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Review Article

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Chronobiology and Chronotherapy of Hypertension – A Review

Abstract

Hypertension occurs in over 90% of all patients with cardiovascular disease (CVD) in the United States and it is a major risk factor for end-organ damage, CVD and death. In the treatment of hypertension, investigation of chronobiology, chronopharmacology and chronotherapy began a few decades ago. Studies over the last decade have revealed that blood pressure (BP) and CVD are influenced by our behaviour such as what we eat and even conditioned by the time of day. Also, the ability of the night: day ratio of systolic BP predicts the risk for cardiovascular events more accurately compared with office BP measured only at once. Evidence clearly points to the fact that nocturnal BP is indeed the BP as it is most consistently correlated with prediction of cardiovascular risk and provides more close surveillance of safety. Circadian rhythm is a significant input into the regulation of BP. Hence, a circadian disorder such as hypertension requires chronopharmacotherapy. However, different medications have been studied for their chronopharmacology and potential chronotherapy. This article reviews the chronobiology of hypertension, and the chronopharmacology and chronotherapy of the various medications used in its management.

Keywords: Hypertension, Circadian rhythm, Chronobiology, Chronopharmacology, Chronotherapy.

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Introduction

Hypertension is a chronic medical condition in which the systemic arterial blood pressure (BP) is elevated. It is present in over 90% of all patients with cardiovascular disease (CVD) and affects nearly 74 million individuals in the United States. This condition is a major risk factor for stroke, myocardial infarction, heart failure, arterial aneurysm, and chronic kidney failure. The chronic elevation of BP is a silent disorder in that

its progression occurs largely asymptomatically. However, its impact is deafening, causing CVD, end-organ damage, which eventually leads to shortened life expectancy. Simple relationship between high BP and CVD that is heavily influenced by our behaviour and what we eat is also conditioned by the time of day. Hence, circadian rhythm is a significant input into the regulation of BP[2-4].

Chronobiology of Hypertension

Chronobiology is a branch of science that objectively explores and quantifies mechanisms of biological time structure including important rhythmic manifestations of life right from molecular level of living being, unicellular organism to complex organism such as human being. Technologic and scientific advancements in the last 30 years have allowed a greater understanding of the chronobiology of BP and also a detailed analysis of a patient BP risk profile. Research studies over the last few decades have revealed some important findings regarding the typical 24-hour BP profile. One of the strongest among these findings is the ability of the night: day ratio of systolic BP to more accurately predict risk for CV events compared with office BP[5].

Heart rate (HR) and BP have distinct circadian rhythms in both normotensive and hypertensive persons. The BP and HR in both normotensive and hypertensive patients are higher during the morning hours (04:00– 06:00 h) than any other time of the day due to a decrease in sympathetic output occurring at night while the individual is asleep[6-9]. Upon waking, the systolic blood pressure (SBP) rises rapidly by 20–25 mmHg and diastolic blood pressure (DBP) by 10–15. A schematic representation of the change in BP during a 24 hr period is shown in Figure 1. However, different forms of hypertension may exhibit different circadian patterns. In normotension as well as in hypertension, there is a general night drop in BP, whereas in secondary hypertension caused by any of the following conditions such as renal disease, gestation, Cushing's disease, the rhythm in BP is abolished or even reversed with highest values at night in about 70% of the cases. Ghergel et al[10-13] represented the extent of the drop in BP during the night in the region of 10–20%. However, approximately two thirds of the world's population present with a BP drop of this magnitude during the night and they are known as dippers. The remaining one third present with a BP drop of < 10% and are known as non-dippers. Prolonged exposure to a higher BP level seen in non-dippers, contributes to an increase in CVD such as myocardial infarctions, angina and strokes during the early hours of the morning[14-16]. Douglas reported that there is a 40% higher risk of a heart attack, a 29% increased risk of cardiac death and a 49% increased risk of stroke between 06:00 am and 12:00 noon[8]. Conversely, vasospasms in Prinzmetal angina and congestive heart failure symptoms are common during sleep[17]. Since then, an impressive evidence base has occurred regarding the prognostic value of *Ambulatory blood pressure monitoring (ABPM)*, in both treated and non treated. However, night time BP and stratification by dipping status appear even more closely related to prediction of stroke, myocardial infarction, and incident chronic heart failure [18-22]. Some authors, who first described optic nerve ischemia associated with low BP at night, hypothesized that the reduction in blood flow below a critical level plays a role in the multifactorial pathogenesis of anterior optic neuropathy and glaucomatous neuropathy [23,24]. Anterior ischemic optic neuropathy is not the only potential collateral damage occurring from excessive lowering of BP at night; a higher rate of cerebral lacunae has also been reported in extreme dippers[25]. The incidence of thrombotic and hemorrhagic stroke is greatest in the morning around the time of commencing diurnal activity. Ischemic events, chest pain, and ST-segment depression of angina are strongest during the initial three to four hours of daytime. The manifestation of ST-segment elevation in Prinzmetal's angina is most frequent during the middle to latter half of the nighttime. Within the past 10 years, special bedtime tablet and capsule BP-lowering medications have been introduced that proportion the drug level in synchrony with the day-night pattern of systolic and diastolic BP in primary hypertension [26- 31]. The occurrences of coronary infarction as well as of angina pectoris attacks and of pathologic electrocardiography

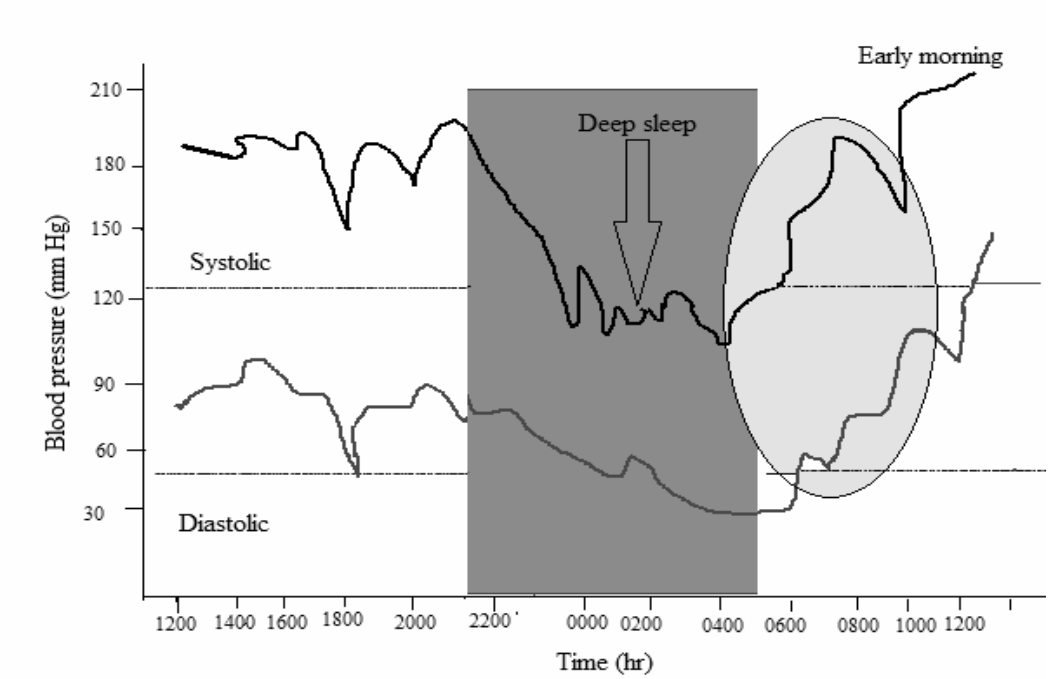

Figure 1: Schematic representation of the change in BP in a patient with untreated hypertension. The dotted lines represent the normal limit for ambulatory systolic and diastolic BP. The green zone indicates the sleeping period.

(ECG) - recordings are unevenly distributed over the 24-hour span of a day with a predominant peak in the early morning hours. Moreover, subtypes of a disease entity such as forms of vasospastic and stable angina pectoris or of primary and secondary hypertension may exhibit pronouncedly different 24-hour patterns in their symptoms[32].

With each day, the human body experiences a reproducible rhythm in behaviour, waking in the morning and sleeping in the evening a circadian rhythm. This is a consequence of the brain "resting" and "waking" as evidenced by changes in electrical activity [33, 34.] Moreover, in human hypertension, there are significant deviations to this rhythm in BP. Recent evidence suggested that the genetic components of the circadian clock exert a key and fundamental role in the regulation of BP. The time at which antihypertensives are actually administered, chronotherapy, also impacts BP control [35, 36].

Chronotherapy and Chronopharmacology

The term chronotherapy is defined as medical treatment administered according to a schedule that corresponds to a person's daily, monthly, seasonal, or yearly biological clock or the treatment of a sleep disorder by altering an individual's sleeping and waking times and resetting his or her biological clock. On the other hand, chronopharmacology investigates the effects/side effects of drugs upon temporal changes in biological functions or symptoms of a disease as well as drug effects as a function of biologic timing. The treatment of hypertension includes various types of drugs such as diuretics, β- and α-adrenoceptor blocking drugs, calcium channel blockers, converting enzyme inhibitors, and others that differ in their sites of action.

β-adrenoceptor antagonists

The main steps in the mechanisms regulating the BP are circadian phase-dependent showed that β-

adrenoceptor antagonists do not affect or reduce or even abolish the rhythmic pattern in BP[37]. In general, however, there is a tendency for β-adrenoceptor antagonists to predominately reduce daytime BP levels and not to greatly affect night-time values, being less/not effective in reducing the early morning rise in BP [38, 39]. Consistently, decreases in HR by β-adrenoceptor antagonists are more pronounced during daytime hours. In healthy subjects, a cross-over study with propranolol similarly showed a more pronounced decrease in HR and BP during daytime hours than at night [40].

Interestingly, the agent with partial agonist activity, pindolol, even increase HR at night [41]. Clinical data indicate that β-adrenoceptor mediated regulation of BP dominates during daytime hours and is of less or minor importance during the night and the early morning hours. This correlates well with the circadian rhythm in sympathetic tone as indicated by the rhythm in plasma noradrenaline and cAMP [42].

Calcium channel blockers

In primary hypertensives, 3 times daily dosing of non retarded verapamil did not greatly change the BP profile, however, less effective at night[43]. A single morning dose of a sustained-release verapamil showed a good 24-hour BP control[44.] Dihydropyridine derivatives [DHP] differing in pharmacokinetics, seem to reduce BP to a varying degree during day and night, drug formulation and dosing interval may play an additional role. In eight studies in essential hypertensives using a cross-over design, DHP did not differently affect the 24-hour BP profile after once morning or once evening dosing[45-53]. Most interestingly, the greatly disturbed BP profile in secondary hypertensives due to renal failure was only normalized after evening but not after morning dosing of isradipine[54].

In primary hypertension, antihypertensive drugs should be given at early morning hours, whereas in secondary hypertension it will be necessary to add an evening dose. Some studies have shown that different cardiovascular active compounds such as propranolol oral nitrates and nifedipine showed higher peak drug concentrations [C_{max}] and/or a shorter time-to-peak concentration [t_{max}] after morning than evening oral drug dosing, at least when non-retarded formulations were used [55-58]. In the case of retard formulation of IS-5-MN (Elantan® long sustained release) and nifedipine, no circadian phase-dependency in their pharmacokinetics were found[59-62].

For chronopharmacodynamics of calcium channel blockers (CCB) several trials have investigated the differential effects of morning vs. evening administration of CCB, including amlodipine, cilnidipine, diltiazem, isradipine, nifedipine, nisoldipine, and nitrendipine in diurnally active subjects[63-75] . A sustained-release formulation of diltiazem was found to be more effective in controlling the 24-hour BP mean when administered at night, while also reducing the diurnal/nocturnal BP ratio towards a more non-dipper profile. In some cases, evening administration of these medications resulted in a more marked effect on nocturnal BP and a significant modification of the circadian BP profile.

Angiotensin-converting enzyme inhibitors (ACEI)

Angiotensin-converting enzyme inhibitors (ACEI) clinical studies demonstrated a different effect of the ACEI benazepril, enalapril, perindopril, quinapril, ramipril, spirapril, and trandolapril when dosed in the morning vs. the evening. Kuroda et al[76] investigated the effects of the long-acting lipophilic ACEI trandolapril when ingested just before going to bed or in the morning in 30 hypertensive patients. Bedtime administration of the medication was found to be safe and effective means of controlling morning BP in hypertensive patients without the induction of excessive BP reduction nocturnally. The fixed combination of captopril and hydrochlorothiazide was slightly more effective in reducing nocturnal BP when administered in the evening [77]. More recently, Hermida et al[78]. investigated the administration-time-dependent efficacy of spirapril, an ACEI recommended for once-daily administration because of its extended duration of action due to its long elimination half-life of about 40h. They studied 100 patients with grade 1–2 essential hypertensions randomly assigned to

receive 6 mg/ day sprirapril as a monotherapy, either upon awakening in the morning or at bedtime at night. The efficacy of spirapril was slightly higher with morning dosing, 10.3 and 8.3 mm Hg reduction in the 24-hour mean SBP and DBP, respectively, as compared with bedtime dosing, 8.5 and 5.2 mm Hg reduction in SBP and DBP, respectively. Morning administration of spirapril, was significantly more effective than bedtime administration in reducing the diurnal BP mean and is significantly less effective in controlling nocturnal BP. Accordingly, the diurnal/nocturnal BP ratio was significantly reduced with spirapril ingestion on awakening and significantly increased with spirapril ingestion at bedtime [78].

α-adrenoceptor antagonists

α-adrenoceptor antagonist's effectively reduces peripheral resistance in the early hours in the morning than at other times of the day and night. Indeed, a single night time dose of the α-blocker doxazosin reduces both SBP and DBP throughout day and night, but its greatest effect is exerted early in the morning[79]. Interestingly, the peak effect of doxazosin following night time dosing occurs later than predicted based upon its pharmacokinetics (PK) [79]. Circadian-stage dependency in the dose – response relationship was detected for nifedipine, enalapril, and propranolol.

A recent study explored the administration-time dependent effects of the new doxazosin gastrointestinal therapeutic system (GITS) formulation[80]. In this study, 91 subjects were involved with stage 1 or 2 essential hypertension. Thirty nine (39) patients had been previously untreated and received the single doxazosin GITS formulation (monotherapy group), while the remaining 52 patients had been treated with two antihypertensive medications with inadequate control of their hypertension (polytherapy group). The subjects of the monotherapy and polytherapy groups were randomly assigned to ingest the daily 4 mg/day dose of doxazosin GITS, either upon awakening or at bedtime, for 3 months. Daily ingestion of doxazosin GITS upon awakening caused only a small and non-statistically significant BP reduction, because of unavailability of drug effect on nocturnal BP. In contrast, daily ingestion of the new doxazosin GITS formulation at bedtime resulted in a statistically significant BP reduction (P>0.05), mainly of the nocturnal BP. In summary, doxazosin GITS ingested daily upon awakening failed to provide full 24-hour therapeutic coverage, while bedtime dosing, resulted in a significant reduction of BP throughout the 24 h, whether ingested alone as a monotherapy or as part of a combination polytherapy [80]. In a recent study, Calvo et al[81] evaluated the effects of nebivolol on the 24-hour BP profile of 67 hypertensive patients who received 5 mg/day of the drug on awakening. The effects of nebivolol were significantly greater on the diurnal than nocturnal mean SBP and DBP, resulting in a significant reduction of their diurnal/nocturnal ratios [81-82]. The efficacy of nebivolol was comparable independent of its dosing time, 13.0 and 11.3 mm Hg reduction in the 24-hour mean SBP and DBP with nebivolol ingested upon awakening; 12.8 and 10.3 mm Hg reduction in the 24-hour mean SBP and DBP with nebivolol ingested at bedtime. At both treatment times, efficacy was more pronounced on the diurnal than nocturnal BP, although differences between the diurnal and nocturnal BP reduction were greater with the morning dosing schedule. Accordingly, there was a significant reduction in diurnal/ nocturnal BP ratio when nebivolol was administered upon awakening, but not at bedtime. The prevalence of nondipping was doubled with the morning nebivolol dosing schedule and remained unchanged with the bedtime nebivolol dosing schedule. These results thus suggested that the optimum dosing time for nebivolol is at bedtime. This ingestion-time schedule, avoids loss in drug efficacy during the 24-hour dosing interval and even the undesired reduction in the diurnal/nocturnal BP ratio that is associated with increased patient cardiovascular risk.

Angiotensin II receptor blockers:

Angiotensin II receptor blockers (ARB) selectively and specifically antagonize the action of angiotensin II, a potent vasoconstrictor impacting BP regulation. ARBs are becoming increasingly popular for the treatment of hypertension because they are effective and well

tolerated [66]. A recent study used 48-hour ABPM to assess the antihypertensive efficacy of the ARB valsartan when ingested by stage 1 or 2 essential hypertension patients for 3 months as a monotherapy, either in the morning upon awakening from night time sleep or at bedtime [83]. The highly significant BP reduction after treatment with the 160 mg/day dose of valsartan was similar for both treatment times. A 17.0 and 11.3 mm Hg reduction in the 24-hour mean SBP and DBP with morning administration as well as 14.6 and 11.4 mm Hg reduction in the 24-hour mean SBP and DBP with bedtime administration was observed by the researchers[83]. Valsartan administration at bedtime has resulted in a highly significant average increase by 6% in the diurnal/nocturnal BP ratio, corresponding to a 73% relative reduction in the number of non-dipper patients [83]. In another study, Morgan et al[84] involved 100 elderly patients with grade 1–2 essential hypertension who were randomly assigned to receive the 160 mg/day dose of valsartan as a monotherapy, either upon morning awakening or at bedtime at night. There was a significant BP reduction after 3 months of valsartan treatment, irrespectively of dosing time. The reduction was slightly greater with bedtime dosing, 15.3 and 9.2 mm Hg reduction in the 24 hour mean SBP and DBP than with morning dosing, 12.3 and 6.3 mm Hg reduction in the 24hour mean SBP and DBP. The diurnal/nocturnal BP ratio was unchanged in the group ingesting valsartan upon awakening (−1.0 and −0.3 for SBP and DBP; $p>0.195$). This ratio significantly increased (6.6 and 5.4 for SBP and DBP; $p<0.001$) when valsartan was ingested at bedtime. The reduction of the nocturnal mean was doubled in the group that routinely ingested valsartan at bedtime as compared with the group that did so in the morning ($p<0.001$). In the second trial, Hermida et al[85] used a similar design to investigate the administration-time-dependent effects on BP of the same dose of valsartan (160 mg/day) in a selected population of 148 non-dipper hypertensive patients. The significant BP reduction after 3 months of valsartan treatment ($p<0.001$) was similar for both dosing times (13.1 and 8.5 mm Hg reduction in the 24-hour mean SBP and DBP with morning administration; 14.7 and 10.3 mm Hg reduction in the 24-hour mean SBP and DBP with bedtime administration; $p<0.126$ for the treatment-time effect). The diurnal/nocturnal BP ratio was significantly increased only when valsartan was administered before bedtime, which resulted in 75% of the patients in this group reverting to dipper status.

Other classes of antihypertensive medications have rarely been studied in relation to possible circadian variation of effects. In the first, trial investigating the administration-time-dependent effects of a loop diuretic, Hermida et al[85] studied 90 hypertensive patients randomly assigned to receive 5 mg/day of torasemide as a monotherapy ingested either upon awakening in the morning or at bedtime at night. The efficacy of torasemide treatment was significantly greater with dosing at bedtime (12.9 and 8.9 mm Hg reduction in the 24-hour mean SBP and DBP) as compared with dosing upon awakening (6.1 and 3.2 mm Hg reduction in the 24-hour mean SBP and DBP; $p<0.004$ between groups).

Chronotherapy in resistant hypertension

Patients with resistant hypertension are at a greater risk for stroke, renal insufficiency, and morbid cardiovascular events than are patients whose BP is well controlled by pharmacotherapies [86]. Results of the studies on the chronotherapy of resistant hypertension summarized by these researchers revealed the importance of dosing time with combination therapy.

Some antihypertensive chronotherapeutically-designed market medications

There are some chronotherapeutically-designed market medications for the treatment of hypertension. The calcium channel blocker (CCB) controlled-onset, extended-release (COER)-verapamil was the first special drug-delivery tablet medication specifically designed for the chronotherapy of hypertension (and stable angina pectoris) [87, 88]. COER-verapamil (USA: Covera HS™; other markets: Chronovera™) was approved in the United States by the Food and Drug Administration (FDA) in 1996 for marketing by the then Searle Pharmaceutical Company. The drug-delivery technology of this tablet medication delays the release of verapamil

Table 1: Some antihypertensive chronotherapeutically-designed market medications available in the market

Generic names	Brand names	Manufacturer
Verapamil HCl	Covera-HS® extended release tablets	Searle Pharmaceuticals
Verapamil HCl	Verelan® PM Extended release capsules	Schwarz Pharma
Diltiazem HCl	Cardizem® LA	Biovail Pharmaceuticals
Propranolol HCl	Innopran® XL	Reliant Pharmaceuticals.
Diltiazem HCl	Cartia XT	Andrx Laboratories

for approximately 4–5 h following its recommended bedtime ingestion. Medication is released thereafter so the highest blood concentration is achieved in the morning around the time of awakening, generally between 6 and 10 a.m., with an elevated level sustained throughout diurnal activity. Chronotherapeutic oral drug absorption system (CODAS)-verapamil is a second special drug-delivery-based CCB chronotherapy of hypertension. CODAS-verapamil (Verelan PM™; Schwarz Pharma) was approved by the FDA in 1999. Release of verapamil from the polymer-coated beads of this capsule medication following recommended bedtime ingestion is delayed for approximately 4 h. Medication is then dispersed in an increasing amount so that peak blood concentration is achieved in the morning, between 6 and 10 a.m., Graded-release long-acting diltiazem (Cardizem LA, Biovail Pharmaceuticals) was approved by the FDA in 2003 for once daily dosing either in the morning or evening. Multiple-dose studies show ingestion of the 360 mg dose of this special drug-delivery form of diltiazem at 10 pm results in the desired PK profile for a chronotherapy of essential hypertension [89]. Trough blood diltiazem concentration occurs during night time sleep at 2 a.m. due to the retarded and slow release of medication following dosing, peak concentration occurs during the morning between 10 a.m. and 12 noon, and an effective drug level is maintained during the remainder of the 24-hour dosing interval. The β-antagonist propranolol chronotherapy (Innopran XL™, Reliant Pharmaceuticals) was approved in 2003 by the FDA. The summary of the few marketed chronotherapeutic formulations are presented in Table 1.

Conclusion

Studies for the last 10 yrs have revealed that the ability of the night: day ratio of systolic BP predicts the risk for cardiovascular events more accurately compared with office BP measured at once. Nocturnal blood pressures are most consistently correlated to the cardiovascular risk and so need more close surveillance for patient safety. For these reasons, it is obvious that night time BP is indeed, the BP. Circadian rhythm is a significant input into the regulation of BP and from the above evidences it can be concluded that time is one of the major factor that influence the management. Hence, circadian disorder such as hypertension requires chronopharmacotherapy. With this review, it is of the opinion that researchers will design more novel chronopharmaceutical formulations used for the management or treatment of hypertension knowing the risk factors involved with this disease condition.

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