

Efficacy of morning and evening dosing of amlodipine/valsartan combination in hypertensive patients uncontrolled by 5 mg of amlodipine

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Objectives This study compared the effects of morning and evening dosing of amlodipine/valsartan combination on 24-h blood pressure (BP) in patients uncontrolled by amlodipine (5 mg).

Methods This was a multicenter study that used a prospective, randomized, open-label, blinded endpoint design. Patients with essential hypertension, who's ambulatory BP was uncontrolled after 4 weeks on amlodipine (5 mg) were randomized to receive amlodipine/valsartan (5/160 mg) for 8 weeks in the morning or evening ($n=231, 232$, respectively), with optional uptitration up to 10/160 mg after 4 weeks if the office BP was uncontrolled. A 30-h ambulatory BP measurement was taken at randomization and at the end of the study.

Results Morning and evening dosing with amlodipine/valsartan had equivalent effects on systolic BP (mean 24 h, daytime, night-time, and 24–30 h) and diastolic BP (mean 24 h, daytime, night-time, and 24–30 h). There was a small difference in the night-time diastolic BP (-4.92 vs. -6.20 mmHg; $P=0.02$) and a slight but nonsignificant trend for higher BP reduction during daytime for morning intake and during night-time for evening intake. BP control

rates based on 24-h ambulatory BP measurement values ($<120/80$ mmHg) were similar between morning and evening dosing (47 vs. 45%).

Conclusion These results indicate that, in patients with BP uncontrolled by amlodipine (5 mg), morning and evening treatment with amlodipine/valsartan combination have similar effects on circadian BP, especially when 24-h mean values are considered. *Blood Press Monit* 16:80–86 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

A wide variety of cardiovascular parameters, including heart rate, blood pressure (BP), and peripheral resistance, are known to vary throughout the day and night-time. In addition, the incidence of several cardiac and cerebral events has long been reported to be highest in the early morning hours [1]. Since the advent of ambulatory BP measurement (ABPM), it has been possible to closely follow circadian changes in BP for a 24-h period or even more. ABPM measurements showed that BP varies according to a circadian rhythm, wherein there is a typical increase in the morning, a slight decrease during the postprandial period, and a more substantial decrease during sleep or night-time. This morning increase in BP seems to be related to a higher incidence of cardiovascular complications in the morning [2]. Thus, reduction of high BP throughout the 24-h period along with the correction of the BP circadian profile has been promoted as an important therapeutic goal [3].

In addition to the circadian BP changes, the pharmacodynamics of antihypertensive medications can vary for more than a 24-h period according to the time of administration. For example, β -adrenoreceptor blockers tend to reduce daytime BP but have little effect on morning or night-time BP [1,3]. In addition, the effects of angiotensin-converting enzyme inhibitors vary according to whether they are administered in the morning or evening, with evening administration reported to modify the 24-h BP profile [1,3]. The efficacy of calcium channel blockers (CCBs) according to the time of administration remains unclear and seems to be drug-specific. For example, some dihydropyridines have homogenous effects on night-time and daytime BP regardless of dosing time [4,5], whereas others are more effective and have fewer adverse effects when administered in the evening [6]. The angiotensin II receptor blockers (ARBs) have similar effects on BP reduction regardless of whether they are administered at bedtime or waking, but dosing at bedtime seems to increase their effect on the day/night BP ratio and improves BP control [7–9].

Note on previous presentation: parts of data in this manuscript were presented at the 2009 meeting of the European Society of Hypertension (oral presentation).

Chronotherapy, adjusting drug therapy according to an individual's circadian patterns, is a new concept designed to provide an improved BP control and, therefore, reduces the risk of cardiovascular events [3]. In agreement with this concept, a study of hypertensive patients receiving a combination of three antihypertensive drugs showed that adjusting the time of treatment may be more important than changing drug combination in controlling resistant hypertension [10]. ARBs such as valsartan are particularly amenable to be used as chronotherapeutics because of their selective effects according to when they are administered [7].

Combination therapy is often necessary to control hypertension. Several recently completed clinical trials have shown that the combination of amlodipine/valsartan is well tolerated, provides long-term reductions of BP, and is more effective than either drug alone [11–15]. Although the chronopharmacology of amlodipine [16–18] and valsartan [7,19] has been well studied, the chronotherapeutic use of the amlodipine/valsartan combination has not been examined. Therefore, in this study, we examined the efficacy of evening versus morning administration of amlodipine/valsartan in hypertensive patients with BP uncontrolled by amlodipine (5 mg).

Methods

Study design

This was a multicenter study that used a prospective, randomized, open-label, blinded endpoint design [20], comparing two parallel groups of patients receiving the same antihypertensive treatment (amlodipine/valsartan combination) at different times. The study was carried out at 35 study centers in France and 38 study centers in Tunisia. The primary study objective was to compare the systolic BP (SBP) reduction as determined by mean 24-h ABPM between two groups of patients with essential hypertension uncontrolled by amlodipine (5 mg). The study comprised two main periods: a 4-week screening period followed by an 8-week trial period. Patients eligible according to inclusion and exclusion criteria participated in a 4-week phase during which they received only amlodipine (5 mg) once a day. Seventy-two hours before the end of this period, a 30-h ABPM was taken and blood samples were collected for measurement of potassium and creatinine levels. Patients with uncontrolled BP according to the ABPM [mean 24-h SBP/diastolic BP (DBP) $\geq 125/80$ mmHg] were randomly allocated (1:1) to receive amlodipine (5 mg)/valsartan (160 mg) free combination therapy as an evening (18:00–22:00) or morning (06:00–10:00) dose for 4 weeks. At the end of week 4, patients with uncontrolled office BP [mean seated SBP (msSBP)/mean seated DBP (msDBP) $\geq 140/90$ or $\geq 130/80$ mmHg if diabetes or renal insufficiency] received amlodipine (10 mg)/valsartan (160 mg) free combination therapy for another 4 weeks. At the end of the study, 30-h ABPM and office BP measurements were taken and blood

samples were collected for the measurement of potassium and creatinine levels. At all visits, adverse events were recorded. All procedures were performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study was approved by the French Agency for the Safety of Health Care Products and the Paris and the Tunisian ethics committees. All patients participating in this study provided written informed consent.

Patients

The study included outpatients of age 18 years or more with untreated essential hypertension, impaired tolerance to antihypertensive medication (excluding intolerance to ARBs or CCBs), or uncontrolled hypertension. Major exclusion criteria were as follows: known or suspected contraindications to the tested drugs; history of allergy or hypersensitivity to ARBs, CCBs, triple combination of antihypertensive therapy, or more to avoid resistant, severe and/or secondary hypertension; history of serious cardiovascular events; and history of drug or alcohol abuse.

Office blood pressure measurements

Brachial office BP measurements were taken in accordance with European guidelines [21] at each visit using a validated oscillometric device. Three consecutive measurements were recorded in the morning between 08:00 and 11:00 for all patients; before drug intake for patients of the morning dosing group and 12–15 h after drug intake for patients of the evening dosing group. When possible, BP was recorded in the same arm, at the same time, and by the same person for each patient.

Ambulatory blood pressure measurement

Certification and online quality control were carried out by an independent core lab (Cardiovascular Institute, Paris, France). Before participating in the study, all sites were certified according to their ability to take ABPM in accordance with the protocol. ABPM data were electronically transferred to the core lab for quality control. The validation results were made available to the site within 24 h. The following specifications were requested: use of a Spacelabs device (Spacelabs Healthcare Inc., Issaquah, Washington, USA); starting time between 08:00 and 11:00; recordings every 20 min; recording a period of at least 24 h; at least 75% of correct measurements; no consecutive 2-h measuring-free periods; and mean 24-h SBP/DBP of at least 125/80 mmHg at the randomization visit. When the ABPM data did not meet the quality control criteria, the patient was requested to repeat the monitoring period. The assessment of ABPM data included the mean averages of the 24-h period, daytime, night-time, and the 24–30 h). The daytime (07:00–22:00) and night-time (22:00–07:00) periods were defined according to the mean patient's diaries as reported individually at each ABPM recording.

Statistical analysis

Descriptive statistics are used to summarize quantitative data, and frequency tables are presented for qualitative variables. The Student's and Wilcoxon signed-rank tests or χ^2 and Fisher's exact tests were carried out between the treatment groups, depending on the nature of the variables. These tests were carried out according to a two-sided design with a 0.05 level of significance. An analysis of covariance model was used to compare the baseline deviation in the fall in SBP and DBP measured by ABPM (24-h, daytime, night-time, and final mean of 6-h) between the two groups, taking into account the baseline SBP and DBP levels measured by ABPM (continuous variable) as well as the country and uptitration as fixed factors. This analysis was also carried out on BP measured in the doctor's office. The null hypothesis tested was that of a difference between the groups that exceeds 3 mmHg in absolute value. For the primary endpoint (mean 24-h SBP), equivalence was concluded when the 95% confidence interval (95% CI) of difference in adjusted means was fully included in the equivalence interval (-3, +3). An estimated 426 patients were needed to guarantee 80% power using a two-sided α level of 5% and a standard deviation in the SBP changes of 11 mmHg. All statistical analyses were carried out using SAS version 8.2 (SAS Institute, Cary, North Carolina, USA).

Results

Study population and demographic data

A total of 828 patients were selected according to the inclusion and exclusion criteria. Of these, 282 patients were excluded before the randomization; 105 were excluded because their BP was controlled by amlodipine (5 mg) as indicated by the ABPM (24-h mean values of <125/80 mmHg). An additional 177 were excluded for other reasons (one or more); mainly because of ABPM quality recordings ($n = 128$), adverse events ($n = 20$), consent withdrew ($n = 38$), and lost to follow-up ($n = 10$). The remaining 546 patients were randomized to receive amlodipine/valsartan for 8 weeks in the morning ($n = 278$) or evening ($n = 268$).

Demographic data of these randomized patients and their clinical characteristics are shown in Table 1. No significant difference was observed between the two groups for any parameter. A majority of the patients were more than 50 years old, overweight or with abdominal obesity, sedentary, and at higher risk for cardiovascular events. In addition, 40% of all patients had previously untreated hypertension. A total of 231 patients receiving morning administration and 232 receiving evening administration of amlodipine/valsartan completed the study with valid ABPM data. Forty-seven patients in the morning group and 36 patients in the evening group were excluded for major protocol violation ($n = 15$ and 11, respectively) and for invalid ABPM ($n = 32$ and 25, respectively). The clinical characteristics of this population and the

Table 1 Clinical characteristics of the population

Characteristics	Morning dosing (N=278)	Evening dosing (N=268)
Sex: male [n (%)]	148 (53)	143 (53)
Age (year)	56 ± 10	56 ± 10
Height (cm)	166 ± 9	166 ± 9
Weight (kg)	81 ± 13	81 ± 13
BMI (kg/m ²)	29.3 ± 4.7	29.3 ± 4.5
Smoker [n (%)]	61 (22)	61 (23)
Dyslipidemia [n (%)]	60 (23)	57 (23)
Cardiovascular family history [n (%)]	34 (13)	32 (13)
Diabetes [n (%)]	56 (20)	46 (17)
Abdominal obesity [n (%)]	133 (48)	134 (50)
Sedentary [n (%)]	161 (58)	151 (56)
Global cardiovascular risk ^a		
Low [n (%)]	14 (5)	13 (4)
Mild [n (%)]	106 (38)	112 (42)
High [n (%)]	158 (57)	143 (52)

No significant difference was observed between the two groups.

N, total number of patients in the group; n, number of patients.

^aCardiovascular risk factors were assessed according to the European Society of Hypertension guidelines [21].

intention to treat one were similar. At the end of the study, 33.3% of all patients had been uptitrated to amlodipine (10 mg)/valsartan (160 mg), with equal distribution among the morning and evening groups.

Blood pressure

Ambulatory blood pressure measurement

Table 2 shows the mean ABPM values at baseline and after 8 weeks of treatment in both the morning and evening dosing groups. Both groups showed significant ($P < 0.001$) reductions in SBP and DBP for all analyzed periods (24 h, daytime, night-time, and the 24–30 h).

The mean change in 24 mean SBP was equivalent between morning and evening intake [-11.94 vs. -11.03; difference = -0.91 (95% CI: -2.54 to 0.72); $P = 0.28$]. There was no significant difference in mean changes of SBP and DBP for morning and evening administration for any of the periods (daytime, night-time, and 24–30 h; Table 2). There was a nonsignificant trend ($P = 0.07$) for better lowering of the daytime SBP when using morning dosing than evening dosing.

For DBP, the effects on mean 24-h, daytime, and 24–30 h, were not statistically different; however, evening dosing resulted in a slightly larger decrease in the night-time DBP than morning dosing, although the absolute difference was relatively small [1.28 mmHg (95% CI: 0.19–2.36 mmHg); $P = 0.021$; 2].

The comparison of the mean hourly ABPM SBP and DBP values showed that there was a significant ($P < 0.001$) reduction in SBP and DBP throughout the 30-h ABPM for both morning and evening administration (Fig. 1). Similar results were obtained when these analyses were repeated for all randomized patients, intended to treat the population (data not shown).

Table 2 Mean values and changes of ambulatory blood pressure measurement before and after morning and evening dosing of amlodipine/valsartan in patients previously treated with amlodipine (5 mg) with uncontrolled BP

ABPM	Period	Morning dosing ^a (N=231)			Evening dosing ^a (N=232)			Intergroup difference (95% CI)	Intergroup P value
		Baseline	Visit 4	Changes	Baseline	Visit 4	Changes		
SBP (mmHg)	24 h	137 ± 11	126 ± 11	-11.94	138 ± 12	127 ± 12	-11.03	-0.91 (-2.54 to 0.72)	0.28
	Day	144 ± 12	130 ± 12	-13.37	144 ± 12	132 ± 13	-11.65	-1.72 (-3.55 to 0.11)	0.06
	Night	128 ± 12	120 ± 12	-9.71	129 ± 13	120 ± 13	-10.13	0.42 (-1.31 to 2.14)	0.64
	24-30 h	143 ± 12	130 ± 13	-12.16	143 ± 14	132 ± 14	-11.30	-0.86 (-2.93 to 1.20)	0.41
DBP (mmHg)	24 h	81 ± 9	75 ± 7	-6.46	81 ± 9	75 ± 8	-6.70	0.23 (-0.76 to 1.23)	0.64
	Day	86 ± 9	79 ± 8	-7.51	86 ± 9	79 ± 8	-7.06	-0.45 (-1.61 to 0.71)	0.44
	Night	74 ± 9	70 ± 8	-4.92	74 ± 9	69 ± 8	-6.20	1.28 (0.19-2.36)	0.02
	24-30 h	87 ± 10	79 ± 9	-7.64	87 ± 10	80 ± 9	-6.98	-0.66 (-2.05 to 0.73)	0.35

Blood pressure values are means ± standard deviation. P values were determined by the analysis of covariance.

ABPM, ambulatory blood pressure measurement; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

^aIn all cases, $P < 0.001$ for baseline versus visit 4.

Office blood pressure

Mean office BP values decrease significantly from baseline to visits 2 and 4 in both the morning (161/93, 147/86, and 129/77 mmHg) and evening groups (161/93, 146/87, and 130/77 mmHg). Changes in office BP are shown in Table 3; both groups presented a similar and significant ($P < 0.001$) reduction in SBP and DBP.

Control and response rates

On the basis of ABPM data, control rates in both morning and evening dosing groups were 47 versus 45% for the 24-h period as defined by SBP/DBP ($< 125/80$ mmHg). For the daytime period, control rates were 65 versus 58% as defined by SBP/DBP ($< 135/85$ mmHg), and for the night-time period, they were 41 versus 46% as defined by SBP/DBP ($< 120/70$ mmHg). There were no significant differences between the two groups.

For office BP measurements, controlled BP rates were similar for both morning (72%) and evening (73%) dosing. Responders were defined as patients with an msSBP/msDBP reduction of at least 20/10 mmHg or with an msSBP/msDBP of less than 140/90 mmHg ($< 130/80$ mmHg for patients with diabetes or renal insufficiency). Accordingly, responder rates were similar in both treatment groups for msDBP (93.9%, morning; 93.1%, evening), and for msSBP (81.0%, morning; 79.7%, evening). Using both SBP and DBP criteria, response rates were 79.7% for morning dosing and 78.0% for evening dosing.

Adverse events

Safety results for this study are summarized in Table 4. The frequencies of patients reporting at least one adverse event after enrollment were similar for the morning (36 patients; 13%) and evening (40 patients; 15%) treatment groups. The majority of adverse events were considered mild to moderate in intensity. The most frequently reported events were peripheral edema (18 patients; 3.3%), headache (seven patients; 1.3%), and palpitations (five patients; 0.9%). Peripheral edema occurred more frequently with amlodipine/valsartan (10/160 mg; eight

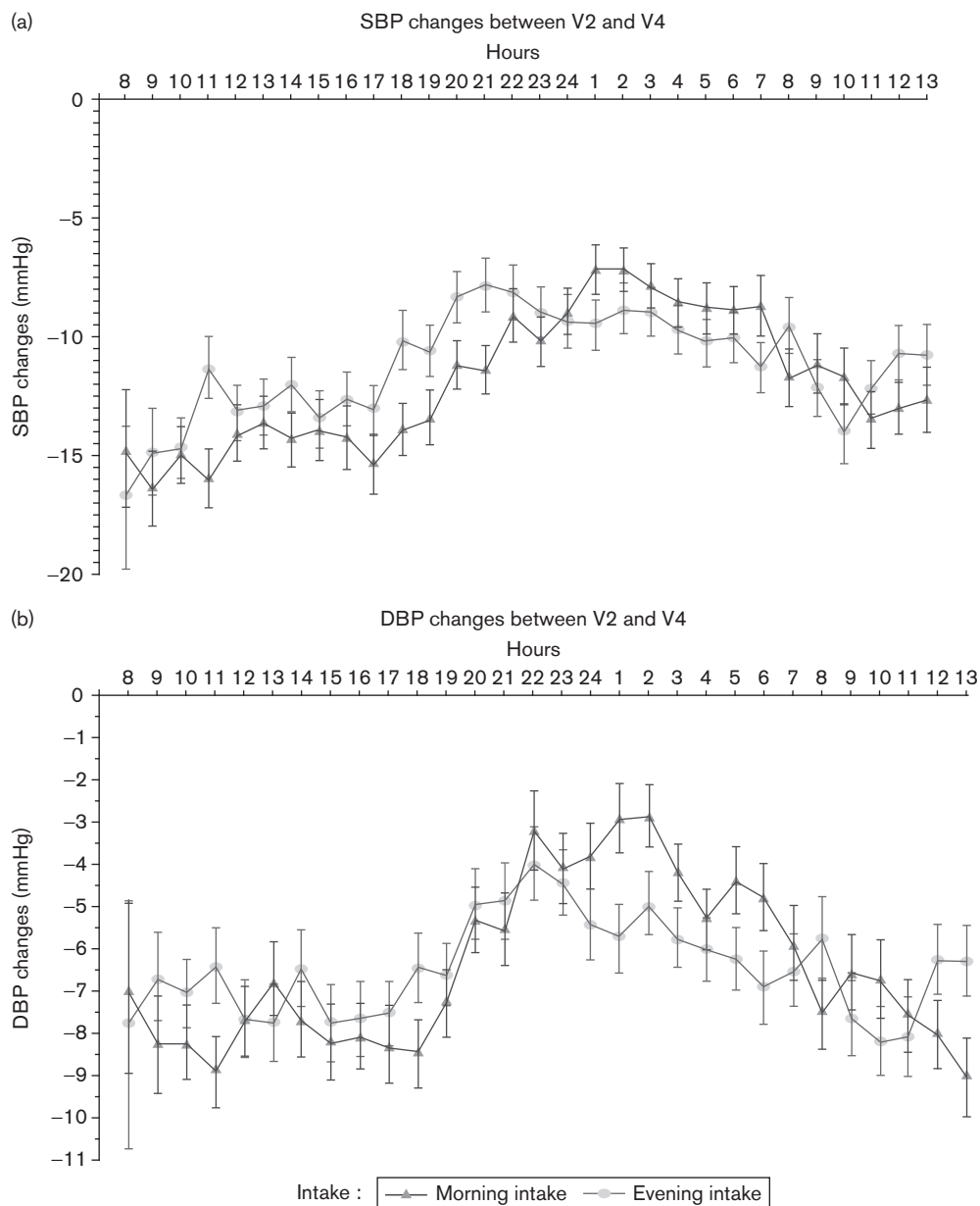
patients; 4.6%) than with amlodipine/valsartan (5/160 mg; eight patients; 1.5%). Five serious adverse events were reported in each treatment group, only one of the events was considered to be related to the treatment. There were no deaths during the study.

Discussion

This study compared the effects of morning and evening administration of the combination of amlodipine/valsartan on BP control as measured by 30-h ABPM in hypertensive patients with BP uncontrolled by amlodipine (5 mg) alone. Although the chronotherapeutic effects of both amlodipine [16-18] and valsartan [7,19] have been well studied and the amlodipine/valsartan combination is known to be effective for controlling office BP [11-15], this was the first study to investigate the chronotherapeutic use of this combination. In addition, this study included a relatively large number of patients (546) compared with the previous monotherapy studies, most of which included less than 100 patients [7,16-19].

This study showed that morning and evening dosing with the combination of amlodipine/valsartan have equivalent effects on the primary endpoint, mean 24-h SBP as measured by ABPM. Morning and evening dosing also had equivalent effects on the mean daytime and 24-30 h values of SBP and DBP, although the decrease in the night-time DBP was slightly higher for evening dosing ($P < 0.02$). Despite the absence of a clear difference between the morning and evening dosing, there was a trend for a greater decrease in BP during the daytime period for morning intake and during the night-time for evening intake. Furthermore, similar trends were detected in the ABPM control rate: the daytime control rate was slightly higher for morning intake, whereas the night-time control rate was slightly higher for evening intake. Together, these results suggest that morning and evening dosing with the combination of amlodipine/valsartan have equivalent effects on the 24-h period, although there is a tendency for higher efficacy during the day with morning intake and for higher efficacy during the night for evening intake. Similarly, there were

Fig. 1



Mean hourly changes of systolic blood pressure (SBP; a) and diastolic BP (DBP; b) after morning and evening dosing of amlodipine/valsartan. V2 and V4, visits 2 and 4.

no differences in control or response rates between morning and evening dosing.

These observations differ from those reported by Hermida *et al.* [7,19] for valsartan monotherapy. They found that, when compared with morning administration, evening administration of valsartan improves the day/night BP ratio and significantly increases the control rate, although it does not have a greater effect on the 24-h mean BP. There may be several reasons for the differences between these monotherapy studies and this

amlodipine/valsartan combination study. First, our population included treated patients with BP uncontrolled by amlodipine (5 mg), whereas patients in the other studies were selected only on the basis of their BP level or profile. Second, we carried out 30-h ABPM recordings, whereas Hermida *et al.* [6–10] used 48-h recordings and therefore a different analysis method. Third, amlodipine may have blunted valsartan's chronotherapeutic effects in this study. Indeed, Qiu *et al.* [18] reported that, in contrast to valsartan, morning administration of amlodipine has a greater effect on circadian BP than evening

Table 3 Mean changes of office blood pressure measured in the morning in patients receiving morning or evening dosing of amlodipine/valsartan

Comparison	Adjusted mean difference		Difference	
	Morning dosing ^a (N=231)	Evening dosing ^a (N=232)	Adjusted mean	P value
Visit 2 versus visit 4 (mmHg)				
SBP (mmHg)	-18.7 (0.9)	-17.3 (0.9)	-1.3	0.2
DBP (mmHg)	-10.1 (0.6)	-8.6 (0.7)	-1.5	0.1
Visit 1 versus visit 4 (mmHg)				
SBP (mmHg)	-32.2 (1.1)	-29 (1.2)	-3.2	0.052
DBP (mmHg)	-16.6 (0.8)	-14.3 (0.8)	-2.0	0.08

DBP, diastolic blood pressure; SBP, systolic blood pressure.

^aValues are adjusted means with standard errors shown in parentheses. In all cases, $P < 0.001$ versus baseline defined as visit 1 or 2.

Table 4 Adverse events in patients receiving morning and evening dosing of amlodipine/valsartan

Category	Morning dosing (N=278)	Evening dosing (N=268)	Total (N=546)
Patients with ≥ 1 AE [n (%)]	36 (12.9)	40 (14.9)	76 (13.9)
Patients with ≥ 1 SAE [n (%)]	2 (0.7)	2 (0.7)	4 (0.7)
Total number of AEs	49	60	109
Treatment-related AEs	28	31	59
Total number of SAEs	5	5	10
Treatment-related SAEs	0	1	1
Patients with ≥ 1 AE causing premature termination of treatment [n (%)]	3 (1.1)	6 (2.2)	9 (1.6)
Patients with ≥ 1 treatment-related AE causing premature termination of treatment [n (%)]	2 (0.7)	5 (1.9)	7 (1.3)
Total number of treatment-related AEs causing premature termination of treatment	2	9	11

%, percentages based on the total number of AEs; AEs, adverse events; SAE, serious adverse events.

dosing, which could counteract the chronotherapeutic effect of valsartan.

The amlodipine/valsartan combination as used in this study provided high control rates, regardless of the time of administration. The response rates reported here are similar to those reported for amlodipine/valsartan in a recent study by Sinkiewicz *et al.* [13] [68% for amlodipine/valsartan (5/160 mg) and 81% for amlodipine/valsartan (10/160 mg)].

One possible limitation of this study is that we recorded a 30-h ABPM, whereas the chronotherapeutic studies carried out by Hermida *et al.* [7–10] used 48-h measurements. Such 48-h measurements are used to confirm the reproducibility of the ABPM, but we felt that this relatively long collection period would have a negative impact on patient compliance. The 30-h collection period was chosen to reduce the collection time while allowing evaluation of BP during the morning surge. Given our strict site certification and quality control measures, we felt that the validated ABPM data were of sufficiently higher quality and that a 48-h measurement was unnecessary.

Another possible limitation of the study is that the trial period was only 8 weeks. However, an 8-week trial period has been used in other studies on the effects of the amlodipine/valsartan combination [13,14,22], and most studies on the chronotherapeutic effects of antihypertensive drugs have been 8–12 weeks in length [4,5,9,16,19]. Further studies are needed to determine whether differences in the efficacy appear over longer periods of treatment.

Collectively, our results indicate that the effects of the amlodipine/valsartan combination in hypertensive patients do not differ according to dosing time when 24-h mean values are considered. Moreover, the reduction in BP tended to be higher during the day for morning intake and higher during the night for evening intake. In addition, the high control rates found here combined with the low incidence of drug-related adverse events support previous studies showing that the amlodipine/valsartan combination is well tolerated and effective at controlling BP in hypertensive patients [11–15].

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Conflicts of interest statement: Roland Asmar has 'expert consultant' activities for several pharmaceutical and devices industries. He is also acting as speaker in symposia organized or sponsored by industries. Philippe Gosse has received expert consultant and speaker fees from Novartis, Boehringer Ingelheim, and Servier.

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