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Review Article

Chronopharmacological aspects of Antihypertensive Drugs: A Short Review

Maria Raju, Venkateswaramurthy N, Sambath Kumar R

Department of Pharmacy Practice, J . K . K . Nattraja College of Pharmacy. Kumarapalayam -638183, Tamilnadu, India.

ABSTRACT

Circadian and other rhythmic changes in biological susceptibility and response of organisms to a large variety of physical and chemical agents including medications and food are rather common phenomena. Time related differences in drug effects depend upon endogenous circadian rhythms, which include metabolic pathways. The study of rhythmic, predictable in time differences in time effects or pharmacokinetics of drugs both in experimental animals and in men is called chronopharmacology. It investigates the side effects of drugs upon temporal changes in biological functions or symptoms of a disease as well as drug effects as a function of biological timing. In this review, we will focus on mammalian chronopharmacology of hypertensive drugs. Moreover, we will try to discuss about the physiological effects of drugs on the body, the mechanism of drug action, the relationship between drug concentration and effect in relation to circadian clock.

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*Corresponding author details:

Dr. N. Venkateswaramurthy
Professor
J. K. K. Nattaraja college of pharmacy
Komarapalayam, Tamil Nadu, India.

Tel: +91 9842724689

E-mail address:
venkateswaramurthy.n@jkkn.org

1. Introduction

Having a mind the organisation in time of living systems, including humans, it is easy to conceive that not only must the right amount of the right substance be given at the right place, but also that this must occur at the right time. In 1836, Kreutzer had first mentioned that the time of day can have an influence on the dosage and the effect of drugs. For several years, chronokinetics studies have been reported for many drugs both to partly explain chronopharmacodynamic phenomena and to demonstrate that the time of administration of a drug is a possible factor of variation of its kinetics. According to several periodicities the kinetic changes will occur, for example, time of day (circadian) as well as day of the month (infradian, menstrual).

"To produce its characteristic effects, a drug must be present in suitable concentration at its sites of action" (Hardman *et al.*, 2001). Thus, after introduction into the organism, a drug is absorbed, distributed (most frequently by protein binding) in order to diffuse into tissues and act on specific receptors to produce its pharmacological effects, and then is metabolized and elimination. The moment of administration determines the fate of the drug in the organism: this constitutes chronopharmacokinetics (or chronokinetics), which postulates that the different steps in pharmacokinetics (e.g. absorption, distribution, metabolism, and elimination) are influence by different physiological functions of the body which may vary with time of day. Thus pharmacokinetic parameters characterizing bioavailability, distributions, and elimination, which are conventionally considered to be constant in time, are circadian time dependent (Belanger *et al.,* 1997). Chronokinetic studies have been reported for many drugs in order to partly explain chronopharmacodynamic phenomena and to demonstrate that the time of administration of a drug is a possible factor of variation of its kinetics. Many chronokinetic studies have been reviewed elsewhere (Reinberg, 1992; Reinberg & Smolensky, 1982; Bruguerolle, 1987; Lemmer, 1999; Bruguerolle, 1993; Lemmer & Bruguerolle, 1994a). From the studies it appears that, in humans (bioavailability of many drugs taken orally is

higher when the drug is taken in the morning (e.g., theophylline, salicylates, benzodiazepines, digoxin, nonsteroidal anti-inflamatory drugs); temporal variations are more often observed and marked for liposoluble compounds sustained released forms decrease chronokinetics; and the route of administration may be involved in a chronokinetic change (Bruguerolle, 1992; Bruguerolle 1998; Reinberg, 1982). Absorption the oral route is the most often used route of drug administration. Among the different mechanisms by which a drug may be absorbed (e.g. passive or facilitated diffusion, active transport), passive diffusion is the most important process. Many factors may have pronounced effects on drug absorption and the variability of absorption processes: the physicochemical properties of the drug (lipophilicity or hydrophilicity), the structure of the biomembrane, gastric emptying time, pH, motility, gastrointestinal blood flow (Lemmer, 1999), the drug formulation, and the posture and feeding conditions (eg. possible influence of food). Most of these factors, such as gastric acid secretion and pH, motility, gastric emptying time and gastrointestinal blood flow, vary along the 24-hour scale, and it is not surprising that many studies have reported temporal variations of drug absorption (Bruguerolle, 1993; Lemmer & Bruguerolle, 1994a). Such variations may be predicted by physicochemical properties of a drug since most of the lipophilic drugs seem to be absorbed faster when the drug is taken in the morning as compared to evening dosing. At the opposite end, the absorption processes of highly water-soluble drugs were not demonstrated to change according to time of day. The underlying mechanisms of the chronokinetic pattern of lipophilic drugs involve a faster gastric emptying time and a higher gastrointestinal perfusion in the morning (Lemmer, 1991)

2. Characteristics of the Patients

Chronokinetics may vary according to many physiopathological factors, such as fasting or feeding habits, posture, gender, pathology, mode of synchronization, type of meal, meal timing, working habits, sleeping times, or age. These factors of variability must be strictly controlled in setting up a study design. Since they all participate to the intra-subject variability, it is of particular importance to control and standardize them in a chronokinetic study. Most of these factors are often not taken into account in inclusion/non-inclusion criteria of clinical studies, which may introduce a bias or at least an increased variability.

3. Chronopharmacology of hypertension

Circadian fluctuations in blood pressure (BP) with higher daytime than night time values have been established in both normotensive and hypertensive patients. Bed-bound subjects, either normal or hypertensive, and patients with fixed heart rate still show a significant nocturnal decline in BP, which remains unaltered by antihypertensive therapy. The circadian rhythm of uncomplicated essential hypertensive patients is set at higher BP levels, but has the same circadian time pattern as in normal subjects. Drug treatment of hypertension includes various types of drugs such as diuretics, beta and alpha adrenoceptor blocking drugs, calcium channel blockers, converting enzyme inhibitors, AT1-receptor blockers and all of which differ in their sites of action as well as in half-life, pharmaceutical formulations and, thus, in dosing interval. The typical circadian pattern of BP exhibits two daytime peaks (around 09:00 hours and 19:00 hours, respectively), a small afternoon nadir (around 15:00 hours) and a profound nocturnal drop (around 03:00 hours). The amplitude of the 24-h variation is slightly larger for diastolic than for systolic BP, ranging between 10% and 20% of the daytime mean. This blood pressure pattern is modified by age: In elderly patients the amplitudes of systolic BP and heart rate are reduced, a greater ultradian component (12-h period) is present and the secondary afternoon decline is more prominent than in young patients. A decreased nightly drop in BP of elderly male patients was also observed by Imai *et al*., 1993. Before awakening, a significant increase in BP was originally found by Millar Craig *et al*., 1978; and questioned by Floras *et al*., 1978; and Littler *et al*., 1979; who believed that it was due to an averaging artefact. Reanalysis of the original work, however, confirmed the initial findings (Gould & Raevery, 1991). Over many years, the pre-waking rise was alternately denied and confirmed (Athanassiadis *et al*., 1969; Mancia *et al*., 1983; Degaute *et al*., 1991; Broadhurst *et al*., 1990). Recent intra-arterial data in a large group of normal subjects, aligned to the time of waking, show that the early morning rise in BP starts hours before awakening, so that its sole attribution to arousal seems highly unlikely (Broadhurst *et al*., 1990). Moreover, animal data using telemetry clearly gave evidence for a dominant endogenous component of the blood pressure rhythm under free-run conditions (Witte *et al*., 1993; Lemmer *et al*., 1995), also supported by experiments in which the suprachiasmatic nucleus was lesioned (Janssen *et al*., 1994; Witte *et al*., 1995).

Considerable evidence exists for the driving role of the sympathetic system on the circadian rhythm of BP. Intra-arterial studies on the effect of a variety of antihypertensive agents indicate that the morning rise (both before awakening and upon arousal) appears to be due to increased adrenoceptor activity (Gould & Raftery, 1991). Propranolol reduces the pressure range (difference between basal and maximum BP readings) in most patients and an inverse relationship can be demonstrated between changes in pressure range and noradrenaline (Gould & Raftery, 1991). The circadian rhythms of BP and sympathoadrenergic activity (catecholamine concentrations in plasma and urine, CAMP concentrations in plasma or in lymphocytes, and adrenoceptor density and affinity on lymphocytes) are synchronous both in normotensives and in patients with primary hypertension with normal circadian rhythm, and in abnormal catecholamine secretion with an abnormal circadian BP curve (Leeuw *et al*., 1977). The circadian variations of sympathoadrenal and pressure reactivity to exercise are strongly correlated. Spectral analysis of BP and inter-beat interval recordings provides markers of autonomic activity and arterial baroreflex sensitivity. Using this technique, a recent study demonstrated that a clear 24-h variation in sympathetic and vagal tone, but not in arterial baroreflex sensitivity, persists, independent of changes in activity and position (Hickey *et al*., 1993). In addition to the driving role of the autonomous nervous system, the circadian

pattern of BP is likely to be influenced by the circadian rhythmicity of the endogenous opioid system, the hypothalamic-pituitary hormonal axes, the renin-angiotensin-aldosterone system and the vasoactive peptides. Evidence in favour of this view comes from the study of many diverse pathological conditions in which the alterations in the circadian rhythm of the above-mentioned neurohumoral factors, either inherent or secondary to disturbances in autonomic nervous system activity, are reflected by consistent modifications of the 24-h pattern of BP. Reduced or reversed nocturnal decline in BP has been reported with the following conditions: orthostatic autonomic failure (Borne *et al*., 1994); Shy-Drager syndrome (Mann *et al*., 1983), brainstem infarct (Martinelli *et al*., 1981; Stoica *et al*., 1983; Shimada *et al*., 1992), neurogenic hypertension (Matsumura *et al*., 1993), fatal familial insomnia (Franklin *et al*., 1986) and diabetes (Portaluppi *et al*., 1994; Hornung *et al*., 1989).

4. Twenty four hour blood pressure profile

The typical circadian pattern of BP exhibits two daytime peaks (around 9 AM and 7 PM. respectively), a small afternoon nadir (around 3 PM), and a profound nocturnal drop (around 3 AM) (Wiegmann *et al*., 1990). Though the BP level is higher in uncomplicated essential hypertensive patients, the circadian pattern is about the same as in normotensive subjects. Recent intraarterial data in normal subjects confirm that the early morning rise in BP begins hours before awakening, so that its sole attribution to arousal seems highly unlikely. Moreover, telemetric data in normotensive and hypertensive rats clearly gave evidence for a dominant endogenous component of BP rhythm under free-run condition. In hypertensive patients mainly with secondary hypertension due, for example, to chronic renal failure, diabetes, Cushing's syndrome, exogenous glucocorticoid administration, renal and cardiac transplantation, and fatal familiar insomnia and in hypertensive pregnancies the nightly decrease in BP is reduced/abolished or even higher levels arc found at night. The loss of a nocturnal BP fall is likely to determine a higher cardiovascular and cerebral risk correlating with an increased damage to target organs such as the heart, brain, and kidneys. This could indicate that restoration of a normal circadian BP pattern is likely to be of prognostic relevance and should be regarded as an additional therapeutic goal in antihypertensive drug treatment.

5. Antihypertensive drug treatment

Drug treatment of hypertension includes different types of drugs such as diuretics, beta and alpha adrenoceptor blocking drugs, calcium channel blockers, and converting enzyme inhibitors. There are many studies on the effects of various antihypertensive drugs on the 24-hour BP profile (Halberg, 1969; Idema *et al*., 1992; Stanton *et al*., 1992). In most studies, however, time of day of drug application was not a specific point of investigation. Since the drug's mechanisms of action and its target tissues, its half-life, galenic formulation as well as the circadian time of drug dosing may influence the degree and duration of the BP-lowering effect, it is difficult to draw final conclusions about the clinical importance of circadian time-dependent drug dosing. This issue can only be adequately addressed by cross-over studies comparing morning and evening drug dosing. The few data available on this aspect will mainly be considered in this review (Steitberg *et al*., 1989; Germano *et al*., 1984; Mattes *et al*., 1991; Witte *et al*., 1992; Staessen *et al*., 1993; Anlauf *et al*., 1993; Sheps *et al*., 1994).

Ambulatory blood pressure monitoring (ABPM) is now generally regarded as the method of choice in evaluating BP profiles, and guidelines have been published (Lemmer & Portaluppi, 1996). However, the method of analyzing a set of 60-80 ABPM data is of additional importance. Profiles were generally compared by visual inspection, or only mean values for the whole 24-hour period or the daytime and night time periods were taken into account. Both procedures are unable to detect subtle disturbances in the circadian profile. Different types of rhythm analyses seem to produce better results (Mengten *et al*., 1992). Using Fourier series, 34 fitting to the individual data seems to be advantageous.

In order to compare adequately the results obtained mainly by ambulatory BP-monitoring (ABPM) devices, the method of analysing the 24-h BP profile consisting of 30-80 data points within 24 h is also of importance. BP profiles were mostly compared by visual inspection, which is not able to detect subtle disturbances in the circadian profile. Less frequently, comparison of mean daytime versus mean night-time values has been carried out using the cosinor method according to Halberg (Fogari *et al*., 1993), square wave-fit method (Portaluppi *et al*., 1995), cumulative sums method (Greminger *et al*., 1994) and spline functions (Umeda *et al*., 1994). Recently analyses by non-linear partial Fourier series were introduced which take into account the multiphasic and asymmetrical profiles of BP and HR in individual patients as well as in grouped patients (Palatini *et al*., 1993; Midekke *et al*., 1991; Witte *et al*., 1993; Palatini *et al*., 1992; Anlauf *et al*., 1993; Sheps *et al*., 1994). Moreover, one of the methods combines linear and rhythm analyses by partial Fourier series, including calculation of the area under the curve (AUC), slope and statistical evaluations (Lemmer & Portaluppi, 1996). In general, it is important to note that ABPM is now regarded as the method of choice to evaluate BP profiles, and guidelines have been published (Rafteny, 1983; Gould & Raftery, 1991).

5.1. Beta-adrenoceptor antagonists

Beta-adrenoceptor antagonists inhibit sympathetic nervous system function in organs supplied with beta adrenoceptors such as the heart, kidneys, and smooth muscles of the blood vessels and bronchi. Of great therapeutic importance is the decrease in heart rate, cardiac output, and cardiac oxygen consumption and the inhibition of renin release. Concerning the circadian phase-dependency of the BP lowering effect of beta adrenoceptor antagonists in hypertensive patients, final conclusions are difficult to draw, because neither cross-over (morning versus evening) nor equieffective dose studies have been published. A resume of about 20 studies (Stanton, 1992) shows that beta adrenoceptor antagonists, either selective or nonselective, with intrinsic agonist activity, do not either affect, reduce, or

even abolish the rhythmic pattern in BP. However, there is a general tendency for adrenoceptor antagonists not to greatly affect night time values and to be less effective in reducing the early morning rise in BP" (Quyyumi *et al*., 1984; Langner & Lemmek, 1988). Drugs with partial agonist activity, mainly pindolol, evenincrease heart rate at night (Koopmans *et al*., 1993). Decreases in heart rate by propranolol and oxprenolol are also more pronounced during daytime hours (Gould *et al*., 1982a; Gould *et al*., 1982b).

The circadian phase dependency in the dose-response relationship of antihypertensive subjects including beta adrenoceptor antagonists will be discussed. In conclusion, clinical data indicate that beta adrenoceptor mediated regulation of BP dominates during daytime hours and is of minor importance during the night and early morning hours. This correlates well with circadian rhythm in sympathetic tone as indicated by the rhythm in plasma noradrenalin and CAMP (Mengten *et al*., 1992).

5.2. Calcium channel blockers

Inhibition of calcium influx relaxes arterial smooth muscle, leading to vasodilatation mainly of the arteries. At the site of the heart this results in a negative inotropic effect. Coronary artery tone is reduced and vasospasms are attenuated, which is important in variant angina. With all calcium channel blockers vasodilatation occurs at lower concentrations than do the cardiodepressant effects. However, the difference between vasodilating and cardiodepressant effects is greater with the 1,4-dihydropyridines (e.g., nifedipine, nitrendipine, isradipine, and amlodipine) than with the verapamil and diltiazemlike compounds. Thus, nifedipine like compounds may lead to a reflexly induced increase in heart rate.

Studies with calcium channel blockers were also analyzed mainly by visual inspection of BP profiles or by linear analysis. In primary hypertensive subjects, three times daily dosing of nonretarded verapamil did not greatly change the BP profile, being, however, less effective at night (Caruana *et al*., 1987; Lemmer *et al*., 1994b). A single morning dose of sustained-release verapamil showed good 24-hour BP control (Lemmer *et al*., 1991) whereas a sustained-release formulation of diltiazem was less effective at night.Dihydropyridine derivatives seem to reduce blood pressure to a varying degree during the day and at night (Portaluppi *et al*., 1995); differences in half-life, drug formulation, and dosing interval may play a role. Seven studies using a cross-over morning versus evening design have been reported. In essential hypertensive subjects amlodipine, isradipine, and nifedipine GITS (gastrointestinal therapeutic system) and in normotensive subjects immediate-release nifedipine did not affect the BP profile differently after once morning or once evening dosing, whereas in two studies with nitrendipine the profile was either preserved or disturbed after evening dosing. In primary hypertensive patients twice daily nifedipine lowered BP throughout a 24-hour period (Raftery *et al*., 1981). Most interestingly, the disturbed BP profile (nondippers) in secondary hypertensive subjects due to renal failure was only normalized after evening but not after morning dosing of isradipine. In conclusion, the effect of calcium channel blockers on the 24-hour BP profile of primary hypertensive patients greatly depends on the type of calcium channel blocker. Cross-over studies of morning versus evening dosing were presented only for dihydropyridines.

5.3. Converting enzyme inhibitors

These drugs are competitive inhibitors of the converting enzyme by which they reduce the conversion of angiotensin-I into angiotensin-II in plasma and tissues. Angiotensin-I is a highly potent vasoconstrictor. Degradation of the vasodilating substance bradykinin is also reduced. Converting enzyme inhibitors reduce peripheral resistance, the formation of aldosterone, and aldosterone-mediated retention of water and sodium. Converting enzyme inhibitors not only are effective antihypertensive drugs but also can increase the life expectancy in congestive heart failure. Several studies with converting enzyme inhibitors, given once in the morning or twice daily, showed that these drugs did not greatly modify the 24-hour BP pattern. However, intraarterial studies with enalapril or ramipril showed that while causing sustained daytime reduction in BP, these drugs had only marginal effects on nighttime pressures (Langner *et al*., 1988). Thus, the findings obtained with converting enzyme inhibitors in conventional clinical studies are not equivocal. Four cross-over studies (single morning versus single evening dosing) with converting enzyme inhibitors in essential hypertensive patients were reported. They demonstrated that evening dosing of benazepril and enalapril changed the BP profile, resulting in a more pronounced nightly decrease which was even observed after a 3-week single dose evening treatment with enalapril. After chronic treatment with quinapril, evening dosing also resulted in a more pronounced effect than did morning dosing; the BP pattern, however, was not greatly modified. A fixed combination of captopril and the diuretic hydrochlorothiazide only slightly reduced BP after both morning and evening dosing; the latter treatment, however, was less effective on the next day.

5.4. Other antihypertensive drugs

Antihypertensives of other classes have rarely been studied in relation to possible circadian variation. Interestingly, once-daily morning dosing of the diuretics xipamide (Could *et al*., 1981) and indapamide (Weber *et al*., 1987) reduced BP in essential hypertensive subjects without changing the 24-hour BP pattern. On twice-daily dosing the alpha adrenoceptor antagonist's indoramin (Pickering *et al*., 1994) and prazosin (Panza *et al*., 1991) also did not change the BP profile. Recently, Pickering and his colleagues (1994), reported that a single nighttime dose of the a-adrenoceptor antagonist doxazosin reduced both systolic and diastolic BP throughout the day and night, but that the greatest reduction occurred in the morning hours. Because alpha adrenoceptor blockade more effectively reduced peripheral resistance during the early morning hours than at other times of the day, these findings point to the importance of alpha adrenoceptor-mediated regulation of BP during this time of day.

6. Conclusion

The studies on the effects of various antihypertensive drugs belonging to different drug classes indicate that different

mechanisms of regulation of the 24-h BP pattern may predominate at certain times of the 24-h day. It would, therefore, be surprising if antihypertensives did not affect the 24-h BP profile differently. In line with this is the observation that a drug's pharmacokinetics may not predict its treatment profile, mainly when considering the correlation between time-to-peak drug concentration (t_{max}) with time-to-peak drug effect (T_{max}). This again supports the notion that circadian variations in the regulatory mechanisms of the BP have an important impact on the drug effect. This is also supported by animal data obtained from five strains of normotensive and hypertensive rats in which the long-acting calcium channel blocker amlodipine, the rx-adrenoceptor antagonist doxazosin and the converting enzyme inhibitor enalapril differed greatly in their efficacy and their dose and circadian phase dependency of their BP-lowering effects as evaluated in unrestrained rats by telemetry. In general, it can be concluded that in uncomplicated, essential hypertensive patients or those who show a nightly drop in BP (dippers) antihypertensive drugs should be given in the morning. Whether the cardiovascular risk during the morning hours is decreased by evening dosing of an adrenoceptor antagonist needs additional confirmation. In secondary hypertension (or in non-dippers) evening dosing may be advantageous in better normalizing the disturbed BP pattern. Possible chronokinetics seem to be of less importance for drug efficacy, with the exception that peak drug effects are often correlated with side effects.

Conflict of interest

Authors report no conflict of interest.

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