www.ijrps.pharmascope.org

ISSN: 0975-7538
Review Article

Chronotherapeutics: An advanced approach to decrease the mortality in cardiovascular events

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ABSTRACT

Chronobiology is the technical study of biologic rhythms and their fundamental mechanisms. Chronotherapeutics is defined as a treatment system where the in vivo drug availability has been timed in accordance to cyclic rhythms of drug related biological phenomena to create maximum benefit minimizing harm. A highly significant circadian variation was observed with many adverse cardiovascular events in human body. The increased frequency of cardiovascular events in the early morning is related to factors that activate increased myocardial oxygen demand and also in chorus to reduction of oxygen supply. Blood pressure is not steady over a 24-hour period and also it is fluctuating according to a circadian pattern. There is a high increase in incidence of mortality cases with cardiovascular events these days. Now a days, new chronotherapeutic antihypertensive products proving their success with decrease in mortality with cardiovascular events.

Keywords: Chronotherapeutics; Chronobiology; cardiovascular events; antihypertensive agents.

INTRODUCTION

For centuries, the biological rhythms of the human body and their association to conventional environmental cycles have been studied. It has been reproved by ancient healers that, to be successful, treatment had to be offered with regard for various external and internal cycles.

A biological rhythm is a self-sustaining process inside the human body. It is defined as the process that occurs periodically in an organism in conjunction with and often in response to periodic changes in environmental condition.

Biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours. Term *Circadian* is derived from the Latin term *circa* meaning “about" and *dies* which is derived from "a day". (Lamberg L, et al., 1991) Also, each term indicating an oscillation period of time, Table 1 shows the various measurement of biological rhythm.

An inherited master clock network composed of the paired suprachiasmatic nuclei (SCN) controls circadian rhythms. These are placed in the hypothalamus and the pineal gland of the human brain (Maronde E et al., 2007). Orchestration the period and phase of the amplitude peripheral circadian clocks positioned in cells, tissues, and organ systems is called the master clock (Kalsbeek A et al., 2006). Figure 1 depicts human circadian time structure.

Chronobiology

Chronobiology is the technical study of biologic rhythms and their fundamental mechanisms (Smolensky et al., 1993). So it is the formal study of biological temporal rhythms like tidal, annual, seasonal, weekly and daily rhythms. It was introduced into clinical as well as laboratory medicine in the 1950s for the purpose of disease prevention. The term "Chrono" pertains to time and "Biology" is the science of life, thus, chronobiology concerns with the observation of every metabolic event goes through rhythmic changes in time that can be measured from seconds to seasons (Lamberg et al., 1991). Typical examples are levels of plasma testosterone and cortisol, which typically peak in the early morning, and the secretion of growth hormone, which peaks during sleep. Applying this science could help in prevention and/or early diagnosis and treatment of diseases, and consequently, reduction in the overall health care costs (Moore et al., 1991).

Chronopharmacology

Chronopharmacology is the examination of drug effects in the basis of biologic timing and rhythm attributes. In addition, it includes the study of the time-dependent dosing of pharmacologic agents. Chronopharmacology also considers the particular chronobio-

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Received on: 17-03-2011
Revised on: 22-03-2011
Accepted on: 23-03-2011

tics, which are agents that can control biologic rhythms (Clench et al., 1981).

Table 1: The various measurements of biological rhythm (Smolensky M.H, et al., 1993)

Period (τ)	Main rhythmic components
Short period [τ<0.5h]	S<τ<1 s
Intermediate period [0.5h<τ<6 days]	Circadian (20h<τ<28h) Ultradian (0.5h<τ<20h) Infradian (28h<τ<6 days)
Long period [τ>6 days]	Circamensual (τ~30 days) Circaseptan (τ~7days) Circannual (τ~1 year)

Chronopharmacokinetic

Studies have been reported for many drugs in an attempt to explain chronopharmacological phenomena and demonstrate that the time of administration is a possible factor in variation of the pharmacokinetics of a drug. Different pharmacokinetics constraints of time like elimination rate, peak concentration, volume of distribution, and AUC of a number of drugs are affected by circadian rhythms (Lemmer et al., 1994).

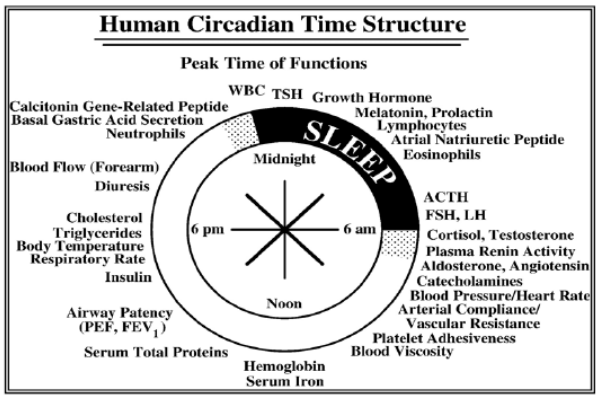


Figure 1: Human Circadian time structure (Kalsbeek A et al., 2006)

Chronodynamics

Relates to the dosing-time, which could be expressed as rhythm-dependent, under the divergences in the effects of drugs. The variations in drug effect are associated with varying the time of administration which attributed to the rhythms in the free-to-bound drug fraction, drug-specific receptor numbers and conformations, rate limiting step(s) in metabolic pathways, and second messenger and ion channel dynamics (Lemmer et al., 1994).

CHRONOTHERAPEUTICS

It refers to the clinical practice of harmonizing delivery of the drug in accordance with body's circadian rhythm including ailment states to create maximum benefit and minimizing harm (Smolensky et al., 1997). Biological rhythms at the cellular and sub cellular level can give rise to significant dosing-time differences in the pharmacodynamics of medications that are unrelated to their pharmacokinetics. This phenomenon is termed chronesthesy. Rhythms in receptor number or conformation, second messengers, metabolic pathways, or free-to-bound fraction of medications help to explain this phenomenon.

Chronotherapeutics is defined as a treatment system where the in vivo drug availability has been timed in accordance to cyclic rhythms of drug related biological phenomena to create maximum benefit minimizing harm. Important determinants in chronotherapeutics include (Traynor et al., 1992):

1. Chronopathology or disease pathophysiology.
2. Period, amplitude, phase and level of the human circadian time structure to find out the dose, drug-delivery pattern and administration time.
3. Chronopharmacology including chronotoxicology, chronokinetics, chronoesthesy and chronodynamics of drugs.

Chronotherapeutics clinical studies overview

Chronotherapeutics also grant new challenges for scientists and also regulators. As for an instance, according to FDA, chronotherapeutic clinical studies need more additional parameters, which are not applied for other clinical trials including (FDA Consumer magazine., April 1997):

• Drug administration time of the day.

• Patients' normal habits and sleep patterns.

• Biological factors which are time-related, like seasonal disorders.

According to the 1996 American Medical Association review, more consideration of chronotherapy in clinical trials is highly welcomed by the whole medical community. The results of a survey showed that 75 percent of the doctors are in favor of more patient's circadian, or daily rhythm oriented treatment (Stehlin et al., 1997).

CHRONOTHERAPY FOR CARDIOVASCULAR DISEASES

Hypertension is a common chronic condition affecting up to 35% of human adults (W.B Kannel et al., 1969). This condition is an important risk factor for strokes, heart attacks and other vascular and renal diseases. Pharmacologic treatment of high blood pressure (BP) reduces the incidence of these complications and prolongs life.

A highly significant circadian variation was observed with many adverse cardiovascular events in human body. It was concluded from 30 studies in 66,635 patients that timing of acute myocardial infarction was definite. A forty percent increase in risk of myocardial infarction between 6 am and noon was found. Also studies involving 19,390 patients found an increase in sudden cardiac death by 29% during the early-morning

hours, and increase in stroke risk by 49% between 6 am and noon.

The increased frequency of cardiovascular events in the early morning is related to factors that activate increased myocardial oxygen demand and also in chorus to reduction of oxygen supply. Blood pressure is not steady over a 24-hour period and also it is fluctuating according to a circadian pattern. Lorgelly and colleagues (2003) stated that blood pressure was soaring in the morning, with a rise at about 6 am and increasing further from 7 am. Blood pressure reaching its lowest point around 3 am by gradual declination throughout the day and especially during sleep. This is due to many factors like the time of awakening, an increase in physical activity, serum cortisol level and catecholamine levels which all increases blood pressure, heart rate and myocardial contractility. A pathophysiologic explanation for the myocardial infarction, sudden cardiac death and angina pectoris in the early-morning hours is explained by the above factors (Lorgelly et al., 2003).

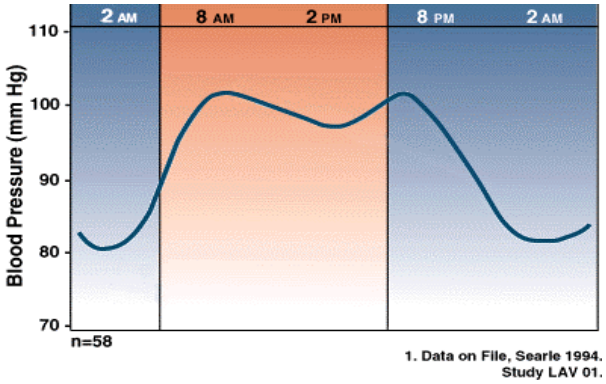


Figure 2: Graph showing the circadian rhythm of blood pressure (Evans et al., 1996)

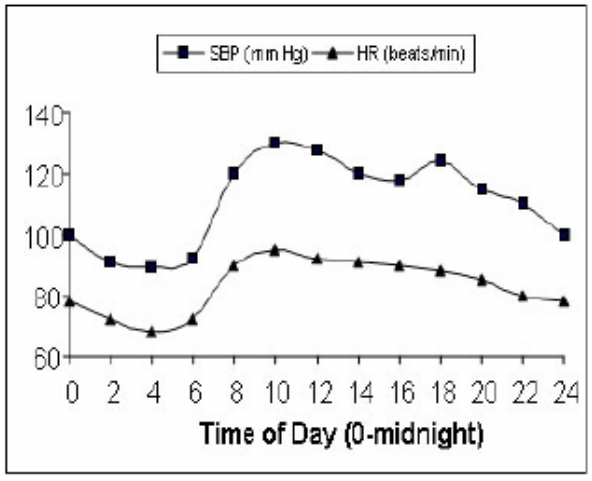
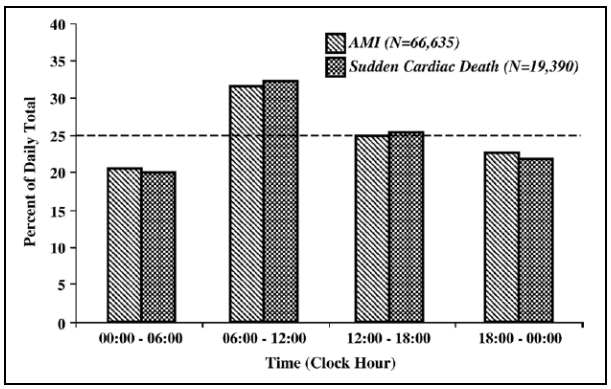


Figure 3: Schematic diagram of circadian variation in systolic blood pressure and heart rate.
(Mayank et al., 2010)

The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented. Medications have been formulated, and dosing schedules established, in an attempt to provide appropriate concentration of a drug in the target area of the body when the drug is most needed. For example, it has often been found that the blood pressure of a hypertensive patient increases rapidly in the morning after awakening, typically peaks in the middle to late time of the day, decreases in the evening, and is lowest while the patient sleeps at night (figure 2 and 3). It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening.



Note the single very prominent peak in both AMI and SCD between 6 a.m. and noon. Clock time along the x-axis expressed in military units: e.g., 10:00=10 a.m.; 16:00=4 p.m. Adapted from Cohen et al.

Figure 4: Time of day of 66,635 AMI and of 19,390 SCD events summarized according to the respective four 6-h intervals of the day and night.

Cohen et al, was carried out the Meta analysis of the morning excess of acute myocardial infarction and sudden cardiac death. They found that the incidence rate of Acute Myocardial Infraction (AMI) onset between 6 a.m. and noon was 40% (the relative risk being 1.38) higher than during the rest of the day in presumably diurnally active persons. Based on the metaanalysis, approximately one of every eleven AMIs was found to be attributable to the observed morning excess (Fig 4). (M.C Cohen et al., 1997)

Portaluppi et al, summarized the occurrence of Several types of common cardiac arrhythmias with predictable-in-time patterns (table 2). From the table 2 it was evident that arrhythmiasis is more prone during the morning hours. (Francesco et al., 2007)

Approved chronotherapeutic medications for treating the cardiovascular diseases

Currently, there are some antihypertensive products in the market that are chronotherapeutic medications with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon upon administration of medications at 10 pm. Some of these are listed in Table 3.

Table 2: Circadian onset patterns of arrhythmias (Francesco et al., 2007)

Arrhythmia	Major peak	Minor peak
Sinus tachycardia	6 a.m. – 12 p.m.	--
Atrial premature beats	6 a.m. – 12 p.m.	--
Atrial flutter	6 a.m. – 12 p.m.	--
Atrial fibrillation (adrenergically mediated)	6 a.m. – 12 p.m.	--
Atrial fibrillation (vagally mediated)	11 p.m. – 6 a.m.	2 p.m. – 4 p.m.
Premature supraventricular tachycardia	6 a.m. – 4 p.m.	6 p.m. – 12 a.m.
Ventricular premature beats	6 a.m. – 12 p.m.	--
Ventricular tachycardia	10 a.m. – 6 p.m.	--
Ventricular fibrillation	7 a.m. – 11 a.m.	4 a.m. – 8 p.m.
Atrio-ventricular block	6 a.m. – 12 p.m.	

Table 3: Some chronotherapeutic antihypertensive products (Cohen et al., 1997, Francesco et al., 2007, N.R. Cutler et al., 1995)

Product	Generic name		Manufacturer
InnoPran XL	Propranolol		GlaxoSmithKline, USA
Cardizem LA	Diltiazem		Biovail corporation, Canada
Veralan PM	Verapamil		Schwars Pharma, Germany
Covera HS	Verapamil		G. D. Searle, USA.

Calcium channel blocker chronomedications

Controlled-Onset, Extended-Release (COER)-Verapamil (USA: Covera HS™; other markets: Chronovera™) constituted the first special drug-delivery tablet IHD and hypertension chronotherapy (Cohen et al., 1997). It 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 CCB tablet medication delays the release of verapamil for approximately 4–5 h following the recommended bedtime ingestion. Medication is released thereafter so highest blood concentration is achieved in the morning between 6 and 10 a.m., with an elevated level sustained throughout diurnal activity. The half-life kinetics of verapamil results in a progressive decline of drug level in the evening and over night, so minimal concentration occurs during the first half of nighttime sleep, when the risk of myocardial ischemia (as well as HR and BP) is low. (Francesco et al., 2007)

Chronotherapeutic Oral Drug Absorption System (CODAS)- Verapamil: A second special drug-delivery CCB, CODAS-verapamil (Verelan PM™; Schwarz Pharma) was approved in the United States by the FDA in 1999; however, it was approved only for the treatment of hypertension. 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 drug blood concentration is achieved in the morning, between 6 and 10 a.m. (N.R. Cutler et al., 1995)

Graded-Release Long-Acting Diltiazem: (Cardizem LA, Biovail Pharmaceuticals): This medication was approved in the United States 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 Cardizem LA at 10 p.m., before bedtime, results in a kinetic profile which is suitable for the chronotherapy of hypertension and IHD: trough blood diltiazem concentration occurs in the middle of the night, then rises to achieve a maximum in the morning, and maintains an elevated drug level during the afternoon and early evening. A multi-center trial found bedtime Cardizem LA in doses of up to 540 mg/day to be significantly more effective in controlling morning BP, HR, and RPP than the ACE inhibitor ramipril ingested at bedtime in doses of up to 20 mg/day. (W.B. Whitw et al., 2004)

β-adrenoceptor antagonist chronomedication

Propranolol Chronotherapy (Innopran XL™, Reliant Pharmaceuticals): This chronotherapy was approved in the United States in 2003 by the FDA. Multiple-dose study of this capsule medication shows its ingestion at bedtime as recommended results in trough drug blood concentration during the night due to the intentional delay of propranolol release for 4–5 h, peak drug concentration between 4 a.m. and 10 a.m., and an elevated plateau of drug concentration in the afternoon and early evening. Hence, Innopran XL exhibits an appropriate PK for the treatment of IHD and hypertension. (D. Sica et al., 2003)

CONCLUSION

There is a high increase in incidence of mortality cases with cardiovascular events these days. Even though a wide range of molecules available for controlling cardiovascular events, there is still increase in mortality rate with cardiovascular events. Hence, to control the mortality a proper medication with timely manner to match the circadian variation in systolic blood pressure and heart rate will be beneficial. There is growing interest on how to best tailor blood pressure (BP)-lowering medications according to the circadian (24 h) BP pattern of individual patients, that is, chronotherapy. Now a days, new chronotherapeutic antihypertensive products proving their success with decrease in mortality with cardiovascular events.

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