REVIEW

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Chronotherapy of hypertension with combination treatment

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In the last decade, a number of clinical studies identified an additional improvement of blood pressure control if the single drug treatment is time-targeted in hypertensive individuals. On the other hand, only a few of them investigated whether any different antihypertensive effects with combination therapy can be confirmed between morning and evening dosing. This article reviews those studies employed various combinations of antihypertensive agents including calcium channel blocker with angiotensin-receptor blocker, calcium channel blocker with diuretic, angiotensin-receptor blocker with diuretic, angiotensin-receptor blocker with angiotensin-converting enzyme inhibitor and angiotensin-converting enzyme inhibitor with diuretic. Interestingly, the majority of studies confirmed that evening dosing is more effective in reducing asleep and/or mean systolic and/or diastolic blood pressure, one study found no difference and one study suggested that morning dosing could be more effective. Three studies showed a positive shift from non-dipping to dipping pattern with evening dosing and an opposite effect was found with morning dosing. Importantly, while the data strongly suggest that efficacy can be improved with evening dosing when drug combination is used, no thought was given to safety comparison. Thus, the complex benefit-risk ratio comparison between morning and evening dosing of blood pressure reducing drug combinations remains to be elucidated.

1. Introduction

Hypertension is a well known major risk factor for stroke, myocardial infarction, heart failure and several cardiovascular diseases (Lee and Cooper 2009). Recently, chronically increased blood pressure has been associated with dysfunctional circadian rhythms in some subjects. Blood pressure (BP) in patients with primary hypertension has its typical day-night variations with morning surge starting already before awakening and a drop in BP during the night, while the drop of BP during the night is abolished or even reversed in secondary hypertensive subjects (Middeke and Schrader 1994). Circadian rhythms are naturally present in the majority of intrinsic factors driving the 24 h variations of BP such as the sympathetic predominance during the day with peak concentrations of plasma catecholamines and cAMP in the morning and their nadir during night, the renin-angiotensin-aldosteron system (RAAS) pronounced diurnal variations with peaks of aldosteron, plasma renin and angiotensin-converting enzyme (ACE) activity, angiotensin I and II and aldosterone in the early morning hours, as well as the nitric oxide peaking at night (Hurwitz et al. 2004). Indeed, circadian rhythms of BP are systematically documented from the beginning of 18th century (Lemmer 2009).

Based on the knowledge of circadian rhythms in BP regulation, synchronous timing of BP lowering medication with rhythm of endogenous factor to be affected has been proposed to provide more individualized therapy for patients. In recent years, many data have been collected from clinical trials suggesting that monotherapy of hypertension could bring additional improvement in control of BP, if the time of administration is specifically targeted, which is called chronotherapy. This applies for all major classes of antihypertensive drugs, *e.g.* α-blockers, β-blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs) and renin inhibitor (Smolensky et al. 2010; Hermida et al. 2011a; Lemmer 2006; Hermida-Ameijeiras et al. 2010). Supporting this, recent a meta-analysis incorporating results from 21 randomized controlled trials in 1,993 patients with primary hypertension suggested that a better BP control was achieved with bedtime dosing than with morning administration of antihypertensive monotherapy medication, though the effect on death and adverse cardiovascular outcomes is unclear (Zhao et al. 2011). However, monotherapy is rarely used in clinical practice as combination treatment is needed in the majority of patients to control blood pressure given. This approach offers better BP control and is usually better tolerated than monotherapy with higher doses (Ruilope et al. 2005; Dahlőf 2009; Milani 2005). Given the growing evidence in single drug therapy of hypertension proposing time targeted-dosing, it is of high relevance to turn the attention on chronopharmacological aspects of combination therapy and its effect on circadian BP pattern. This paper aims to review all available data on targeted chronotherapy of hypertension with combination products. While the data for combination therapy are still limited, both fixed combination and free combination are discussed in this review. Importantly, we have focused not only on efficacy but also on safety issues.

2. Randomized trials with combination medicinal products

Six clinical trials with combination medicinal products published recently have studied the time dependence of administration of BP lowering medication (Table 1). In the majority

Table 1: Administration-time differences on BP lowering effect of combination medication

Combination treatment	Dosage (mg per day)	Treatment times	Measurements	Study length (weeks)	No. completed subjects	Comparison of morning vs. evening dosing	Author
Captopril/HCT (fixed combination)	25-100/25-50	7:00-8:00 18:00-20:00	24-h ABPM	6	13	significant reduction in awake SBP/DBP with morning dosing	Middeke et al., 1991
Valsartan/Amlodipine (free combination)	160/5-10	06:00-10:00 18:00-22:00	30-h ABPM	8	463	no difference in mean, asleep and awake SBP/ DBP with evening or morning dosing	Asmar et al., 2011
Valsartan/Amlodipine (fixed/free combination)	160/5	Awakening bedtime	48-h ABPM	12	203	significant reduction in asleep SBP/DBP and mean SBP with evening dosing	Hermida et al., 2010
Valsartan/HCT (fixed combination)	160/12.5	Awakening bedtime	48-h ABPM	12	204	significant reduction in asleep SBP with evening dosing	Hermida et al., 2011
Amlodipine/HCT (fixed combination)	5/25	8:00 22:00	24-h ABPM	12	80	significant reduction in mean and asleep SBP/DBP with evening dosing	Zeng et al., 2011
Amlodipine/Fosinopril (free combination)	5/10	7:00-8:00 7:00-8:00/20:00-21:00	24-h ABPM	4	40	significant reduction in asleep SBP/DBP with split evening dosing	Meng et al., 2010

of cases a fixed combination was used, though some studies employed also free combination of two single antihypertensive agents. In chronotherapy the most commonly used combinations are comprising either valsartan, amlodipine or hydrochlorothiazide combined themselves or with ACE inhibitors (fosinopril and captopril).

2.1. Captopril/hydrochlorothiazide combination

The first investigation on the difference between morning and evening administration in antihypertensive combination products has been provided by Middeke et al. (1991). For the period of one year, patients received a fixed combination of 25-100 mg captopril and 25-50 mg hydrochlorothiazide. Doses increased gradually when needed to lower DBP below 90 mmHg. After this period, patients received halve the dose for 3 weeks in the evening (18.00-20.00), thereafter the same dose in the morning (7.00-8.00) for another 3 weeks. After 6 weeks, a significant difference was observed for awake BP, when this was significantly higher ($p < .01$) under evening dosing as compared to morning dosing. (SBP/DBP of 147/94 mm Hg *vs.* 136/88 mmHg). Thus, when medication was applied only in the evening, the blood pressure was not sufficiently controlled during daytime. No significant difference was observed for mean SBP/DBP. Authors did not present data for safety comparison. This study being the first one to introduce the concept of chronopharmacology into field of hypertension brought new perspectives and treatment options.

2.2. Amlodipine/valsartan combination

When considering the chronotherapy concept in treatment of hypertension, the long acting calcium channel blocker amlodipine and the angiotensin II receptor antagonist valsartan are the most frequently combined drugs. Two studies investigated the combination of both drugs. Asmar et al. (2011) conducted a multicenter, randomized, open label, blinded endpoint study with parallel design comparing the reduction of systolic blood pressure (SBP) in two groups with the same antihypertensive treatment given either in morning (06:00-10:00) or in the evening (18:00-22:00) in patients with essential hypertension uncontrolled by 5 mg of amlodipine (Asmar et al. 2011). The study treatment comprised of amlodipine 5 mg and valsartan 160 mg free combination. The dose of amlodipine was increased to 10 mg for the second half of the study in 33.3 % of patients (with equal distribution between both groups) due to uncontrolled office BP. The reduction in SBP was determined by mean 24-h ambulatory BP measurement (ABPM). Study medication has been administered for 8 weeks. Results of the study showed no statistically significant differences in 24 mean SBP between morning or evening dosing, i.e. equivalence was shown = −0.91 (95% CI: −2.54 to 0.72), Reduction for 24-h mean SBP was 11.94 and 11.03 mm/Hg for morning and evening doses, respectively. For 24-h mean DBP the difference was 6.46 and 6.70 mm/Hg for morning and evening doses, respectively. Similarly, no differences were observed in control or response rates between both groups. Distribution of adverse events was comparable in both groups with a total number of 49 adverse events in the morning group and 60 adverse events in the evening group.

Hermida et al. (2010) studied this combination by conducting a prospective, randomized, open-label, blinded endpoint study with parallel design. Subjects received a fixed combination of amlodipine 5 mg and valsartan 160 mg per day either upon awakening or at bedtime or one of the medications in single form upon awakening and the other at bedtime. Duration of treatment was 12 weeks. Results revealed that BP reduc-

tion from baseline in the 48-h mean SBP/DBP was significantly largest when both medications were administered at bedtime with 24.7/13.5 mmHg reduction; 18.2/12.3 mmHg with valsartan at bedtime and amlodipine upon awakening; 17.4/13.4 mm Hg with both medications upon awakening and 15.1/9.6 mm Hg reduction with valsartan upon awakening and amlodipine at bedtime ($p < .001/.018$ for SBP/DBP between groups). Similarly, bedtime dosing was most effective in BP reduction of asleep SBP/DBP ($p < .001/.001$). Bedtime dosing resulted in the largest percentage of controlled subjects among all of assessed therapeutic schemes (69.2% with both medications at bedtime; 58.3% with both medications upon awakening; 54.2% with valsartan at bedtime and amlodipine upon awakening and 43.6% with valsartan upon awakening and amlodipine at bedtime; p = .003 between groups). A significant increase ($p < .001$) in decline to a normal dipping pattern was observed only when both medications were administered at bedtime. A comparison of the distribution of adverse events between the groups was not provided.

Both studies confirmed the efficacy of this combination, though a difference in morning *vs*. evening dosing was only found by Hermida et al. (2010).

2.3. Valsartan/hydrochlorothiazide combination

In another clinical study of Hermida et al. (2011b), a combination of valsartan with the diuretic hydrochlorothiazide has been investigated. Authors compared morning and evening dosing of valsartan/hydrochlorothiazide (HCT) fixed combination. Adults with previously untreated uncomplicated essential hypertension were enrolled to take valsartan 160 mg/day alone for 12 weeks, either in morning or at bedtime. After this period, HCT 12.5 mg/day was added to therapy in a fixed combination with valsartan for another 12 weeks respecting the time of treatment. A significant difference between the groups in BP lowering effect was observed only for asleep SBP, with bedtime and morning dosing reduction of 20.1 mmHg and 16.0 mmHg respectively (p = .015). However, no significant difference was observed between the groups in awake SBP/DBP, 48-h mean SBP/DBP and asleep DBP. Of note is the observation of the authors that while the BP lowering effect on SBP/DBP was quite constant during the 24-hour period after morning intake, evening dosing resulted in more pronounced reduction of SBP/DBP in the first 8 h after dosing and then remained constant. A comparison of the distribution of adverse events was not presented. This was the first study to found a "chrono" effect with an angiotensin-receptor blocker/diuretic combination.

2.4. Amlodipine/hydrochlorothiazide combination

The fixed combination of amlodipine and HCT was investigated in the study of Zeng et al. (2011). They conducted a randomized trial to compare morning *vs*. evening dosing. Study medication comprised 5 mg of amlodipine and 25 mg of hydrochlorothiazide in fixed combination given either in the morning (08:00) or at bedtime (22:00). If adequate lowering of BP (office blood pressure 140/90 mmHg) was not achieved, the dosage of medicine was titrated to 1.5 or 2 tablets. Groups were compared by factorial analysis of variance and Duncan's test, with p-value of .05 considered to be significant. After 12 weeks of treatment, there was no significant difference between the groups in awake SBP/DBP, while asleep and mean SBP/DBP were significantly lower after bedtime dosing. The reduction in the frequency of non-dippers was significantly higher in the evening group compared to the morning group (25% *vs*. 8%, $p < .001$). From the data presented, it is not clear, if the distribution of increased dose (1.5 or 2 tablets) was equal between both groups or not. The distribution of adverse events in the groups was not reported. Results revealed another possible combination with pharmacological aspects - calcium channel blocker with diuretic.

2.5. Amlodipine/fosinopril combination

Meng et al. (2010) conducted a randomized prospective open label study to investigate the combination of amlodipine with the ACE inhibitor fosinopril administered at different times. Adults with essential hypertension (conventionally measured SBP/DBP $\geq$ 140/90 mmHg) were included in the study to receive either amlodipine 10 mg and fosinopril 5 mg together in the morning (7:00-8:00) or amlodipine 10 mg in the morning (7:00-8:00) and fosinopril 5 mg in the evening (20:00-21:00). After 4 weeks of treatment, a significant reduction in nocturnal SBP/DBP was found in the group with evening fosinopril dosing compared to the group with both medications administered in the morning (22.38/17.39 mm Hg reduction in SBP/DBP *vs.* 7.61/6.32 mm Hg, $p < .001$). No significant difference was observed between the groups in awake SBP/DBP and 24-h mean SBP/DBP. While in group with split dosing, slight reduction of non-dippers prevalence was observed, in the group with concomitant morning intake, a slight increase of non-dippers prevalence was found. A comparison of the distribution of adverse events between the groups was not provided. This was the second study to investigate the chronopharmacological effects of an ACE inhibitor, and first one in combination with a calcium channel blocker.

3. Discussion

Many chronopharmacological data concerning hypertension medication have been reported after a repeated treatment with a single drug. In general, CCBs equally reduce day and night BP after dosing in the morning and in the evening, and do not change 24-h BP profile. On the other hand, ACEIs lower more day BP after dosing in the morning and night BP after dosing at night, and, therefore, evening dosing of ACEIs change 24-h BP profile from non-dipping to dipping. In addition, the natriuretic and blood glucose-elevating effects of thiazide diuretics are reported to be greater after a repeated dosing in the evening (Fujimura et al. 1991). These chronopharmacological profiles of each drug might contribute to the dosing- time dependent influences on efficacy and safety of combined hypertension medication. The BP lowering effect of valsartan, an ARB, is also reported to be greater, especially during the night after dosing in the evening. However, an animal study using SHR showed that the antihypertensive and subsequent life-prolonging effects of valsartan after dosing at an inactive period are greater than those after dosing at an active period, but those effects of olmesartan, other ARB, after dosing at an inactive period are similar to those after dosing at an active period. These data indicate that chronopharmacological profiles of ARB depend on a drug *per se* (Liu et al. 2011). Compared to the large number of studies investigating the difference between morning and evening dosing in hypertension threatment with monotherapy, studies with combinational therapy are still limited. Only six randomized clinical trials were indentified in the scientific literature. As shown by four studies reported by Hermida, Zeng and Meng, evening dosing is more effective in terms of lowering asleep SBP and/or asleep DBP and/or mean SBP/DBP. Contradictory to this, the study of Asmar showed in fact equivalence between morning and evening dosing, while the study of Middeke showed more effective control of awake SBP and DBP with morning dosing. The study

of Middeke and colleagues, being the first one in this field, had several limitations. Mainly, the study was conducted on a very low number of subjects (n = 13) and relatively short duration of study (6 weeks). Hence the power of the study to compare between morning and evening dosing can be questioned. The design of this study is to be objected as well, as the comparison between two dosing schemes was conducted with halved dose, just after the controlled patients were switched from full dose, thus there is no relevant baseline to be compared with. More concerning is the discrepancy between data from Hermida and Asmar as both of these studies involved the same combination (amlodipin/valsartan), both were well designed with a sufficient number of patients and adequate methods for measurements. But while Hermida has shown significant reduction in asleep SBP/DBP and mean SBP with evening dosing, Asmar was not able to detect any difference. While both authors employed the same combination, Asmar used a free combination, while Hermida used a fixed combination. It is questioned, if this could contribute to difference in results. Thus further research is necessary in this area to elucidate conflicting results, particularly with the well established combination of amlodipine with valsartan.
Based on the current guideline on clinical investigation of medicinal products in the treatment of hypertension from the European Medicines Agency (EMA), which is relevant for marketing approval for antihypertensive agents, response criteria for antihypertensive therapy should also include reduction of SBP < 140 mmHg and DBP < 90 mmHg and/or reduction of SBP ≥ 20 mmHg and/or DBP ≥ 10 mmHg. Taken the first criterion into account (reduction of SBP < 140 mmHg and DBP < 90 mmHg), all studies were able to prove efficacy of both evening and morning dosing. As to the second criterion, interestingly all authors able to show a difference between morning and evening dosing (studies form Hermida, Zeng and Meng) were also able to achieve a reduction in particular SBP ≥ 20 mmHg with evening dosing, while this margin was not crossed with morning dosing, suggesting then evening dosing could be more effective. However clinical relevance of this finding needs to be studied further.
Except for differences in BP, the change from non-dipping to dipping profile was evaluated in some of these studies. Increase in dipping pattern was observed only with evening dosing (studies from Hermida and Zeng), while with morning intake, slight increase of non-dippers prevalence was found (study from Meng). This observation may have even more clinical impact than the difference in BP reduction, as normalization of the circadian rhythm of blood pressure is one of the primary targets in treatment of BP and has been shown for example to increase free survival of patients with heart failure, while non-dipping is associated with increased incidence of cardiovascular events (Ingelsson et al. 2006; Boggia et al. 2007; Okhubo et al. 2002). Except for Asmar, who reported a comparable distribution of adverse events between morning and evening dosing, none of the authors attempted to compare safety between dosing regimens. Safety, however, is of particular importance as too strong reduction in blood pressure may lead to several adverse events including orthostatic hypotension, renal dysfunction and cerebral hypoperfusion. Dosing to be shown more effective thus may be marked by a non-favourable safety profile.

4. Conclusion

Yet, results from only six randomized clinical trials have been published to compare morning *vs.* evening dosing of free or fixed combinations in the treatment of hypertension. While the results suggest that evening dosing might be more effective in terms of BP reduction and normalization of the circadian rhythm of blood pressure, clinical relevance of long term treatment and safety outcomes are still unknown. Further research is needed in this field to confirm the difference in efficacy but also evaluate safety aspects to allow overall conclusions on benefit-risk ratio and recommendations for medical practice.

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