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Review Article

Chronobiology of hypertension and its chronotherapeutical management - A review

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ABSTRACT

Hypertension / High blood pressure is a very common disease and is a major risk factor for total organ failure, cardiovascular diseases (CVD) and premature death around worldwide. Prevalence of hypertension varies across regions and country and is dramatically variable in presentation. Sometimes it act as a silent killer i.e. the patients are unaware that they have the condition. According to estimation 46.5% of adults are unaware about their hypertensive condition, 36.9% are diagnosed and treated and the remaining 13.8% with hypertension have it under control. The investigation regarding the chronobiology, chronotherapy and chronopharmacology in treatment of hypertension began a long back ago. Hypertension is a lifestyle disease largely exhibit circadian variation. Also the condition is more evident to surge during early morning hours. Hence this requires chronotherapy. The chronobiology of hypertension along with its treatment in relation to the circadian variation is reviewed in this article.

1. Introduction

Hypertension or chronic elevation of blood pressure BP is a serious medical condition that can lead to severe complications and escalate the risk of heart diseases, stroke. Sometimes it can be fatal. Excessive calorie intake, stress, dormant lifestyle are the major factors that contribute to the growing prevalence of hypertension around the world. BP is a silent killer and its progression occurs asymptomatically. [1]

Hypertension exhibits circadian variation and this contribute to the increase of acute cardiovascular events that rise in early morning hours. The occurrence of these events can be prevented by reducing the morning rise in BP. Thus; there is the implication of chronotherapeutics in hypertensive management.

Chronotherapy refers to the application of circadian, infradian, seasonal or rhythmic cycles in the management of a medical condition. Circadian rhythm regulates various functions in human body like sleeping pattern, metabolism, physiology, hormone production etc. Those technologies that are designed as per the circadian behavior of diseases are referred to as pulsatile drug delivery technologies. The release pattern of these drugs is preferred in pulses only after the lag time (release free interval). [2]

Chronopharmaceutics is a branch of pharmaceutics and the development of a chronopharmaceutics drug delivery system includes the application of human chronobiology and the circadian rhythm dependency of various disease conditions and the pharmacodynamics of medications. Chronopharmacology is a science that deals with the optimization of drug effects along with minimization of side effects by tailoring dosage timing based on the biological rhythm.

2. Chronobiology of Hypertension

Chronobiology is a branch of biology dealing with biological rhythms, i.e. the time related periodic (cyclic)

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phenomena in living organisms. Circadian rhythms, ultradian rhythms and ultradian rhythms are the examples of biological rhythms. These are the cyclic patterns that are driven by the biological clock in living organisms. Biological clocks helps to regulate biochemical and physiological activities like sleep wake cycle, pattern of hormone secretion, body temperature, blood pressure, digestive secretion etc.

Blood pressure in normal and hypertensive subjects exhibits circadian variation with minimal level during sleeping hours. Both normotensive and hypertensive patients have higher heart rate and blood pressure during morning hours. This inclination is basically due to the decrease in sympathetic output occurring at bed time. By morning when the individual wakes up have a rapid rise in both systolic blood pressure (SBP) 20-25mmHg ,and diastolic blood pressure (DBP) 10-15mmHg.[1] In CVD, the capillary resistance and the vascular reactivity are higher in early morning and then declines slowly during the day time. Increase in platelet aggregation and decrease in fibrinolytic activity at morning leads to hypercoagulability of blood. Also the BP reduction during sleep cycle and steep rise early morning awakening time. This shows the risk of myocardial ischemia, acute myocardial infarction, angina pectoris, cardiac failure and sudden cardiac arrest are unevenly distributed throughout 24 hour with higher expectancy during first hours of morning or in the late afternoon.

Different forms of hypertension vary with their difference in circadian behavior. Normotensive as well as hypertensive patients experience a night drop in BP, so they are known as dippers while secondary hypertensive patients are non dippers. Their rhythm of BP is about 70% of cases abolished /reversed with high values at night.[1] Expert studies reported that the risk of heart attack and cardiac death are greater between 6.00 am and 12.00 noon.[3] At the same time Prinzmetal angina and congestive heart failure symptoms occur mostly during sleeping hours. Thus indicates the prognostic value for Ambulatory Blood Pressure Monitoring (ABPM).[1]

Nocturnal hypertension can pave the way for cognitive dysfunction, chronic kidney disease and endothelial dysfunction. BP reduction during night time is often neglected but it should be considered to reduce cardiovascular disease, especially in patients who are already under antihypertensive drugs. Patients with chronic angina typically experience a surge in BP on ABPM, which is followed by episodes of silent ischemia which is clinically demonstrated by ST-segment depression. These events occur strongly during first 3-4 hours of day time. The clinical manifestation of ST-segment elevation in prinzmetal angina occurs frequently during middle half of the night time. The electrocardiogram, ECG recordings of coronary infarction, angina attacks are unevenly distributed over 24 hour span of a day with a peak in early morning period. Moreover the cardiovascular events especially primary and secondary hypertension exerts different symptoms throughout the 24 hour span. In recent years, there was a numerous development of novel devices to continuously monitor BP and heart rate in humans. These ABPM devices not only monitor BP level but also the influence of drugs in BP rhythm depending on time of drug dosing.

2.1. *Chronotherapy of hypertension*

Many antihypertensive can't control the early morning rise in blood pressure with once daily morning dose. Hermida et al, studied the impact of antihypertensive drugs and the treatment time on the circadian pattern of BP in 585 hypertensive patients with diabetes mellitus.[4] BP was measured at 20 min intervals from 07:00 to 23:00 h and at 30 min intervals at night for 48 consecutive hour. Blood pressure was reduced during diurnally active hour, but not during night time sleep, as compared to untreated patients ($P<0.001$).This study demonstrate the importance to establish a proper chronotherapeutic scheme that could reduce BP and modify the distorted circadian profile into a dipper pattern. Konga et al conducted a chronotherapeutic test with β – blockers in order to prevent the morning escalation of hypertension with evening dose of carvedilol. They treated 12 males and 5 female hypertensive patients for 4 weeks at controlled blood pressure. Patients exceeding BP 140/90 mmHg were treated with 10 mg/day single evening dose of carvedilol. The study results showed that the morning surge in BP was suppressed and 24 hour mean systolic pressure was also reduced with carvedilol.[5]

2.2. *Chronopharmacology of antihypertensive drugs*

Management of hypertension include various types of drugs like calcium channel blockers, Angiotensin converting enzyme inhibitors (ACEI), Angiotensin II receptor blockers. β and α adrenoreceptor blocking agents, diuretics and so on. Antihypertensive drugs exhibit circadian behavior in their pharmacokinetic activities as the BP regulation is always circadian phase dependent.

2.3. β – *Adrenoreceptor blockers*

A conventionally performed studies showed that β adrenoreceptor antagonist do not affect / reduce the rhythmic pattern of BP. A fourfold crossover study in healthy subjects with propranolol shows a pronounced decrease in both heart rate and BP during day time than at night. The study also reveals that the dose – response relationship can be circadian phase dependent.

Thus, clinical data obtained from various studies indicate that the β-adrenoreceptor blocking agents regulate BP during day time and are less or no prominence during night and early morning hours. This can correlates well with

sympathetic tone of circadian rhythm as indicated by the rhythm in Camp and plasma noradrenaline.

2.4. ACE Inhibitors

Various crossover studies, morning vs. evening dosing with ACE inhibitors in essential hypertensive patients demonstrated that in dippers evening dosage of benazepril, enalapril, peridopril, quinapril shows more nightly drop than morning dosage. Investigation with trandolapril found that bed time administration of this can be considered as safe and effective in morning BP regulation without an excessive reduction in nocturnal BP.

Spirapril, an ACE inhibitor with extended duration of action also studied in hypertensive management. Their efficacy was found to be higher with morning dose as compared with bed time dosing. [6]

2.5. Calcium channel blockers

Studies in primary hypertensives shown that a 3 time daily dosing of non retarded verapamil did not cause any considerable changes in BP profile but slightly effective at night whereas a single morning dose of sustained release varapamil showed an excellent 24 hour BP control. [7] The crossover studies in essential hypertensives with dihydropyridine derivatives (DHP) did not differently affect the BP profile after once morning/once evening dose.

The dosing time of drugs will be different in case of both primary and secondary hypertension i.e. drugs should be given at early morning hours whereas an additional evening dose should be there in secondary hypertensives. This got better evidence from the study with isradipine. In secondary hypertensives (non dipper) due to renal failure, there will be a great disturbance in BP. This was only got normalized after evening dosing of isradipine whereas amlodipine and nisoldipine, normalized the disturbed BP profile after both morning and evening dosing.

All those studies finally demonstrated that calcium channel blockers can lower the high BP in both dippers and non dippers without disturbing the normal BP profile and can also transform non dipping behavior to a dipping one. Evening time dosing could be more preferable here. [8,9]

2.6. Angiotensin II receptor blockers

Angiotensin II receptor blockers selectively and specifically block the angiotensin II which is a potent vasoconstrictor, resulting in BP regulation. They are very effective and well tolerated hence increasing their demand in treatment of hypertension. A study was conducted by ingesting ARB valsartan to stage 1 or 2 essential hypertensives for 3 months either in morning just after the night sleep or at bed time. Interestingly; the BP reduction was similar for both treatment times. The diurnal/nocturnal BP ratio was found to be increased by 6% upon its bed time administration. Another study with valsartan monotherapy either on morning or at bed time showed significant BP reduction after 3 months of treatment, independent of dosing time. This reduction was slightly greater with bed time dosing than with morning dose.

2.7. Diuretics

A study was performed with diuretics in both dippers and non dippers and the study demonstrated that diuretics are not considered to affect the normal circadian BP profile in dippers but it can transform non dippers into dipping one.Xipamide and indapamide reduced the BP in essential hypertensives without distorting the 24 hour BP pattern, with their once in daily morning dose. [10] Study with torsemide, ingested either upon awakening in morning / at bed time showed that the BP reduction was significantly greater with bedtime dosing.

2.8. α – Adrenoreceptor antagonists.

Twice daily dosing of indoramide and prazosin did not change BP profile. Night time dosing of doxazosin reduced both systolic and diastolic BP throughout day and night but more prominent reduction occurred in morning hours. A recent study in dippers with retard formulation of doxazosin, doxazosin GITS showed a significant reduction in BP throughout 24 hour even without changing normal BP profile.

α – adrenoreceptor blockade found to reduce the peripheral resistance more effectively during early morning than all other times of the day. Hence this proved the importance of α adrenoreptor mediated BP regulation at early morning hours. Another study was conducted to evaluate the effect of nebivolol on 24 hour BP profile. The tests were carried out in two different treatment times, upon awakening and at bed time. The efficacy was found to be more pronounced on diurnal than nocturnal BP in both times. However reductions in diurnal/nocturnal BP ratio were greater when it was administered upon awakening. The non dipping prevalence remained unchanged with bedtime dosing schedule but got doubled with morning time dosage schedule. This suggested that the optimum dosage time for nebivolol is on bed time, so that it can avoid the drug efficacy loss during 24 hour interval.

3. Chronopharmacokinetics

Kinetics of cardiovascular agents surely dependent on time of the day. Evidents got from various studies shown that cardiovascular agents like propranolol, oral nitrates, and calcium channel blocker nifedipine showed high C_{max} and shorter t_{max} after morning than evening oral dose, when non retarded formulation is used. There will be no circadian phase dependency in pharmacokinetics of retarded formulation like IS-5-MN and nifedipine. Also, kinetics

of sustained release molsidomine or hydrophilic β blocker atenelol was also found to be circadian time independent.

A faster gastric emptying time and high gastrointestinal perfusion in morning than evening time is responsible for the chronokinetic behavior of these lipophilic compounds.

4. Duration of Antihypertensive Effect

Duration of drug action can be evaluated by using ABPM. This is performed for a duration of 24 hour span. ABPM is restricted to 24 hours so that it may cause potential pitfalls. A 4 week treatment with β_1 selective adrenoreceptor blocking agent bisoprolol in hypertensive patients showed that the duration persisted up to 48 hour after the therapy halted. Chronic morning usage of atenelol will not exhibit BP lowering effect 20-24h after the last dose. However ABPM being continued for 48hr will reduce the BP again on next day of therapy. A 3 week treatment with ACE inhibitor enalapril also shown similar effect, when BP profile was monitored for 48 h after the last dose. On the contrary, the duration of antihypertensive effect of 3 week treatment with a sustained release diltiazem was restricted to 18 hours when BP was monitored for 48 hours after the last dose by ABPM. These data showed that the conventional method to estimate the duration of action of an antihypertensive agent by the peak – to – trough ratio within 24 h can be misleading. The peak to trough ratio does not take account the fact that the mechanism of BP rhythm regulation predominate at certain times of day. For example, β adrenergic tone is higher during day time than at night. The vascular tone is higher in morning and then decreases which leads to a pronounced peripheral resistance reduction by α adrenoreceptor blocker phentolamine in morning than other times of the day. Consequently, it may be useful not to restrict ABPM to a 24 hour period in order to skip false conclusions about the duration of an antihypertensive effect.

4.1. Chronotherapy in resistant hypertension

In spite of the continuous use of optimal dose of three antihypertensive agents including diuretics and lifestyle changes, the BP level remains above 140/90mmHg.This condition can be referred to as resistant hypertension. These patients are at great risk for stroke, renal insufficiency and morbid cardiovascular events. The resistant hypertension can be treated with nonpharmacological and pharmacological approach. A study with conventional antihypertensive therapy in 28 hypertensives. The ABPM was performed weekly to see whether the patient was cured by the therapy. The result by the end of sixth week showed that no case remained resistant to the antihypertensive chronotherapy, suggests that combination of ABPM with chronotherapy is highly recommended in case of resistant hypertension.

4.2. List of marketed chronotherapeutical antihypertensive medications

The calcium channel blocker (CCB) controlled onset, extended release (COER)-verapamil was the first designed special drug delivery tablet for the chronotherapy of hypertension. The drug delivery mechanism of the specially designed COER-verapamil tablet delays the release of verapamil for about 4-5 hours after the bedtime administration. CODAS-verapamil i.e. the chronotherapeutic oral drug absorption system is the second special drug delivery system. This was approved by FDA in 1999. These are recommended to administrate during bed time. The verapamil release from the polymer coated beads of this capsule is delayed for approximately 4 hour. Graded release long acting diltiazem (cardizem LA) was approved by FDA in 2003 for daily dosing either in morning or evening. Innopran XL™ which is the β antagonist propranolol chronotherapy got approval in 2003 by the FDA. The list of few marketed chronotherapeutical formulation are given in table 1.

Table 1: List of marketed chronotherapeutic antihypertensive formulations.

Generic names	Brand names	Manufacturer
Verapamil HCl	Covera-HS® extended release tablet	Searle Pharmaceuticals
Verapamil HCl	Verelan® PM extended release capsules	Schwarz Pharma
Nifedipine	ADALAT GITS	Bayer
Propranolol HCl	Innopran® XL	Reliant Pharmaceuticals
Diltiazem HCl	Cardizem® LA	Biovail Pharmaceuticals
Diltiazem HCl	Cartia XT	Andrx Laboratories

5. Conclusion

Blood pressure and heart rate are well synchronized with time. A disease or a medical condition is able to disturb, reverse, or distort the rhythmic pattern. Various study results revealed the ability of night: day ratio of systolic blood pressure to predict the risk of cardiovascular diseases. Nocturnal BP are more predominantly correlated to cardiovascular events so that it need more close surveillance for the safety of patients.

Various drugs like propranolol, oral nitrates and calcium channel blockers CCB are generally absorbed by passive diffusion and they exhibit high peak plasma drug concentration C_{max} and t_{max}. This is due to faster gastric emptying time and higher gastrointestinal perfusion in the morning. This is responsible for the chronokinetics of these

cardiovascular agents.

In hypertensive dippers, antihypertensive drugs should be given during early morning hours. Whereas in non dippers, it is necessary to add an evening dose not only to reduce BP but also to normalize the distorted 24 hour BP profile. Recent studies clearly depicted that the kinetics of cardiovascular agents is circadian phase dependent. Anyway; circadian disorder such as hypertension strongly requires chronopharmacotherapy. There will be a great scope for development of chronopharmaceutical formulation not only for CVD but also for other disease that exhibit circadian behavior.

6. Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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