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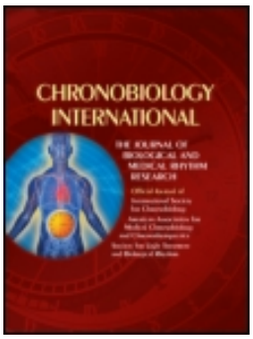

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PERSPECTIVES ON THE CHRONOTHERAPY OF HYPERTENSION BASED ON THE RESULTS OF THE MAPEC STUDY

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Appreciation of chronotherapy in hypertension continues to lag, despite clear demonstrations by many studies of (i) clinically relevant dosing-time differences of the beneficial and adverse effects of most blood pressure (BP) medications and (ii) significant association between reduced sleep-time BP decline of non-dippers and their heightened risk of cardiovascular disease (CVD). The Syst-Eur and HOPE outcome trials showed evening administration of nitrendipine and ramipril in these respective studies impacts sleep-time BP, converting the 24-h BP pattern to a more dipper one and in the HOPE study decreasing CVD risk. The CONVINCE study intended to compare BP control and CVD protection afforded by conventional β-blocker and diuretic medications versus a special drug-delivery verapamil formulation as a bedtime hypertension chronotherapy; however, the trial was terminated prematurely, not based on inadequate performance of the chronotherapy but on a corporate business decision. The just completed MAPEC study is the first trial specifically designed to prospectively test the hypothesis that bedtime administration of ≥1 conventional medications exerts better BP control and CVD risk reduction than the traditional approach of scheduling all medications in the morning. The results of this 5.6-yr median follow-up study establish that bedtime chronotherapy more effectively improves BP control, better decreases prevalence of non-dipping, and, most importantly, best reduces CVD morbidity and mortality. This chronotherapeutic approach to hypertension is justified by the fact that BP is usually lowest at night as is sodium excretion, but when sodium intake is excessive or its daytime excretion hampered, nocturnal BP is adjusted higher, to a level required for compensation overnight, via the pressure/natriuresis mechanism, resulting in non-dipping 24-h BP patterning. In diurnally active persons, the entire circadian BP pattern may be reset to a lower mean level and to a "more normal" day-night variation, simply by enhancing natriuresis during the night—the time-of-day when it can be most effective. A modification as simple and inexpensive as switching ≥1 hypertension medications from morning

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to evening may be all that is needed to normalize nighttime BP, exerting an effect exactly like sodium restriction. Current clinical concepts such as "normotensive non-dipper" (with higher CVD risk than a hypertensive dipper), broad recommendation of pharmacotherapy with exclusively high "smoothness index" medications (without attention to individual patient needs defined by the features of the 24-h BP pattern), and reliance upon static daytime diagnostic BP thresholds based solely on single office cuff assessment necessitate urgent reconsideration. (Author correspondence: prf@unife.it)

Keywords Ambulatory blood pressure monitoring; Cardiovascular risk; Chronotherapy; Dipper; Essential hypertension; Non-dipper; Pressure natriuresis; Smoothness index

INTRODUCTION

Although chronobiology—the science devoted to the study of biological rhythms—is widely accepted as a valid and valuable field of investigation today, the concept of homeostasis continues to prevail as the major, if not sole, basis of both the education of students in the medical and pharmaceutical sciences and the practice of clinical medicine and pharmacology. This is the situation in spite of the fact that the field of chronobiology has contributed significantly to the understanding of the pathophysiologic mechanisms of disease, diagnostics, and effective and safer treatment through chronotherapeutics—the timing according to circadian or other biological rhythms of pharmaceutical and other treatment interventions—thus benefiting the clinical practice of many medical specialties, including allergy, endocrinology, gastroenterology, internal medicine, neurology, pneumology, rheumatology, oncology, psychiatry, as well as occupational, reproductive, sleep, and sports medicine (Akerstedt et al., 2008; Atkinson et al., 2009; Axelsson et al., 2008; Biggi et al., 2008; Bougard et al., 2009a, 2009b; Bruguerolle, 2008; Burioka et al., 2008; Burkhart & Phelps, 2009; Camerino et al., 2008; Cariou et al., 2008; Costa & Di Milia, 2008; Coudert et al., 2008; Danilenko et al., 2008; Dispersyn et al., 2008; Edwards et al., 2008; Esquirol et al., 2009; Ferguson et al., 2008; Fietze et al., 2009; Folkard, 2008a, 2008b; Gander et al., 2008a, 2008b; Grundy et al., 2009; Harma et al., 2008; Ingre et al., 2008; Iskra-Golec & Smith, 2008; Kantermann & Roenneberg, 2009; Kloog et al., 2008; Larsson et al., 2008, 2009; Lee et al., 2008; Lericollais et al., 2009; Lin et al., 2009; McLaughlin et al., 2008; Monk et al., 2009; Paul et al., 2009; Reinberg & Ashkenazi, 2008; Sallinen et al., 2008; Signal et al., 2008; Soreca et al., 2009; Su et al., 2008; Suwazono et al., 2009; Tonetti et al., 2008; Waterhouse et al., 2008). Nonetheless, appreciation of the chronobiology and chronotherapy of some medical conditions continues to lag. Hypertension is one of these medical conditions. The purpose of this article is to first explore the

role of ambulatory blood pressure (BP) monitoring (ABPM) in the diagnosis of different forms of hypertension and thereafter to emphasize the latest developments in the chronotherapy of hypertension, in particular those stemming from the recently completed MAPEC trial, as reported by Hermida et al. (2010) in their ground-breaking article published in this issue of *Chronobiology International*.

CIRCADIAN PATTERNS OF BP

With but few exceptions, the diagnosis of hypertension throughout the world is accomplished by clinical cuff BP assessment performed by a doctor, nurse, or other qualified medical practitioner almost exclusively during the daytime—the traditional hours of clinical practice. In this manner, the differential diagnosis of normotension versus hypertension is based on systolic and diastolic BP (SBP and DBP) values obtained by a few daytime measurements that are interpreted in relation to published static threshold criteria unqualified for circadian time. It is assumed that in the absence of provoking environmental situations BP is quite constant during the day and night, such that the time of the assessment is inconsequential, although admittedly an increasing number, but still a small minority, of health professionals have begun to recommend supplementation of the clinic BP assessment with at-home measurements performed during different times of the activity span. However, the assumption of BP constancy is invalid, thus leading to the risk of misdiagnosis of hypertension and approach to optimal treatment. Nowadays, in some mainly academic centers, BP is being assessed over extended periods of time (usually 24 h, sometimes 48 h) by noninvasive ABPM methods for, among other purposes, the clinical trialing of hypertension medications—now required by most governmental agencies for new drug applications—and population-based hypertension outcome studies. The results of these and many other ABPM studies reveal, without doubt, that BP is not at all constant during the 24 h, but that it displays several specific day-night patterns.

ABPM: BEST MEANS OF DIFFERENTIATING HYPERTENSION FROM NORMOTENSION

ABPM was introduced many decades ago as a comprehensive method to assess the 24-h variation in BP outside of the office setting, more thoroughly diagnose essential and secondary forms of hypertension, better appraise response to therapeutic interventions, and explore features of the 24-h BP profile potentially associated with elevated risk and triggering of acute cardiovascular accidents (Ayala et al., 2009; Bergheanu et al., 2009; Cabezas-Cerrato et al., 2009; Hermida et al.,

2007a, 2007b, 2008, 2009; Jones et al., 2008, 2009; Perez-Lloret et al., 2008; Portaluppi & Hermida, 2007; Portaluppi & Lemmer, 2007; Portaluppi et al., 2009; Shiotani et al., 2009; Smolensky et al., 2007).

Different circadian BP patterns have been identified in hypertensive patients, and they are differentially associated with cardiovascular disease (CVD) risk (Boggia et al., 2007; Dolan et al., 2005; Ohkubo et al., 2002; Salles et al., 2008; Staessen et al., 1999; Verdecchia et al., 1994). In normotensive individuals, the BP circadian pattern is characterized by nighttime SBP and DBP mean levels that are 10% to 20% lower than daytime ones. The SBP and DBP of this so-called sleep-time dipper pattern show an abrupt rise in the morning beginning just before the commencement of diurnal activity, with peak values achieved generally during the morning or afternoon hours; thereafter, they gradually decline, reaching lowest levels during nighttime sleep. This 24-h pattern is also typical of uncomplicated essential hypertension. However, the BP pattern is often very different in complicated and resistant hypertension and when it occurs secondary to an existing medical condition, e.g., renal disease, diabetes, or sleep apnea, or advancing age. In such patients, SBP and DBP commonly fail to decline during nighttime sleep from daytime mean levels by the expected 10% to 20%, and the sleep-time values may even be greater than the daytime ones. This so-called non-dipper pattern has been found to be associated with greater risk of injury, e.g., to the blood vessels and tissues of the eye, kidney, brain, and heart, and much greater risk of CVD morbid and mortal events than the dipper pattern (reviewed by Hermida et al., 2007a, 2007b).

Thus, after many decades of investigation, it is now well established that (i) target organ damage is more closely associated with ABPM than with clinic BP and (ii) some specific features of the 24-h BP pattern are linked to the progressive injury of target tissues and triggering of cardiac and cerebrovascular events. In particular, the extent of the asleep BP decline is deterministic of cardiovascular injury and risk. In several large-scale, population-based studies, attenuation of the normal 10% to 20% sleep-time BP decline from the daytime level, manifesting as a non-dipper pattern, has been shown to be associated with elevated risk of left ventricular hypertrophy and myocardial infarction, stroke, and albuminuria, and progression to end-stage renal failure (Boggia et al., 2007; Brotman et al., 2008; Dolan et al., 2005; Ingelsson et al., 2006; Kario et al., 2001; Ohkubo et al., 2002; Staessen et al., 1999; Verdecchia et al., 1994). The pioneering work of Verdecchia and coworkers (1994) revealed that hypertensive nondippers have a much higher CVD risk than normal dippers. Other more recent reports have also demonstrated that hypertensive persons who retain the normal dippering 24-h pattern show a higher probability of CVD event-free survival (Ingelsson et al., 2006) and significantly lower CVD mortality risk (Brotman et al., 2008)

compared to non-dippers. These studies document the signficant association between BP dipping status and risk of target-organ injury and CVD events, but they further suggest the goals of hypertension therapy ought to include the preservation or reconstitution of the normal dipping 24-h BP pattern, which entails proper regulation of sleep-time SBP and DBP.

CHRONOPHARMACOLOGY OF BP-LOWERING MEDICATIONS

Appreciable ingestion-time differences in the pharmacokinetics (PK)—absorption, distribution, metabolism, and elimination—and pharmacodynamics (PD)—independent of PK phenomena—of BP-lowering medications are well known (Lemmer & Portaluppi, 1997). The former result from the influences of circadian rhythms in gastric pH and emptying, gastrointestinal motility, biliary function and circulation, liver enzyme activity, blood flow to the duodenum and other organs of the gastrointestinal tract, and glomerular filtration rate, among other factors (Labrecque & Beauchamp, 2003). Hence, one might expect hypertensive medications to be cleared more slowly overnight, thereby potentially prolonging their duration of action when ingested at bedtime as compared to in the morning upon awakening (Hermida et al., 2007a). Administration-time differences in the PD of BP medications, in the absence of differences in PK, are also known (see Smolensky et al., 2010); they result from circadian rhythms in circulating drug-free fraction, rate-limiting steps of key biochemical and metabolic processes, receptor number and conformation, and/or second messenger and signaling pathways (Witte & Lemmer, 2003). In this regard, clinically relevant dosing-time differences in the beneficial and adverse effects of the BP-lowering medications of six different therapeutic classes have been reported (Smolensky et al., 2010). Nonetheless, in spite of the great number of published evaluations of hypertensive medications, rarely has the time-of-day of their administration been a primary or even secondary interest of investigations. As presented in Table 1 (Smolensky et al., 2010), a variety of highly prescribed calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, α-blocker, β-blocker, and diuretic medications when studied by around-the-clock ABPM methods displays very significant (and some dramatic) morning-evening, dosing-time differences in their BP-lowering effects. For example, the mean enhancement of BP control relative to baseline levels by the bedtime compared to the upon-awakening schedule of the diuretic torasemide (5 mg/day) amounted to 8.4/6.1 mm Hg in the 48-h SBP/DBP, 8.3/6.2 mm Hg in the awake SBP/DBP, and 8.2/5.5 mm Hg in the asleep SBP/DBP. The bedtime versus conventional upon-awakening treatment regimen of the angiotensin-converting enzyme inhibitors ramipril (5 mg/day) and spirapril (6 mg/day) more effectively reduced the asleep SBP/DBP means

TABLE 1 Changes from baseline (in mm Hg) in ABPM-determined 48-h, awake, and asleep SBP and DBP means of different hypertension medications when routinely ingested upon awakening (Awakening Rx) or at bedtime (Bedtime Rx) by diurnally active hypertensive subjects

		Effect on 48-h SBP/DBP means		Effect on awake SBP/DBP means		Effect on asleep SBP/DBP means	
Medication (dose, Rx duration)	No. of subjects	Awakening Rx	Bedtime Rx	Awakening Rx	Bedtime Rx	Awakening Rx	Bedtime Rx
Doxazosin GITS (4 mg, 12 wks)	39[a]	−1.8/ − 3.2	−6.9/ − 5.9[‡]	−2.9/ − 3.7	−6.0/ − 5.4	0.7/ − 1.3	−8.2/ − 6.5[†]
Doxazosin GITS (4 mg, 12 wks)	52[b]	−2.2/ − 1.9	−5.3/ − 4.5	−3.4/ − 2.9	−5.9/ − 4.4	0.1/ − 0.5	−4.9/ − 5.3[‡]
Nebivolol (5 mg, 8 wks)	173	−13.0/ − 11.3	−12.8/ − 10.3	−14.7/ − 12.4	−13.4/ − 10.9	−7.9/ − 7.4	−10.2/ − 8.1
Torasemide (5 mg, 6 wks)	113	−6.4/ − 3.4	−14.8/ − 9.5*	−7.3/ − 3.7	−15.6/ − 9.9*	−4.3/ − 2.5	−12.5/ − 8.0*
Ramipril (5 mg, 6 wks)	115	−8.5/ − 6.2	−11.2/ − 9.5[†]	−10.1/ − 6.9	−10.5/ − 9.0	−4.5/ − 4.1	−13.5/ − 11.5*
Spirapril (6 mg, 12 wks)	165	−8.7/ − 7.0	−9.8/ − 6.6	−9.9/ − 8.0	−8.5/ − 5.7	−5.7/ − 4.6	−12.8/ − 8.6*
Valsartan (160 mg, 12 wks)	90	−17.0/ − 11.2	−14.6/ − 11.4	−17.0/ − 11.1	−12.0/ − 9.8	−15.9/ − 10.8	−17.9/ − 13.3
Valsartan (160 mg, 12 wks)	100[c]	−12.3/ − 6.3	−15.3/ − 9.2[‡]	−12.8/ − 6.6	−13.0/ − 8.5	−10.9/ − 5.5	−20.5/ − 11.1*
Valsartan (160 mg, 12 wks)	200[d]	−13.0/ − 8.1	−15.2/ − 10.6[‡]	−13.1/ − 8.3	−12.6/ − 9.3	−12.9/ − 8.1	−21.1/ − 13.9*
Olmesartan (20 mg, 12 wks)	123	−13.8/ − 11.2	−13.9/ − 10.2	−14.5/ − 12.1	−13.3/ − 9.6	−11.2/ − 8.7	−15.2/ − 11.5[‡]
Telmisartan (80 mg, 12 wks)	215	−10.6/ − 7.9	−11.7/ − 8.3	−11.7/ − 8.8	−11.3/ − 8.2	−8.3/ − 6.4	−13.8/ − 9.7*
Nifedipine GITS (30 mg, 8 wks)	180	−9.1/ − 5.8	−12.7/ − 7.6[‡]	−9.9/ − 6.4	−12.7/ − 7.6	−7.8/ − 4.7	−12.6/ − 7.8[†]

Note. All studies followed a prospective, randomized, open-label, blinded endpoint (PROBE) design. Participants of all studies (1565 individuals in total) were stage 1 and 2 essential hypertension patients, evaluated by 48-h ambulatory BP monitoring and wrist actigraphy before and after treatment. Comparison of effects on BP between treatment-times: $^{*}p < .001$; $^{\dagger}p < .01$; $^{\ddagger}p < .05$.

[a]Hypertensive subjects treated with doxazosin GITS monotherapy.

[b]Hypertensive subjects treated with doxazosin GITS (in combination with other hypertension medications) as a polytherapy.

[c]Study on elderly hypertensive participants (≥60 yrs of age), large proportion being non-dipper subjects.

[d]Study on non-dipper hypertensive subjects evidencing sleep-time relative SBP decline index <10%. The sleep-time relative BP decline, an index of BP dipping, is defined as the percent decline in mean BP during the hours of nocturnal sleep relative to the mean BP during the hours of diurnal activity and calculated as: [(awake BP mean − asleep BP mean)/awake BP mean] × 100.

from baseline by 9.0/7.4 and 7.1/4.0 mm Hg, respectively. In two studies on different cohorts of mainly non-dipper hypertensive patients, bedtime scheduling of valsartan (160 mg/day) better attenuated the asleep SBP/DBP means from baseline than its scheduling upon-awakening by 9.6/5.6 and 8.2/5.8 mm Hg, respectively. Finally, the differential asleep BP mean decrease from baseline by the long-half-life angiotensin II receptor blocker telmisartan (80 mg/day) ingested at bedtime, compared to upon awakening, amounted to 5.5/3.3 mm Hg SBP/DBP. It is these and other such findings that lay the foundation for hypertension chronotherapy.

HYPERTENSION CHRONOTHERAPY

The immediate aim of hypertension therapy is the normalization of abnormal SBP and DBP; however, the ultimate and most important long-term objective is protection against end-organ injury and cardiovascular morbidity and mortality. It is common practice for doctors and other health care workers to recommend that hypertensive medications be administrated in the morning, upon awakening or with breakfast. Moreover, it is clinical practice that BP control be judged solely by the SBP and DBP values measured in the clinic during the daytime, in the absence of any knowledge whatsoever of sleep-time values or circadian patterning, both before or with treatment. In most countries, ABPM is still considered a technique that should be reserved for research purposes or limited to subgroups of hypertensive subjects with specific indications. Thus, most doctors have no knowledge at all about the BP levels of their patients during nighttime sleep. Even when ABPM is applied, the majority of doctors either do not know how to interpret the nighttime BP data provided by this assessment technique, and nor do they appreciate the importance of the nighttime BP level in terms of CVD risk. As shown by Dolan et al. (2005), the sleep-time BP level is the most sensitive predictor of one's 5-yr CVD mortality risk, much more so than either the daytime clinic cuff-assessed values or the daytime or 24-h ABPM means. The absence of sleep-time BP and dipper status information constitutes a critical limitation to the optimal patient management of hypertension, since non-dipping BP patterning is quite common in clinical practice (de la Sierra et al., 2009; Salles et al., 2008). With this in mind, and taking into account that most marketed medications do not provide homogeneous long-lasting efficacy throughout the entire 24 h, we do not consider it good clinical practice to treat all hypertensive patients by the same once-a-day morning-dosing strategy.

SYST-EUR AND HOPE BEDTIME TREATMENT OUTCOME TRIALS

The chronotherapy of conventional hypertension medications involves their optimal timing, with reference to the patient's sleep-wake

routine and circadian rhythms, to best control daytime and nighttime SBP and DBP, normalize and preserve the circadian BP profile, e.g., in terms of dipping status, and avert undesired and adverse side effects. However, the ultimate aim of the chronotherapy of hypertension is lessening the risk of associated injury to the vessels and tissue of the eye, brain, kidney, and heart as well as cardiac and cerebrovascular accidents and deaths. The advantage of nighttime dosing of conventional once-daily, extended-action hypertension medications is suggested by the results of earlier conducted studies, such as those summarized in Table 1, plus the findings of two earlier conducted morbidity trials—the Syst-Eur (Staessen et al., 1999) and the Heart Outcomes Prevention Evaluation (HOPE) (Yusuf et al., 2000) studies—that relied exclusively on an evening treatment schedule. In the Syst-Eur trial, participants were randomized to an evening schedule of either placebo or the dihydropyridine calcium channel blocker nitrendipine. In the HOPE study, participants in the active-treatment group ingested the angiotensin-converting enzyme inhibitor ramipril at bedtime, a critical piece of information withheld from the original publication. Both studies found that the evening drug administration schedule reduced the incidence of the non-dipping BP pattern among treated hypertensive patients. Furthermore, the HOPE trial demonstrated that the treatment-conferred normalization of the 24-h BP dipping pattern was associated with a lower incidence of stroke and myocardial infarction relative to those displaying the abnormal non-dipper pattern (Svensson et al., 2001). Collectively, the findings of the two trials infer treatment at bedtime, as demonstrated with the respective hypertension monotherapies, is the most meaningful way of successfully reducing the asleep SBP and DBP to recommended values and normalizing the 24-h BP pattern, and most importantly decreasing CVD risk (Staessen et al., 1999; Svensson et al., 2001). However, the major shortcoming of both the Syst-Eur and HOPE trials is that each was devoid of a comparison treatment group randomized to morning therapy.

BEDTIME CONTROLLED-ONSET VERAPAMIL CHRONOTHERAPY: THE CONVINCE TRIAL

The first proposed prospective, large-scale assessment of hypertension chronotherapy was the 5-yr international multicenter (Controlled Onset Verapamil INvestigation of Cardiovascular Endpoints: CONVINCE) outcomes trial involving 15,000 hypertensive patients with identified CVD risk. This trial intended to assess the advantage of a Covera HS® (Searle Pharmaceutical Company, Chicago, Illinois, USA), a special formulation of verapamil designed to delay the release of medication for ~4–5 h following the recommended bedtime ingestion, so peak blood concentrations

are achieved around the time of morning awakening. The CONVINCE trial was designed to compare the degree of BP control and protection against cardiovascular events afforded by a regimen of conventional β-blocker and diuretic medications versus Covera HS® chronotherapy (Black et al., 1998). This community-based outcomes study, however, was terminated prematurely, not because of inadequate performance of the chronotherapy, but because of a corporate business decision by the pharmaceutical company that acquired the rights to the medication. Because the trial was terminated prematurely, there were far too few cardiovascular events to enable a valid assessment of the bedtime verapamil chronotherapy (Black et al., 2003). Thus, its merit relative to conventional therapy remained unresolved. Unfortunately, the great majority of doctors, pharmacists, and public health officials misinterpreted the premature termination of the CONVINCE trial and the lack of significant differences in cardiovascular events between the trialed medications as evidence against the utility of hypertension chronotherapeutics.

THE MAPEC STUDY: HYPERTENSION CHRONOTHERAPY AND CVD RISK

In view of the paucity of available data, the prospective MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) study conducted in Spain by Hermida and collaborators (2010), reported in this issue of *Chronobiology International*, constitutes a most important advance. The MAPEC study was specifically designed (Hermida, 2007) to test the hypothesis that bedtime chronotherapy with ≥1 medications exerts better BP control and CVD risk reduction than the conventional schedule of treatment consisting of all medications ingested in the morning. A total of 2156 hypertensive subjects were evaluated by 48-h ABPM at baseline and with identical assessment conducted annually, or more frequently (quarterly) if adjustment of treatment was required. At baseline, the two treatment-time groups were mostly comparable in terms of their clinic and mean ambulatory SBP and DBP and prevalence of non-dipping BP pattern. Subjects who ingested ≥1 of their medications at bedtime showed at their last available evaluation significantly lower mean sleep-time BP, higher sleep-time relative BP decline (an index of BP dipping calculated as [(awake BP mean − asleep BP mean)/awake BP mean] × 100), reduced prevalence of non-dipping (34% versus 62%; $p < .001$), and higher prevalence of controlled ambulatory BP (62% versus 53%, $p < .001$). After a median follow-up of 5.6 yrs, the group of subjects ingesting ≥1 BP-lowering medications at bedtime showed a significantly lower relative risk of total cardiovascular events than the group of subjects ingesting all medications upon awakening (0.39 [0.29–0.51];

$p < .001$). The progressive decrease in asleep BP and increase in sleeptime relative BP decline, both indicative of a more normal dipping pattern, were best achieved with bedtime therapy, and they were the most significant predictors of event-free survival. Results from the prospective MAPEC study thus indicate that bedtime chronotherapy with ≥1 hypertension medications, compared to conventional upon-waking treatment with all medications, more effectively improves BP control, better decreases the prevalence of non-dipping and, most importantly, significantly reduces CVD morbidity and mortality.

MECHANISMS UNDERLYING THE ADVANTAGE OF BEDTIME CHRONOTHERAPY

Explanation of the differences in effects upon the 24-h BP pattern based exclusively on time of drug administration in relation to underlying circadian rhythm–dependent mechanisms may be difficult to understand by those whose education is exclusively homeostatic. A unitary explanation entails the classical pressure/natriuresis mechanism proposed many years ago by the renowned physiologist Arthur Guyton (Guyton, 1980; Guyton et al., 1972). Under usual circumstances, BP is normally lowest at night as is sodium excretion. However, in acute and chronic situations when sodium intake is excessive or its excretion hampered during the daytime, BP is adjusted by means of the pressure/natriuresis mechanism to the higher level needed to compensate overnight, thereby resulting in non-dipping 24-h patterning (Bankir et al., 2008; Fujii et al., 1999; Uzu et al., 2001). This is the reason why sodium-sensitive hypertensives, i.e., patients prone to retain sodium to such a degree that BP is significantly increased, tend to be non-dippers. The pressure-natriuresis mechanism and relationship is modulated during the daytime by the effects of upright posture and activity, such that it is mainly during the nighttime when sodium sensitivity (which is present in each person, but to a different extent) most strongly exerts its corrective effects, thus inducing the non-dipping BP patterning. Hence, BP regulation is not constant throughout day and night; on the contrary, it is modulated according not only to the different pathophysiological situations of the individual and the pharmacological properties of the instituted pharmacotherapy, but also to the time-of-day of treatment (Sachdeva & Weder, 2006). A modification as simple and inexpensive as switching the ingestion time from morning to evening or bedtime (in diurnally active patients) of ≥1 hypertension medications may be the only action necessary to achieve proper control of nighttime SBP and DBP, the functional effect being exactly as dietary potassium supplementation and/or sodium restriction, which are known to restore normal dipping (Takakuwa et al., 2002). This simple treatment intervention, i.e., the bedtime dosing of ≥1 hypertension

medications, could enhance the effect of therapy not only on asleep BP, but also on awake BP once an efficient nocturnal excretion of sodium is induced. As a result, the entire circadian BP pattern may be reset to a lower mean level and to a "more normal" day-night variation, simply because natriuresis is enhanced more during the night—the time-of-day in diurnally active persons when it can be most efficient. Circadian sodium excretion patterns also involve other control mechanisms, mainly neurohumoral ones (Portaluppi et al., 1996), such that retention of sodium at night may entail different underlying pathophysiologic mechanisms. However, among the myriad of BP control mechanisms, e.g., arterial baroceptors and chemoceptors, autonomic and central nervous systems, renin-angiotensin-aldosterone system, capillary fluid shift, and vasoactive peptides, the pressure-natriuresis mechanism ultimately dominates, due to its infinite gain (Guyton et al., 1972). Based on the circadian variation of pressure-natriuresis, it is possible to explain the remodeling of the circadian BP pattern through the proper administration time of BP-lowering medications in hypertensive patients of differing etiopathophysiologies.

IMPLICATIONS OF MAPEC STUDY

The results of the prospective MAPEC, which entailed the routine use of ABPM to properly diagnose hypertension and to assess attainment of treatment goals, show that the chronotherapeutic strategy consisting of dosing ≥ 1 hypertension medications at bedtime constitutes a safe and cost-effective means of lowering nocturnal BP and maintaining or restoring normal 24-h BP patterning. Most importantly, this study shows that a bedtime chronotherapeutic strategy prevents or retards the progression of target organ damage and significantly reduces CVD risk. Furthermore, the MAPEC study demonstrates the feasibility and advantage of attaining two new and novel therapeutic goals by the bedtime chronotherapy of hypertension—reduction of the asleep BP mean while avoiding nocturnal hypotension and restoration of the physiological nocturnal BP decline by at least 10% from the daytime BP mean to achieve or preserve the non-dipper status—as a practical and cost-efficient means of reducing CVD and other associated risks.

The primary findings of the MAPEC study provoke many questions, one being if there is differential benefit on CVD risk reduction of the various classes of medications prescribed for the bedtime therapy by the clinicians of the trial. However, sample size calculations of the study were not specifically powered for such (Hermida et al., 2010). Furthermore, the results of the MAPEC study suggest many clinical implications, and additionally they call for urgent reconsideration of a number of commonly accepted concepts and practices currently applied to the diagnosis

and management of hypertension. These include (i) the concept of "normotensive non-dipper," because the CVD risk of this BP phenotype is higher than that of a hypertensive dipper and as such the use of the term "normotensive" is misleading with the consequent risk of poor patient management; (ii) the conceptual approach to treatment that entails achieving the homeostatic goal of constant or relatively invariable effect of BP-lowering throughout the 24-h dosing interval using once-a-day medications of high "smoothness index," which appears questionable, even contraindicated, in the case of non-dipper patients; and (iii) the reliance on current occasional cuff assessment of BP and related guideline thresholds/criteria to diagnose hypertension without regard for BP levels at other times of the day and night, particularly the sleep-time level and/or the extent of the nocturnal decline.

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