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Chronopharmacology of high blood pressure—a critical review of clinical evidence

Original Paper

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Abstract Physiological functions of cardiovascular system (CVS) are exhibiting circadian patterns regulated by complex system of endogenous factors. Preserving this rhythmicity is important for its normal function, whereas disturbing the synchronization with natural day–night cycle can increase the risk of cardiovascular damage. Cardiovascular pathophysiology also follows cyclic variation; time susceptibility and period with maximum risk associated with elevated blood pressure (BP) can be predicted. Given this rhythmic nature, significant changes in efficacy between morning and evening administration of the drug may occur; appropriate timing of pharmacological intervention in therapy of hypertension may affect the efficacy of the treatment.

Keywords *chronopharmacology – blood pressure – circadian rhythm – non-dipping*

INTRODUCTION

The light–dark cycle is the most prominent rhythm on the earth, and organisms have adapted to this rhythm by the evolution of biological rhythms. Rhythmicity of life processes is one of the key factors for survival by adapting to environmental changes. This also applies to the cardiovascular system (CVS); its rhythmic features are important to synchronize the organ response to external changes (Wu et al., 2011). Conversely, loss of synchronization between the circadian oscillator and external stimuli can cause damage to the cardiovascular organs, and in long term, it can lead to increased morbidity and mortality risk. CVS exhibits distinct 24 hours rhythm within its physiological functions; main features such as blood pressure (BP), cardiac output, and heart rate have a clear and characteristic circadian pattern. Likewise, the pathophysiological mechanisms connected to morbidity and mortality display this rhythm.

Values of BP are not constant throughout the day (Portaluppi et al., 2012). A distinct 24-h rhythm given by cyclic alternation of day and night with subsequent changes in behavior (e.g., physical activity and mental stress) and circadian rhythm of endogenous factors can be observed. The rhythm character is largely due to the dominance of the sympathetic nervous system with high levels of circulating noradrenaline, adrenaline, and catecholamines in the first hours after waking. Renin-angiotensin-aldosterone hormone system (RAAS) also plays an important role contributing to the composite rhythm of BP with plasma concentrations of renin activity, angiotensin-converting enzyme (ACE), angiotensin I and II, and aldosterone all of them peaking in the morning before awakening. Conversely, comparatively lower BP during sleep is a result of predominance of parasympathetic action over the sympathetic nervous system, lower RAAS concentration, and maximum vasodilator levels—atrial natriuretic peptide and nitric oxide (Hermida et al., 2011). In organisms with reversed day–night activities, that is, nocturnal animals, the BP rhythm is opposite, so the highest values occur at night when animals are active and seek food, confirming that the day and night rhythm and differences in mental and physical activities are a key factor affecting the circadian rhythm of BP.

CHRONOTHERAPY OF HYPERTENSION

The goal of chronotherapy is to achieve maximum drug concentrations in synchrony with the intrinsic circadian rhythm of the disease or symptoms process, thereby increasing the efficacy as well as reducing the adverse effects of treatment.

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Table 1: Administration-time-dependent effect of BP-lowering medications

Medication	Dosage (mg per day)	Treatment times	Study length (weeks)	No. of completed subjects	Comparison of morning vs. evening dosing	Author
Valsartan	160	Awakening bedtime	12	90	Significant reduction in asleep SBP/DBP with evening dosing	Hermida et al., 2003
Olmesartan	20	Awakening bedtime	12	133	Significant reduction in asleep SBP/DBP with evening dosing	Hermida et al., 2009
Telmisartan	80	Awakening bedtime	12	215	Significant reduction in asleep SBP/DBP with evening dosing	Hermida et al., 2007
Lisinopril	20	08:00; 16:00; 22:00	8	40	Significant reduction in early morning SBP/DBP with evening dosing	Macchiarulo et al,. 1999
Trandolapril	1	Awakening bedtime	8	30	Significant reduction in 24-h BP mean with evening dosing	Kuroda et al., 2004
Ramipril	5	Awakening bedtime	6	115	Significant reduction in 48-h SBP/DBP mean with evening dosing	Hermida and Ayala, 2009
Spirapril	6	Awakening bedtime	12	165	Significant reduction in asleep SBP/DBP with evening dosing	Hermida et al., 2010
Nifedipine	30	Awakening bedtime	8	180	Significant reduction in 48-h SBP/DBP mean with evening dosing	Hermida et al., 2008
Torasemide	5	Awakening bedtime	6	113	Significant reduction in 48-h SBP/DBP mean with evening dosing	Hermida et al., 2008

This can be achieved by specific drug technologies but often by simply adjusting the time of administration of conventional therapy (Smolensky et al. 2010). Research has shown that the majority of patients with hypertension use BP-lowering medication in the morning; some data refer up to 80% of patients with hypertension taking all antihypertensive drugs in the morning (De La Sierra et al., 2009). In contrary to this practice, a number of randomized clinical trials (RCTs) have demonstrated that appropriate timing of administration of an antihypertensive drug can affect the efficacy and safety of the treatment, so that changes in efficacy between morning and evening drug delivery may be significant for individual drugs.

Monotherapy

Clinical trials focusing on monotherapy have been performed with all available classes of drugs used in the treatment of hypertension, that is, ACE inhibitors, diuretics, α-blockers, β-blockers, direct renin inhibitor, angiotensin receptor blockers, and calcium channel blockers (see Table 1). Significant treatment-time differences were confirmed for several classes of antihypertensive drugs. With the RAAS being highly circadian rhythmic, most of the recent and well-designed studies have focused on drugs acting on this cascade—ACE inhibitors and AT1 blockers—and have indeed shown statistically significant changes in chronic non-dipping nocturnal adjustment when monotherapy was given in the evening and not in the morning (Hermida et al., 2013; Schillaci et al., 2015). The thiazide diuretics have also been shown to have a greater efficacy with evening treatment, being significantly more effective in reducing the incidence of severe cardiovascular events, adjustment of circadian pattern, and reduction of nocturnal BP values (Kasiakogias et al., 2015; Liu et al. 2014). A meta-analysis comparing the results of more than 20 RCTs involving almost 2,000 patients with primary hypertension confirmed that more effective BP control was achieved with evening monotherapy (Zhao et al., 2011).

However, this does not apply to all antihypertensive drugs. Given their long elimination half-life, trials with calcium channel blockers have shown no significant difference between morning and evening administration of majority of the dihydropyridines (amlodipine, isradipine, lacidipine) (Qui et al., 2003; Lemmer, 2006); however, studies with nifedipine have shown reduction of the mean BP values to be significantly better with bedtime dosing (Hermida et al., 2008). Conversely, β-blockers appear to be more effective in morning administration and alter the circadian BP toward a

Table 2: Administration-time-dependent effect of selected BP-lowering medications in combination treatment

Combination treatment	Dosage (mg per day)	Treatment times	Study length (weeks)	No. of completed subjects	Comparison of morning vs. evening dosing	Author
Valsartan/ amlodipine (free combination)	160/5-10	06:00–10:00 18:00–22:00	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	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	12	204	Significant reduction in asleep SBP with evening dosing	Hermida et al., 2011
Amlodipine/HCT (fixed combination)	5/25	8:00 22:00	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	4	40	Significant reduction in asleep SBP/DBP with split evening dosing	Meng et al., 2010
Amlodipine/ fosinopril (free combination)	5/10	7:00–8:00 7:00–8:00/ 20:00–21:00	4	40	Significant reduction in asleep SBP/DBP with split evening dosing	Meng et al., 2010

nondipper profile. This can be reasonably expected with the concentration of catecholamines as well as the expression of beta-receptors being lowest during the night, thus owing the administration of β-blockers in the evening lower effect compared with that in the morning (Langner, Lemmer, 1988)

Fixed combination therapy

Although the treatment of hypertension is usually initiated as monotherapy, in most cases, combination therapy, that is, use of multiple antihypertensive agents simultaneously, is also indicated (Dahlöf, 2009). Therapy with lower doses of two or more drugs is preferable to monotherapy at higher doses with one drug, because better control of BP is achieved along with better tolerability and related patient compliance. Compared with large number of studies investigating difference between morning and evening dosing, studies with combination therapy investigating the chrono-effect are still limited (see Table 2). In these cases, it is assumed that chronopharmacological profiles of each drug might contribute to the dosing-time-dependent influences on the efficacy and safety of combined hypertension medication, with results suggesting evening dosing to be more effective in terms of BP reduction and/or normalization of the circadian rhythm of BP (Potúček, Klimas, 2013). However, interesting observation came from the comparison of two independent studies investigating the chrono-effect of the same combination (amlodipine and valsartan). While significant reduction in asleep BP and mean BP values with evening dosing was proven in one of the studies, no difference between time of administration has been observed in the other one (Hermida et al., 2010; Asmar et al., 2011). With the study length being the only difference between these two studies, this fact might indicate that the duration of treatment can also influence the chrono-effect. Similar results were also confirmed in preclinical settings (Potucek et al., 2017).

DISCUSSION

Circadian rhythms at targeted site of action are a primary prerequisite for chronopharmacology. This is confirmed by several experiments showing that the peak pharmacodynamic (PD) effect of drugs does not correlate with the plasma concentration peak, thus suggesting a circadian stage dependency of the drug plasma concentration–antihypertensive effect relationship (Smolensky et al. 2010). However, PD and/or pharmacokinetic (PK) profile of the drug must also be taken into consideration before selecting suitable candidates, because molecules with a longer elimination half-life or slow dissociation from the receptor-binding site are prone to have decreased chronopharmacological effect (Liu et al., 2011).

The appropriate choice of the drug and the timing of its administration must, therefore, respect PK profile of the molecule, but, at the same time, circadian rhythms of body may as well affect the fate of the drug in the body. Gastric emptying, motility, and perfusion are significantly longer in the morning, whereas gastric acid secretion reaches its maximum in the evening. Lipophilic molecules seem to be more prone to circadian rhythms of the body affecting their PK and then hydrophilic one with respect to differences between the maximum plasma concentrations (Cmax) measured after

morning and evening administration (Lemmer et al., 1991; Shiga et al., 1993). However, no significant changes in AUC were observed so far suggesting that circadian changes in the PD of medicines used in chronotherapy of CVS are the result of direct interaction with the target system rather than changes in efficacy because of changes in PK.

Last but not the least; consideration must be also given to the duration of treatment. Short elimination half-life suggests greater drug fluctuations in plasma. In short-term administration, this may also translate to more pronounced differences between morning and evening treatments (Portaluppi et al., 2007), especially when comparing the difference in decreasing the mean BP values. Conversely, once the steady state of drug is reached in the body and the plasma levels of the drug are constant, the chronopharmacological effect may be waning, so the difference between morning and evening doses is less profound. Thus, with respect to the treatment duration, chrono-effect is expected to be more prominent in the beginning rather than after long-term administration. Therefore, chronotherapy might be of clear benefit in settings, where rapid onset of treatment or normalization of BP pattern is needed.

However, it is of important note that significant difference between dosing regimens in terms of dipping prevalence has been observed in long-term treatment even if there was no more effect on the mean 24-h BP values. It is known that loss of the physiological circadian pattern of BP may lead to pathological mechanism associated with increased morbidity and mortality (Ohkubo et al., 2002). Chronically increased BP may even lead to general dysfunctional circadian body rhythms. For all blood pressure profiles with impaired, disturbed, or otherwise deviating rhythmicity compared with normal diurnal pattern, it was confirmed that there is a clear association with the risk of cardiovascular disease (Takeda, Maemura, 2011). Normotensive non-dippers are exposed to almost the same risk of cardiovascular mortality as hypertensive dippers. It has been also shown that when the diurnal rhythm of BP was normalized, free survival of patients with heart failure has increased, whereas non-dipping is associated with increased incidence of cardiovascular events (Salles et al., 2016). Therefore, normalization of the circadian rhythm of BP is one of the primary targets in the treatment of hypertension. Vast majority of reviewed RCT have shown normalization of the dipping profile and/or changes in asleep BP values when applying chronotherapy, and this fact may have even more clinical impact than the differences in the mean 24-h BP reduction alone.

CONCLUSION

The results from the RCTs clearly indicate that appropriate timing for dosing of antihypertensive drugs may increase the control of the hypertension; however, consideration must always be given to the circadian rhythm of the targeted site of action, kinetic profile of the drug, and also to the duration of treatment. Although the comparison between morning and evening dosing has not been always translated into significant difference in the decrease in the mean 24-h BP values, normalization of the circadian rhythm of BP has been achieved with appropriate timing of pharmacological intervention. With the later having the clear clinical relevance in terms of decreased CVS morbidity, these data substantiate the need for chronopharmacological approach in clinical settings.

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