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ORIGINAL ARTICLE

Fixed-combination of amlodipine and diuretic chronotherapy in the treatment of essential hypertension: improved blood pressure control with bedtime dosing—a multicenter, open-label randomized study

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Previous studies have demonstrated that individual anti-hypertension medications have different effects when administered in the morning *vs.* the evening. However, the impact of administration timing on fixed combinations of anti-hypertensive medications on blood pressure control is still unknown. In the present study, we examined the administration time-dependent effects of a fixed combination of amlodipine and diuretics (amlodipine complex) on blood pressure in hypertensive subjects. Eighty patients from Chongqing City were enrolled in this study. Subjects were randomly assigned to receive a single pill (amlodipine complex, each tablet containing amlodipine 5 mg and hydrochlorothiazide 25 mg), either in the morning (0800 hours, *n*=40) or at bedtime (2200 hours, *n*=40). Blood pressure was measured by ambulatory monitoring every 20 min during the day and every 30 min at night for 24 consecutive hours before and after the 12 weeks of treatment. Following treatment, the 24-h mean systolic and diastolic blood pressures were reduced significantly in both the morning and bedtime groups. However, the morning blood pressure surge was reduced to a greater degree in the bedtime group. In addition, the nocturnal blood pressure and the 24 h mean blood pressure were lower in the bedtime group. More patients converted from having a non-dipper to dipper blood pressure in the bedtime group. These findings confirm that amlodipine complexes have different efficiencies depending on treatment time. Administration of amlodipine complexes at bedtime could optimize the anti-hypertensive effect by augmenting blood pressure-lowering effects, increasing the diurnal/nocturnal ratio of blood pressure, normalizing the blood pressure pattern and minimizing the morning blood pressure surge.
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INTRODUCTION

Hypertension, a common risk factor for cardiovascular morbidity and mortality, is highly prevalent, affecting ~one billion individuals worldwide.[1,2] Over the years, concomitant with an increased understanding of the epidemiology of hypertension and the beneficial effects of treatment, there has been a progressive lowering of blood pressure values in treated hypertensives towards optimal targets. Even though awareness and treatment of hypertension have increased, substantial improvements in blood pressure control rates are still needed.[3,4] Currently, it is postulated that hypertension should be considered a multifactorial disease, often requiring multiple drugs for its management, with the majority of hypertensive patients requiring two or more agents to reach a specific blood pressure goal, particularly for those patients with stage 2 or stage 3 hypertension.[2–4] The guidelines in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)[5] recommend the use of fixed combinations of anti-hypertensive medications, including calcium channel blockers (CCBs) and diuretics.[6]

Besides blood pressure level, blood pressure characteristics, including blood pressure pattern, morning surge and the diurnal/nocturnal blood pressure ratio are all independent risk factors for cardiovascular

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disease (CVD).[7–9] Normalization of the circadian rhythm of blood pressure is considered to be an important clinical goal of pharmacotherapy. Due to the time-dependent kinetics of medications, as well as normal circadian rhythms during drug-free times, and the rate-limiting steps of key metabolic pathways, it is not surprising that anti-hypertensive medications would display circadian-dependent effects. Previous studies have demonstrated differing effects of angiotensin-converting enzyme inhibitors, CCBs and diuretics when administered in the morning *vs.* the evening.[10–13] However, rarely has the time of drug administration been a specific investigative focus for fixed combinations of anti-hypertensive medications. This study compared, by 24-h ambulatory blood pressure monitoring (ABPM), the anti-hypertensive efficacy of the administration of a fixed combination of amlodipine (a CCB) and a diuretic (hydrochlorothiazide) in a single pill (amlodipine complex) in the morning *vs.* the evening over a 12-week period.

METHODS

Patient selection

The present study was a multicenter open-label randomized trial on the effects of morning *vs.* evening administration of an amlodipine complex on ambulatory blood pressure. The subjects included Chinese hypertensive patients recruited from three Chinese hospital clinics. The entry period was from March 2008 to June 2009. We studied 80 subjects (43 men and 37 women), 67.8 ± 9.8 years of age, with essential hypertension (stages 1–2), as defined by the JNC VII[5] guidelines. The determination of hypertension stage was based on conventional blood pressure measurements and corroboration by ABPM at the time of recruitment. The prerequisite for inclusion was documented hypertension on three separate visits before enrollment. A patient was diagnosed with hypertension if the mean of three sphygmomanometric blood pressure readings exceeded 140/90 mm Hg and the patient was not taking any anti-hypertensive medication. A positive diagnosis of hypertension based on ABPM required that the 24-h mean patient systolic blood pressure (SBP)/diastolic blood pressure (DBP) was greater than 130/80 mm Hg, the diurnal mean was greater than 135/85 mm Hg, or the nocturnal mean was greater than 125/75 mm Hg.[5] All subjects received their routine medical care from the Department of Cardiology at three hospitals in Chongqing City. Key exclusion criteria were any known form of secondary hypertension, bradycardia (heart rate (HR) <45 beats per min), tachycardia (HR >100 beats per min), stroke or myocardial infarction in the preceding 6 months, congestive heart failure (left ventricular ejection fraction $<40\%$), clinically significant hepatic or renal disease, uncontrolled diabetes mellitus, chronic obstructive pulmonary disease, life-style factors such as night-shift work, history of drug and alcohol abuse, neurological and psychiatric illnesses, and pregnancy or breast-feeding. The study protocol was approved by the ethics committees of the three recruitment hospitals, and all subjects provided informed consent.

After providing informed consent to participate in this open-label, randomized, chronotherapy trial, there was a 2-week washout period when required (17.5% of the participants had not been treated previously for hypertension and an additional 37.5% were untreated for at least 6 months). Following the washout period, all remaining subjects were randomly assigned to receive a single amlodipine complex pill, which contained 5 mg of amlodipine and 25 mg of hydrochlorothiazide (Dongrui Pharmaceuticals Company, Jiangsu Province, China), either in the morning (0800 hours) or at bedtime (2200 hours). If the blood pressure goal (office blood pressure $<140/90$) was not achieved, the dosage of medicine was titrated to 1.5 or 2 pills. The demographic characteristics of the participants, including any previous use of anti-hypertensive medications, are described in Table 1.

Blood samples were obtained in the clinic from an antecubital vein after nocturnal fasting. All samples were taken between 0800 and 0900 hours immediately before treatment on the same day the 24-h ABPM was initiated. Conventional office blood pressure measurements were always obtained by the same investigator to avoid potential observer bias effects. The assignment of subjects to treatment groups was done by one member of the research team, according to the order of recruitment, following an allocation table constructed by a computerized random-number generator. The assignment of subjects to their respective treatment-time groups was blinded from both the research team member conducting the conventional blood pressure measurements and from the team members performing the statistical analysis of the data.

Table 1 Basal characteristics of hypertensive patients

	Dosing in the morning	*Dosing at bedtime*	P-*value*
Patient number	40	40	NS
Never treated (*n*)	7	8	NS
Male (%)	43.2%	40.7%	NS
Age (years)	66.9 ± 9.3	68.5 ± 10.0	NS
Complication (n)			
CAD	9	7	NS
Diabetes	4	6	NS
Hyperlipidemia	11	9	NS
Previously used medicine (n)			
CCB	23	25	NS
Diuretic	3	2	NS
ACEI	7	5	NS
ARB	5	4	NS
β-receptor blocker	6	7	NS
BMI ($kg\,m^{-2}$)	25.5 ± 3.8	24.6 ± 4.1	NS
FG ($mmol\,l^{-1}$)	5.3 ± 0.8	5.4 ± 0.9	NS
Triglycerides ($mmol\,l^{-1}$)	1.95 ± 0.73	1.98 ± 1.59	NS
Total cholesterol ($mmol\,l^{-1}$)	4.92 ± 0.85	4.63 ± 0.97	NS
Urine protein positive rate (%)	10%	15%	NS
Creatinine ($\mu mol\,l^{-1}$)	80.1 ± 16.6	74.5 ± 18.3	NS
GOT ($U\,l^{-1}$)	31.5 ± 15.1	30.2 ± 21.6	NS
GPT ($U\,l^{-1}$)	28.3 ± 8.0	28.8 ± 12.3	NS
Uric acid ($\mu mol\,l^{-1}$)	378.1 ± 88.2	327.9 ± 78.6	NS
Office BP (SBP/DBP, mm Hg)	158.5 ± 9.2/ 92.4 ± 7.8	155.6 ± 9.7/ 92.2 ± 6.5	NS

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, AT_1 receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; FG, fasting serum glucose; GOT, glutamic oxalacetic transaminase; GPT, glutamate-pyruvate transaminase; *n*, number of patients; NS, no significant difference; SBP, systolic blood pressure.

Blood pressure assessment

The SBP, DBP and HR of each participant were automatically measured every 20 min during the day (0600–2200 hours) and every 30 min during the night for 24 consecutive hours[14,15] with an ABPM device (Wuxi Zhongjian, Wuxi City, China). All subjects were examined by ABPM under baseline conditions when they were free of medication (after the 2-week washout for previously treated subjects) both before and after the 12 weeks of timed therapy. The blood pressure of the subjects was assessed while they adhered to their usual diurnal activity schedule (0600–2200 hours for most) and nocturnal sleep routines. Participants were instructed to go about their usual activities with minimal restrictions but were instructed to follow a similar schedule during the day of ABPM. No one was hospitalized during the study period. ABPM was always initiated between 1000–1200 hours. Blood pressures or subjects were eliminated from the analysis when $>30\%$ of the measurements were missing, there were missing data for a >3 h span, or the subject had a night time sleep span <6 h or >12 h during the monitoring period.

Non-dippers were defined as those who did not exhibit a reduction in mean SBP of $\geqslant 10$ mm Hg from daytime to night time. All remaining subjects were classified as dippers. The overall smoothness index was defined as the average of hourly mean blood pressure reductions divided by the s.d. of the average. The trough-to-peak ratio was defined as the average blood pressure reduction during the last 2 h of the dosing interval compared with the average of the maximal reduction in blood pressure over 2 consecutive hours.

Statistical analysis

Data are expressed as mean ± s.d. Comparison within groups was made by repeated measures analysis of variance, and comparison among groups was performed by factorial analysis of variance and Duncan's test (*t*-test when only two groups were compared). A value of $P<0.05$ was considered significant.

RESULTS

Subject characteristics

The baseline characteristics of the two subject groups (Table 1) were comparable in age, body mass index, SBP and DBP (average of the conventional morning measurements obtained just before ABPM). Moreover, there were no statistically significant changes in weight, body mass index, and waist and hip circumferences in any patient after 12 weeks of timed treatment (data not shown). The serum values of fasting glucose, creatinine, cholesterol, triglycerides, uric acid (Table 1) and other laboratory-measured metabolites in the two treatment groups were comparable at baseline and were unchanged after 12 weeks of treatment (data not shown).

Amlodipine complex on awakening

The circadian rhythm of SBP and DBP, as measured by 24-h ABPM before and after 12 weeks of treatment with amlodipine complex upon awakening, is depicted in Figures 1a and b. Dosing in the morning resulted in a statistically significant reduction in blood pressure from baseline after 12 weeks of treatment ($P<0.001$). After 12 weeks of treatment, ABPM showed that 75% of the subjects had diurnal, nocturnal, and 24-h SDP and DBP means below the respective thresholds for a diagnosis of hypertension. Moreover, all patients had a >10% reduction in their baseline 24-h mean blood pressure.

The trough-to-peak ratio was 55.2 and 57.3% for SBP and DBP, respectively, following dosing of amlodipine complex upon awakening. The overall smoothness index was also very high (0.98 ± 0.23 and 1.27 ± 0.35 for SBP and DBP, respectively), indicating a similar blood pressure reduction during the entire 24 h period. Figure 1 further indicates that the mean reduction in blood pressure at each measured time point during the 24-h dosing interval was statistically significant (P always <0.005). Despite the highly significant reduction in blood pressure, no effect of amlodipine complex on HR was observed (Table 2).

Amlodipine complex at bedtime

Table 2, Figures 1a and b show a significant reduction in the 24-h mean of SBP and DBP, respectively ($P<0.001$) after 12 weeks of amlodipine complex being taken at bedtime. The percentage of subjects with controlled blood pressure according to ABPM criteria was 80% in the bedtime group. All patients showed a >10% reduction in the 24-h mean blood pressure. Despite the significant effects of treatment observed on blood pressure, HR remained unchanged after 12 weeks of treatment (increase in the 24-h mean was 0.8 beat per minute; $P>0.05$) (Table 2).

The blood pressure reduction was statistically significant (P always <0.005) at each of the measured times during the 24-h period, as shown in Figures 1a and b. These results indicate that administration of the amlodipine complex at bedtime had a greater blood pressure-lowering effect throughout the entire 24-h dosing interval than when administered in the morning upon awakening. The bedtime trough-to-peak ratio was also higher than the morning observed ratio following administration of amlodipine complex upon awakening (63.7 and 66.9% for SBP and DBP, respectively). The observed smoothness index was also higher when amlodipine complex was administered at bedtime (1.53 ± 0.62 and 1.71 ± 0.68 for SBP and DBP, respectively).

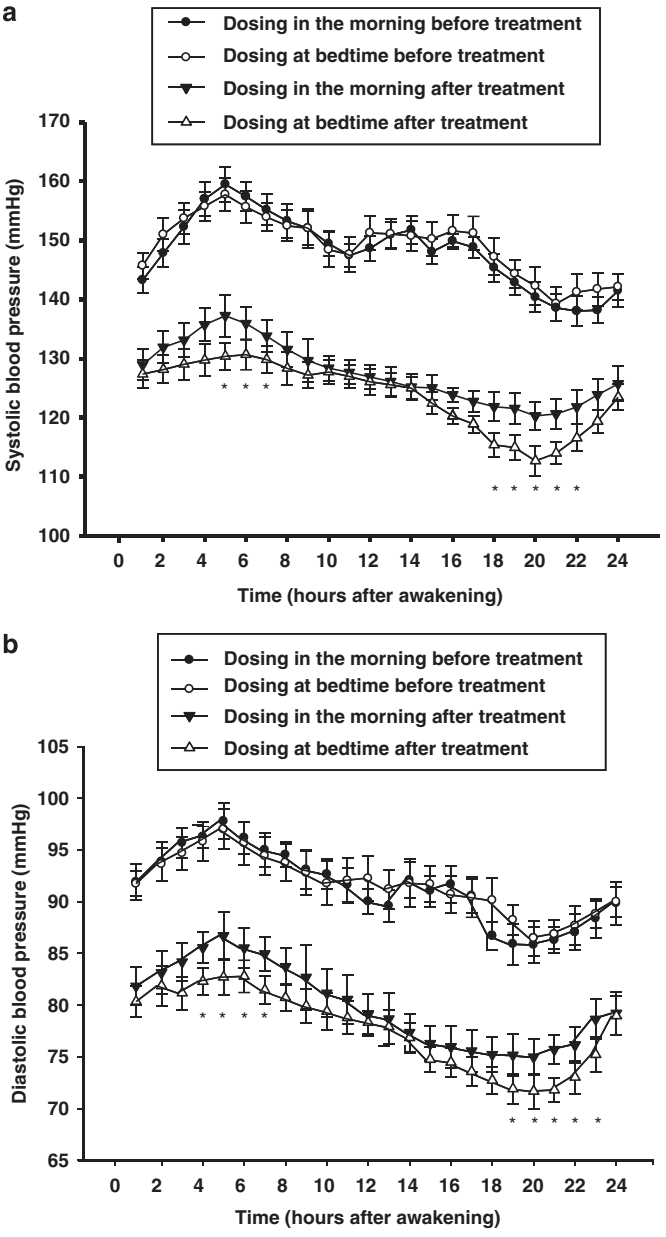

Figure 1 Effects on systolic blood pressure (SBP) (**a**) and diastolic blood pressure (DBP) (**b**) measured by 24-h ambulatory blood pressure monitoring (ABPM) in subjects with stage 1 or 2 essential hypertension before and after 12 weeks of treatment with an amlodipine complex administered either in the morning or at bedtime. All results are expressed as mm Hg (n=40, *$P<0.01$ *vs.* dosing in the morning, analysis of variance, Duncan's test).

Comparison between groups

The comparison of results, as shown in Table 1, reveals lack of statistically significant differences in ambulatory blood pressure at baseline between the two treatment groups. After treatment for 12 weeks, the diurnal mean blood pressure tended to be lower in the group taking the amlodipine complex at bedtime than in the group taking the amlodipine complex in the morning, although statistical significance was not achieved (Figures 2a and b). However, the 24-h mean blood pressure and nocturnal mean blood pressure (Table 2, Figures 2a and b) were significantly lower in the group taking the amlodipine complex at bedtime than in the group taking the amlo-

Table 2 Blood pressure and heart rate in both groups before and after treatment

	Dosing in the morning (n=*40*)	*Dosing at bedtime* (n=*40*)
Before treatment		
24 h mean BP		
SBP	149.7 ± 17.7	147.8 ± 18.5
DBP	92.7 ± 15.22	92.6 ± 11.2
Non-dipper (%, *n*)	53% (21)	55%(22)
Mean HR (beats per min)	75.0 ± 6.6	73.6 ± 7.7
After treatment		
24 h mean BP		
SBP	127.5 ± 15.22*	121.6 ± 13.7*,**
DBP	81.0 ± 8.07*	75.5 ± 9.12*,**
Non-dipper (%, *n*)	45% (18)	30% (12)*,**
Mean HR (beats per min)	75.8 ± 6.5	72.8 ± 6.2

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
*$P<0.05$ *vs.* before treatment; **$P<0.05$ *vs.* dosing in the morning.

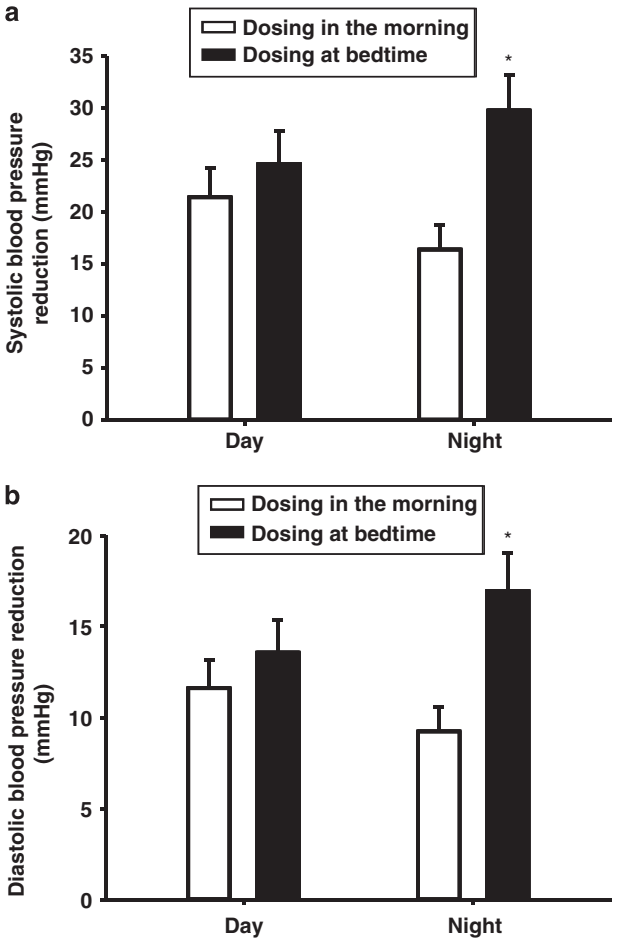

Figure 2 Absolute decrease in systolic blood pressure (**a**) and diastolic blood pressure (**b**) measured by 24-h ambulatory monitoring in subjects with stage 1 or 2 essential hypertension after 12 weeks of treatment with amlodipine complex administered upon awakening or at bedtime. All results are expressed as mm Hg ($n=40$, *$P<0.01$ *vs.* dosing in the morning, paired *t* test).

dipine complex in the morning. Accordingly, there was a highly significantly greater increase ($P<0.001$) in the nocturnal decline in blood pressure relative to the diurnal mean (an index of blood pressure dipping) when amlodipine complex was taken at bedtime (Figures 2a and b). The reduction in the frequency of non-dippers was only 8.0% in the morning group. However, the reduction (25.0%) in the frequency of subjects who at baseline were non-dippers was highly significant ($P<0.001$) when the same dose of amlodipine complex was taken at bedtime for 12 weeks (Table 2).

We also evaluated the effect of treatment time on the diurnal/nocturnal ratio of blood pressure and the slope of morning rise in blood pressure. We found no significant changes in the slope of the morning rise or nocturnal decline for either SBP or DBP when amlodipine complex was taken upon awakening. However, when the amlodipine complex was taken at bedtime, there was a lesser increase in the slope of the morning rise and a greater increase in the slope of the evening decline in SBP and DBP (Figures 1a and b).

DISCUSSION

To the best of our knowledge, the present study is the first to examine how a fixed combination of an anti-hypertensive medicine, amlodipine complex, had a difference in efficacy depending on the time of drug administration. Administration in the evening at bedtime, relative to administration in the morning, minimized the morning blood pressure surge and enhanced both the evening decline and the reduction in the nocturnal blood pressure. More non-dipper patients were converted into dipper status in the bedtime group.

The clinically relevant dosing-time differences in the beneficial and adverse effects of blood pressure-lowering medications are known.[9,16] Previous studies have investigated the chronotherapeutics of several medicines, including diuretics, angiotensin converting enzyme inhibitors and AT_1 receptor blockers and CCBs.[10–13] Studied CCBs include amlodipine,[10,17] diltiazem,[11] and cilnidipine.[18] Portaluppi *et al.*[19] explored the relative advantage of evening *vs.* morning once-a-day treatment with a conventional sustained-release isradipine formulation in non-dipper hypertensive patients with chronic renal failure and found that an evening dosing schedule best reduces and normalizes nocturnal SBP and DBP. However, not all calcium-channel blockers exhibit different efficacies with different dosing-times. Kitahara *et al.*[18] did not find a differential dosing-time effect on cilnidipine during an open, randomized cross-over study.[18] A loop diuretic (torasemide) given in the morning or at bedtime was found to be more efficacious when administered at bedtime. The time-response curves also indicated complete 24-h therapeutic coverage only when torasemide was administered at bedtime. The percentage of patients with controlled ambulatory blood pressure was also significantly greater with the bedtime dosing schedule compared with morning dosing.[20]

Meticulous control of blood pressure is required in hypertensive patients to produce the maximum reduction toward clinical cardiovascular end points. Recent clinical trials suggest that a monotherapy approach for the control of hypertension is not likely to be successful in most patients. Combination therapy may be theoretically favored due to the fact that multiple factors contribute to hypertension, and achieving control of blood pressure with a single agent acting through one particular mechanism may not be possible.[21] Regimens can either be fixed-dose combinations or drugs taken sequentially. Diuretics and CCBs are effective in reducing blood pressure.[22] As mentioned before, previous studies have demonstrated different effects of CCBs or

diuretics when dosed in the morning *vs.* the evening. However, whether fixed combinations of anti-hypertensive medications have circadian effect variations is not known. Our present study found, consistent with the results observed in monotherapy studies, administration of an amlodipine complex at bedtime reduced the 24 h mean SBP/DBP and nocturnal blood pressure to a greater degree than administration in the morning. There was an observed tendency toward lower mean daytime blood pressure in the bedtime administration group compared with the morning administration group. However, this difference was not statistically significant. The lack of statistical significance may be related to the small sample size of the study. Therefore, the results of this study need to be confirmed in a clinical trial with a larger sample size.

The circadian pattern of blood pressure is typically characterized by an increase in the early morning and a decrease during sleep. Non-dipper hypertension is associated with an elevated risk of end-organ injury, particularly to the heart, brain and kidney.[23–25] Ohkubo *et al.*, who followed patients in Japan for more than 9 years,[24] found a linear and inverse relationship between cardiovascular mortality and nocturnal blood pressure decline. Verdecchia *et al.*[23] also demonstrated that non-dipper hypertensive patients experience nearly three times as many adverse cardiovascular events as dippers. Analysis of a subgroup of 808 subjects in the Syst-Eur trial found that non-dippers experience a greater incidence of stroke and myocardial infarction than dippers.[24] After an average follow-up of 9.2 years, a 5% decrease in the decline of nocturnal SBP in hypertensive patients was associated with a 31% increased risk of cardiovascular mortality.[24] The above-mentioned results indicate that cardiovascular risk could be influenced not only by blood pressure elevation but also by circadian variability in blood pressure. However, not all anti-hypertensive medicines have beneficial effects on blood pressure pattern. Hermida *et al.* reported that anti-hypertensive drugs given in the morning increased the prevalence of non-dipping blood pressure from 38 to 62% in resistant hypertensive patients.[26] Thus, the best method of tailoring the treatment of non-dippers is a major concern of chronotherapy. Uzu and Kimura[27] reported that hydrochlorothiazide restores the diminished nocturnal blood pressure decline, and shifts circadian rhythm of blood pressure from a non-dipper to a dipper profile. Hermida *et al.*[28] reported that valsartan administration at bedtime, as opposed to administration upon awakening, resulted in a highly significant average increase in the diurnal/nocturnal ratio of blood pressure, corresponding to a 73% relative reduction in the number of non-dipper patients. In another study, the bedtime administration of trandolapril also significantly reduced morning blood pressure levels.[29]

Besides the circadian blood pressure pattern, increasing numbers of studies indicate that cardiovascular events occur more frequently in the morning, and that this phenomenon may be related to the morning blood pressure surge.[30] An anti-hypertensive medication that reduces the morning blood pressure surge would be useful in the prevention of cardiovascular events in hypertensive patients. The present study, the first prospective randomized trial to focus on a fixed combination of two anti-hypertensive medicines, found that similar to the chronotherapy studies of single medications, administration of amlodipine complex at bedtime significantly minimizes the morning surge, lowers the nocturnal blood pressure, increases the diurnal/nocturnal ratio of blood pressure and reduces the number of non-dipper patients.

Perspectives

Chronotherapeutics aims to proportion the serum and tissue concentrations of medicines in synchrony with known circadian rhythms. Previous studies have demonstrated the differing effects of single anti-hypertensive medication following morning *vs.* evening dosing.[17–20,31,32] The retrospective Syst-Eur[25] and HOPE[33] outcome trials show that evening administration of nitrendipine and ramipril impacts sleep-time blood pressure by converting the 24-h blood pressure pattern to a dipper pattern and decreasing CVD risk in the HOPE study. The CONVINCE trial[34,35] did not show a chronotherapy benefit, but the MAPEC trial[36] results suggest that night time dosing is beneficial. The CONVINCE trial intended to compare CVD protection afforded by conventional β-blocker and diuretic medications *vs.* a special drug-delivery verapamil formulation as a bedtime hypertension chronotherapy. However, the trial was terminated prematurely because of a corporate business decision, not based on inadequate performance of the chronotherapy. The MAPEC study was a prospective study to test the hypothesis that bedtime administration of more than one conventional medication exerts better blood pressure control and CVD risk reduction than the traditional approach of scheduling all medications in the morning. The results of this 5.6-year median follow-up study established that bedtime chronotherapy more effectively improves blood pressure control, better decreases prevalence of non-dipping patients, and, most importantly, reduces CVD morbidity and mortality. However, whether a fixed combination of anti-hypertensive medications, specifically a combination of amlodipine and hydrochlorothiazide, has any long-term protective effects on end-organ injury remains to be investigated.

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