents in regular doses to maintain their BP at less than 140/90 mmHg. The patients were enrolled in the study only

after the BP was under control (ie, less than 140/90 mmHg) and had remained stable for 3 months. No alteration in diet was undertaken during the study. Patients were instructed not to restrict their daily activities during the monitoring periods. Informed consent was obtained from each patient after the study protocol was carefully and clearly explained.

**Study protocol:** All 15 patients needed a combination of more than two antihypertensive agents, which included at least 1 calcium channel blocker (CCB) for ideal BP control. The following 2 treatment regimens were administered to each patient. For regimen 1, CCBs were given in the morning simultaneously with other antihypertensive drugs. For regimen 2, CCBs were administered separately at 4:00 pm, while other antihypertensive agents were given in the morning. After receiving regimen 1 antihypertensive treatment for 4 weeks, the patients underwent 24-hour ABPM to analyze their BP control. After the first ABPM, the patients were switched to regimen 2. After 4 weeks of treatment with regimen 2, the patients underwent the second ABPM. The ABPM for each patient from both treatment regimens were compared to analyze which regimen would achieve more appropriate BP control.

Twenty-four-hour ABPM was performed with an oscillometric (SpaceLabs 90202; Spacelabs, Inc., Redmond, WA) ambulatory blood pressure monitor.[17] The 24-hour ABPM was attached to the patient and programmed to acquire a BP reading every 30 minutes from 6:00 am to 10:00 pm and then at 60-minute intervals from 10:00 pm to 6:00 am. Raw data (hourly means) were stored on a computer, and primary analysis (24-hour, daytime, and nighttime means; standard error, standard deviations; calculation of mean changes in different values and of "hypertension load") was performed on a spreadsheet. Sitting BP, smoking, exercise and dietary habits, body weight, drug compliance, and adverse effects were assessed at each clinic visit.

**Statistical analyses:** All data are expressed as the mean ±SD. SPSS for Windows (version 11.0.1) was used for statistical analyses. Comparisons of (1) the 24-hour mean systolic and diastolic BP, (2) daytime and nighttime systolic and diastolic BP, and (3) 24-hour heart rate change by ABPM recording with these 2 different regimens (regimen 1 versus regimen 2) in each patient were made using a paired-sampled *t*-test. A value of 2-tailed $P < 0.05$ was considered statistically significant.

## RESULTS

Fifteen patients (11 females, 4 males), with a mean age of 59 ± 10 (40 to 73) years, were included in the study (Table I). The pretreatment BP were 179.6 ± 21.7/107.4 ± 19.9 mmHg. One patient had diabetics mellitus and another had cor-

**Table I.** Baseline Characteristics of the Study Population ($n$ = 15)

| Characteristic | |
|---|---|
| Age, years | 59 ± 10 |
| Female/Male | 11/4 |
| BL (cm) | 159.9 ± 6.1 |
| BW (kg) | 68.3 ± 8.4 |
| BMI (kg/m$^2$) | 26.6 ± 2.7 |
| Smokers | 2/15 |
| Pretreatment | |
| SBP (mmHg) | 179.6 ± 21.7 |
| DBP (mmHg) | 107.4 ± 19.9 |
| HR (bpm) | 76.6 ± 6.5 |
| CHD | 2/15 |
| CVD | 0/15 |
| DM | 2/15 |
| LVH | 11/15 |
| CRI | 0/15 |
| Proteinuria | 5/15 |
| Retinopathy | 3/15 |
| PVD | 0/15 |

BL = body length; BW = body weight; BMI = body mass index; CHD = coronary heart disease; CRI = chronic renal insufficiency; CVD = cerebrovascular disease; DM = diabetics mellitus; LVH = left ventricular hypertrophy; PVD = peripheral vascular disease.

onary heart disease. Two patients had a history of smoking cigarettes. Eleven patients had evidence of LVH by ECG and/or echocardiographic criteria. Five patients had proteinuria. No chronic renal insufficiency or peripheral vascular disease was diagnosed in these patients. Hypertensive retinopathy was observed in 5 patients by funduscopic examination.

Table II summarizes the combination regimen of antihypertensive drugs used in each patient. All patients were given calcium-channel blockers. Five patients received felodipine (5 mg), 8 nifedipine-OROS (30 mg), and 3 patients amlodipine (5 mg). Concurrent antihypertensive regimens included beta-blockers (13 patients), angiotensin converting enzyme inhibitors (10 patients), alpha-blockers (2 patients), diuretics (13 patients), and an angiotensin receptor blocker (1 patient). No major side effects were observed.

**Twenty-four-hour BP:** The 24-hour mean systolic and diastolic BP values are presented in Table III and Figure 1. The 24-hour mean systolic BP, diastolic BP,

**Table II.** Summary of Antihypertensive Regimens

| ID | Sex | Age | Antihypertensive Drugs | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | CCBs | β-Blocker | ACEI | α-Blocker | Diuretics | ARB |
| 1 | F | 64 | F | A | E | | | |
| 2 | F | 73 | F | A | E | | T | |
| 3 | F | 58 | F | A | | | T | |
| 4 | F | 48 | F | C | L | | | |
| 5 | M | 71 | R | A | L | Z | T | |
| 6 | F | 60 | R | A | | | T | |
| 7 | F | 44 | R | C | Q | | T | |
| 8 | F | 67 | R | A | E | | T | |
| 9 | M | 40 | R | O | L | D | T | |
| 10 | F | 56 | R | | L | | T | |
| 11 | M | 51 | R | A | | | T | V |
| 12 | F | 67 | R | A | | | T | |
| 13 | F | 60 | N | A | Q | | T | |
| 14 | M | 70 | N | | E | | T | |
| 15 | F | 62 | N | A | | | T | |

ACEI = angiotension converting enzyme inhibitor; ARB = angiotension receptor blocker; CCB = calcium channel blocker; A = atenolol; C = carteolol; D = doxazosin; E = enalapril; F = felodipine; L = lisinopril; N = amlodipine; O = nadolol; R = nifedipine OROS; Q = quinapril; V = valsartan; T = trichloromethizide; Z = terazocin.

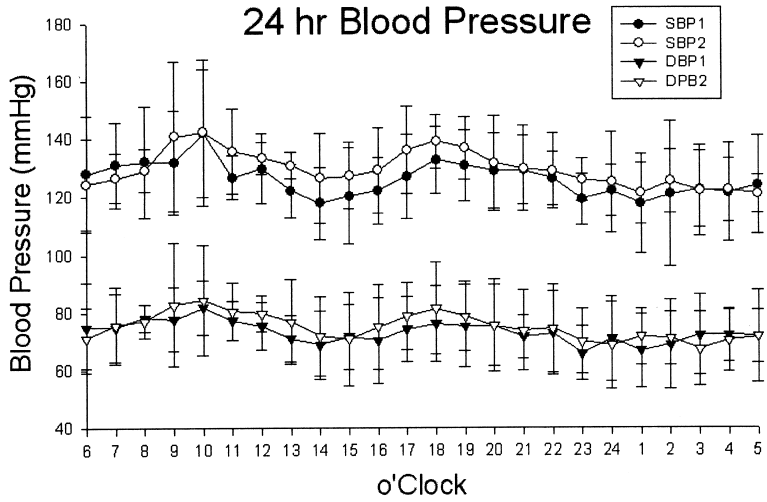


**Figure 1.** Twenty-four hour blood pressure patterns by ABPM analysis. SBP1 and DBP1: systolic and diastolic blood pressure under regimen 1. SBP2 and DBP2: systolic and diastolic blood pressure under regimen 2.

and heart rate in regimen 1 were 126.1 ± 5.8 mmHg, 73.3 ± 3.8 mmHg, and 65.1 ± 3.8 bpm, respectively, while those in regimen 2 were 130.2 ± 6.2 mmHg, 75.1

± 4.7 mmHg, and 64.2 ± 3.5 bpm, respectively. The circadian BP and heart rate profiles were almost identical between regimen 1 and regimen 2. No significant changes in 24-hour mean systolic BP, diastolic BP, and heart rate between regimen 1 and regimen 2 were observed.

**Daytime value and night-time value:** The daytime (6:00 am - 6:00 pm) and nighttime (6:00 pm - 6:00 am next morning) mean systolic and diastolic BP values are presented in Table III and Figure 1. There were no significant differences between regimen 1 and 2 in daytime BP (128.2 ± 6.5/75.3 ± 3.8 versus 132.4 ±

**Table III.** Mean 24-hour, Daytime, and Nighttime Blood Pressure and Heart Rate Values for Two Different Combination Regimens

| | 24 hr Mean BP (mmHg) | | Daytime BP (mmHg) | | Nighttime BP (mmHg) | | HR (bpm) |
|---|---|---|---|---|---|---|---|
| | Systolic | Diastolic | Systolic | Diastolic | Systolic | Diastolic | |
| Regimen 1 | 126.1 ± 5.8 | 73.3 ± 3.8 | 128.2 ± 6.5 | 75.3 ± 3.8 | 125.2 ± 4.9 | 72.4 ± 3.3 | 65.1 ± 3.8 |
| Regimen 2 | 130.2 ± 6.2 | 75.1 ± 4.7 | 132.4 ± 5.8 | 77.2 ± 4.4 | 130.9 ± 6.2 | 73.8 ± 4.1 | 64.2 ± 3.5 |
| *P* Value | NS | NS | NS | NS | NS | NS | NS |

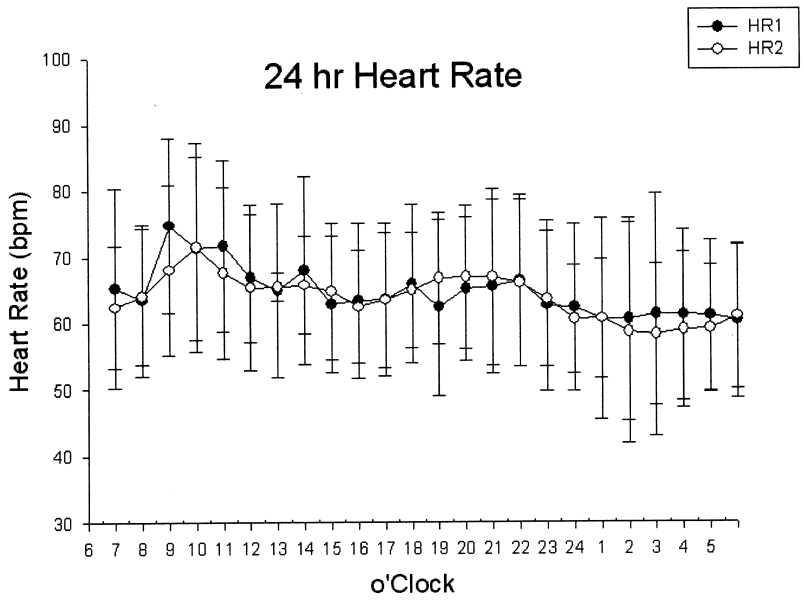


**Figure 2.** Twenty-four hour heart rate changes by ABPM analysis. HR1 = Heart rate change with regimen 1; HR2 = heart rate change with regimen 2.

5.8 / 77.2 ± 4.4 mmHg, *P* = 0.156/0.178, respectively) or nighttime BP (125.2 ± 4.9 / 72.4 ± 3.3 versus 130.9 ± 6.2 / 73.8 ± 4.1 mmHg, *P* = 0.469/0.806, respectively). For regimen 1, no excess reduction in BP in the afternoon was observed, while for regimen 2, no excess reduction in BP in the nighttime was noted. No significant nocturnal fall in BP was seen for either treatment regimen.

**Twenty-four-hour heart rate values:** The 24-hour heart rate values are presented in Table III and Figure 2. There were no significant differences in heart rate between regimen 1 and regimen 2 (65.1 ± 3.8 versus 64.2 ± 3.4 bpm) during the daytime or nighttime periods.

## DISCUSSION

The purpose of this study was to evaluate the changes in ABPM when one of the combination antihypertensive agents was administered at a different time during the day. The results showed that no significant change in the 24-hour BP pattern could be demonstrated when the CCB was administered either in the morning or in the evening.

It has been suggested that better control of BP could be achieved by a combination of 2 or more antihypertensive drugs than by monotherapy in regular doses.[18-19] The superior effectiveness of combined therapy results from better antihypertensive efficacy and higher response rates in the low range of doses. The different mechanisms of the antihypertensive actions of each agent may be additive[20] or synergic.[21-22] It is often necessary to administer 2 or 3 antihypertensive agents. However, the ideal time schedule for administering these different antihypertensive agents is still not well-defined.

The effects of a single antihypertensive agent administered either in the morning or evening on the circadian pattern of changes in BP and heart rate ("chronopharmacology") have been studied using ABPM.[23-32] Greminger, *et al* studied the effect of morning versus evening administration of nifedipine gastrointestinal therapeutic system (GITS) in 15 patients with moderate hypertension and concluded that the time of administration of nifedipine GITS had no impact on daytime or nighttime BP control.[25] Mengden, *et al* reported that different timing of once-daily amlodipine administration does not influence its efficacy for 24-hour BP control.[26] Another chronopharmacology study conducted by White, *et al* found that the different timing of nisoldipine ER administration had no effect on mean changes in BP and heart rate over a 24-hour period. However, a significantly greater effect on awake diastolic BP with morning administration was found compared to evening administration. In the study by Middeke, *et al*[28] comparing morning versus evening administration of captopril plus hydrochlorothiazide, significant differences in daytime BP were found for morning

administration. All these previous studies evaluated BP changes when the monotherapy regimen was administered either in the morning or evening. For patients who require at least three antihypertensive agents for BP control, the manifestation of the 24-hour BP patterns remained unknown when 1 of the 3 antihypertensive agents was administered either in the morning or in the evening.

In the present study, the 24-hour mean systolic and diastolic BP tracing and mean hourly heart rate did not show any significant difference whether the CCB was administered either in the morning or in the evening. Results from this study indicated that for patients who need at least three antihypertensive agents for their BP control, administration of all agents simultaneously in the morning was feasible and did not have a too potent hypotensive effect due to synergistic effects. However, if the CCB was administered separately in the evening, the BP still could be well controlled. We decided to administer the CCB as an indicator because it has a more potent BP lowering effect and the synergistic hypotensive effect may occur more easily when the CCB is administered simultaneously with other antihypertensive agents in the morning dose. No nocturnal fall in BP could be demonstrated from the 24-hour BP recording in either treatment regimen. Since the degree of hypertension in our patient group was relatively severe, the diurnal variation pattern could be perturbed in this study. Furthermore, despite the optimal control of nocturnal BP, shifting CCB administration to the evening was also unable to restore the perturbed diurnal variation pattern back to normal.

In addition to the relatively severe degree of essential hypertension in our patients, the other possible causes of the loss of nocturnal fall in BP may be related to the degree of daytime activity and/or the sleep quality during the 24-hour ABPM monitoring. From the results of regimen 1 and 2, no significant difference in nocturnal BP could be demonstrated. Since the ABPM is by far the standard and best accepted method in clinical practice to evaluate the changes in BP control and our patients were all fully informed about this ABPM study, the results are believed to be related to the severity of hypertension and less likely to sleep quality. Another point that should be mentioned is that in this particular study, CCB was administered at 4:00 PM. If CCB was administered at a later hour in regimen 2, the distribution of the BP curve at nighttime may be different and require further study to confirm. In this study, felodipine, nifedipine-OROS, and amlodipine were given to 4, 8, and 3 patients, respectively. When we analyzed the 24-hour pressure curves according to the 3 different CCB separately, still no significant difference between the 2 regimens could be demonstrated. However, due to the small number of patients in each group, the possibility that different kinds of CCB may have different effects on the circadian BP pattern caused by their dif-

ferent biological half-lives needs to be considered. Further work is needed to determine the different effects of different CCBs on the nocturnal pressure pattern.

There are several limitations to this study. First, our study population was relatively small and the statistical power may be relatively low in comparison, but the changes in BP status were almost identical and did not vary widely. Second, only CCB was chosen as a variable in this study. We chose CCBs because they are the most frequently prescribed antihypertensive agents and have been shown to be both safe and effective. When used in combination with other antihypertensive drugs, CCBs can exhibit a marked BP lowering effect and may induce a too potent hypotensive effect.[29-30] Third, too few ABPM measurements were obtained in this study; therefore, some data points with significant BP changes between these two regimens may have been missed.

In conclusion, for patients who need at least three antihypertensive agents for BP control, the CCB can be administered either with other antihypertensive agents simultaneously in the morning or separately in the evening. No adverse hypotensive effects were observed when the CCB was given simultaneously with other antihypertensive agents in the morning.

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