



Chronotherapy of hypertension: Administration-time-dependent effects of treatment on the circadian pattern of blood pressure[☆]

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Abstract

Some specific features of the 24-hour blood pressure (BP) pattern are linked to the progressive injury of target tissues and the triggering of cardiac and cerebrovascular events. Thus, there is growing interest in how to best tailor the treatment of hypertensive patients according to the circadian BP pattern of each individual. Significant administration-time differences in the kinetics (i.e., chronokinetics) plus beneficial and adverse effects (i.e., chronodynamics) of antihypertensive medications are well known. Thus, bedtime dosing with nifedipine GITS is more effective than morning dosing, while also significantly reducing adverse effects. The dose–response curve, therapeutic coverage, and efficacy of doxazosin GITS are all markedly dependent on the circadian time of drug administration. Moreover, valsartan administration at bedtime, as opposed to upon waking, results in an improved diurnal/nocturnal BP ratio, increased percentage of controlled patients, and significant reduction in urinary albumin excretion in hypertensive patients. Chronotherapy provides a means of individualizing the treatment of hypertension according to the circadian BP profile of each patient, and constitutes a new option to optimize BP control and to reduce the risk of cardiovascular disease (myocardial infarction and stroke) and of end-organ injury of the blood vessels and tissue of the heart, brain, kidney, eye, and other organs.

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1. Introduction

Several attributes of the cardiovascular system, including blood pressure (BP) and heart rate (HR), are characterized by predictable changes during the 24 h, for the most part, in synchrony with the rest–activity cycle [1,2]. This circadian BP variation represents, on the one hand, the influence of internal factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, and hematologic and renal variables [1,3]. BP is also affected by a variety of external factors, including ambient temperature/humidity, physical activity, emotional state, alcohol/caffeine consumption, meal composition, and sleep/wake routine [2,4,5].

During the past two decades specific features of the 24-hour BP pattern have been assessed as potential sources of injury to target tissues and as triggers of cardiac and cerebrovascular events in hypertensive patients. Indeed, the prominent 24-hour variation in the occurrence of a variety of acute cardiovascular events, such as myocardial infarction, angina pectoris, cardiac arrest, sudden cardiac death, and pulmonary embolism, have been shown to be closely related to the circadian BP pattern of hypertensive subjects [6]. Indeed, the rate of rise of BP coincident with the commencement of diurnal activity has been identified as an independent predictor of one's risk of morning stroke and acute coronary syndrome, and it is also hypothesized to be a trigger for myocardial infarction at this time of day [7–12]. Interestingly, recent studies reveal the 24-hour pattern and, in particular, the characteristic morning peak in the occurrence of both ischemic [13] and hemorrhagic [14] stroke is the same in normotensive and hypertensive persons. Moreover, other cardiovascular events, such as acute aortic dissection, display prominent 24-hour variation, with a significant morning peak both in hypertensive and normotensive subjects [15]. Collectively, all these observations strengthen the hypothesis that the morning surge in BP (in the presence or absence of systemic hypertension) is a crucial determinant of the rupture of a vulnerable and critically weakened arterial wall [16].

A growing number of studies also indicate the extent of the nocturnal BP decline is deterministic of cardiovascular injury and risk. The recent VIIth report of the Joint National Committee [17] states “those individuals in whom a 10 to 20% decrease of BP during the night is not present are at increased risk for cardiovascular events”. Loss of this normal 10 to 20% sleep-time BP decline (i.e., conversion to a non-dipper 24-hour BP pattern) is indeed associated with elevated risk of end-organ injury, particularly to the heart (left ventricular hypertrophy and myocardial infarct), brain (stroke), and kidney (albuminuria and progression to end-stage renal failure) [18–21]. In contrast, too great a decline in sleep-time BP (>20% of the daytime mean,

i.e., super-dipping 24-hour pattern) may result in nocturnal hypotension, with heightened risk of nighttime stroke, ischemic ocular disorder, and bone fractures from falls due to syncope with sudden change in posture, for example, upon nighttime bathroom use [22–25]. O'Brien et al. [18] reported that non-dipper hypertensive subjects are significantly more likely to suffer a stroke than dipper subjects. Verdecchia et al. [19] also showed, after an average follow-up period of 3.2 years, that non-dipper hypertensive patients had experienced nearly three times as many adverse cardiovascular events than did dipper hypertensive patients. More recently, Staessen et al. [20], summarizing the results from the Syst-Eur trial in which nitrendipine was consistently dosed at bedtime, reported that non-dippers experienced a greater incidence of stroke and myocardial infarction than persons who had a normal dipping pattern. Results from this trial also suggested that nighttime BP is the best predictor of cardiovascular risk. The evaluation of the data from the Ohasama study indicated, after an average follow-up of 9.2 years, that a 5% decrease in the decline of nocturnal BP in hypertensive patients was associated with a 31% increase in the risk of cardiovascular mortality [21]. Even more relevant is the finding that dipper hypertensives had a relative hazard of cardiovascular mortality similar to that of non-dipper normotensives [21]. These results indicate that cardiovascular risk can be influenced not by the BP elevation, itself, but also by the magnitude of the circadian BP variability. Consistent with the results of the Syst-Eur trial, the most recent evaluation of the Ohasama study data, which represents 10.8 years of follow-up, indicates that the nighttime, as compared to the daytime, BP level is the best predictor of cardiovascular risk [26]. Accordingly, there is growing interest in how to best tailor the treatment of hypertensive patients according to their circadian BP pattern [21,27,28].

Because the main steps in the mechanisms regulating BP are circadian-stage dependent [5], it is not surprising that antihypertensive medications may display a circadian time-dependency in their pharmacokinetics (PK) and pharmacodynamics (PD) [1,27,28]. Chronotherapeutics has been defined as the purposeful timing of medications, whether or not they utilize special drug-release technology, to proportion serum and tissue concentrations in synchrony with known circadian rhythms in disease processes and symptoms as a means of enhancing beneficial outcomes and/or attenuating or averting adverse effects [29]. The chronotherapy of hypertension takes into account the epidemiology of the circadian BP pattern, plus potential administration-time determinants of the PK and PD of antihypertensive medications. Specifically, it entails significant attenuation of the accelerated morning rise of systolic (SBP) and diastolic (DBP) BP, normalization of elevated daytime,

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