

## RESEARCH ARTICLE

**Vital Role of Chronopharmacology in Cardiovascular Therapy**Ahmed Elsharkawy<sup>1\*</sup>, Ahmed Ramadan<sup>1</sup>, Mahmoud Abdo<sup>1</sup>

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## ABSTRACT

Chronopharmacology is an area where the drug administration (dosing regimen) synchronized with biological rhythms so as to maximize therapeutic effect. It involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. The major objective of this article is to inform biologists, clinicians, pharmaceutical scientists and other professional about the importance of biological clocks & Chronopharmacology to human health and disease also motivate the investigator to develop new tools for the treatment of cardiovascular diseases such as cardiac arrhythmia, myocardial infarction etc. this article also provide a new ideas to use of older or already well-established active pharmaceutical ingredients for the treatment of various diseases.

**Keywords:** Chronopharmacology , Cardiovascular Therapy, Circadian Rhythm, Biological Systems.

## INTRODUCTION

Chronopharmacology is the science dealing with the optimizations of drug effect and the minimizations of adverse effects by timing medications in relation to biological rhythm Goal is to improve our understand-ing of periodic and thus predictable changes in both desired effects and

tolerance of medication. Chronopharmacology is the investigative science concerned with the biological rhythm dependencies of medications.<sup>1</sup>

**Chronobiology**

It is the science dealing with the phenomenon of rhythmicity in living organisms is called Chronobiology. It is derived from *chronos* (time), *bios* (life), and *logos* (study of)--is the objective description of biological time structures and plays an important role in medicine. Circadian rhythms

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regulate the behavior, physiology and function of living organisms at many biochemical levels.

Aim of chronobiology is optimization of pharmacotherapeutics, taking into consideration rhythm dependencies in kinetics and dynamics of medications, predictable in time variability in the manifestation and severity of diseases.

#### **Circadian rhythm:**

It is defined as oscillations in the biological, physiological and behavioral function of an organism with a periodicity of 24 hrs. The concepts of chronobiology and chronopharmacology have become more and more important in medical practice nowadays. Today, the circadian variation in blood pressure and heart rate as well as in the occurrence of acute cardiovascular disease is quite obvious (ischemia, infarction, stroke and sudden death). However, biological rhythms are also present in episodes of dyspnoea in nocturnal asthma, in hormonal pulses, in the organization of the immunological system and in the processes of cellular proliferation.

#### **Chronergy:**

It is rhythmic changes of both desired (effectiveness) and undesired (toxicity, tolerance) effects on the organism as a whole.

On a 24 hour scale there are peaks and troughs of physiological variables that are not randomly

distributed, but the controlled by a set pacemaker, so called biological clocks.

#### **Chronokinetics:**

It is study of absorption, distribution, metabolism and excretion of drug according to the time of day, menstrual cycle or year.

#### **Chronesthesia:**

It is rhythmic changes in susceptibility or sensitivity of a target system to a drug, which cannot be explained by chronokinetic changes. In humans, target can be skin, bronchial tree, and stomach.<sup>2,3</sup>

### **CAUSES FOR CHRONOPHARMACOLOGY**

There are different reasons for this which may be summarized as:

**Autoinduction:** A repetitive dose of a drug induces or increases enzymes responsible for its elimination, thereby increasing its clearance. This is called as autoinduction. It is dependent on dose and concentration of the drug. It has a number of therapeutic consequences. It affects the time to achieve steady state and limits one's ability to use information from a single dose to predict kinetics after repeated dose or continuous administration. Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration that either oral

bioavailability decreases or clearance increases with time.

**Autoinhibition:** it may occur during the course of metabolism of certain drugs. In this case, the metabolites formed increase in concentration and further inhibit metabolism of the parent drug. In biochemistry, this phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition.

**Food effects:** food is the major cause of diurnal variations. Gastric emptying is slowed or delayed by food, often resulting in a decrease in the peak concentration and an increase in the time of its occurrence following a single dose. It is a major cause of circadian variations in patients tending to eat more in the evening than at breakfast. When absorption is slowed by food, the rate of input into liver and concentration of drug entering liver are lowered and prolonged and thus metabolism is lowered. Hence, a concurrent intake of heavy food in evening and some drugs reduces bioavailability of them drug.

## CIRCADIAN PHASE

The phase of circadian rhythm is defined with respect to an easily identifiable reference point of the endogenous circadian oscillation such as through of the body temperature rhythm or the onset of metabolism rhythm. Thus circadian phase shift can be determined by measuring the change in

timing of the chosen phase marker from one cycle to the next. During ambulatory conditions, changes in environmental stimuli and behaviour (e.g. - Light/dark, rest/ activity and temperature) often obscure the endogenous component of the underlying circadian oscillation that is being measured. The amplitude of circadian rhythm refers to the half distance from the maximum to the minimum of the observed rhythm.<sup>4</sup> Circadian clocks regulate a number of key behaviours in a wide variety of organisms it also helps organism to restrict their activity to species – specific times of the day, which enable them to find food escape predators & avoid undue competition between sympatric species e.g. - in drosophila parasitism activity peaks of different species occurs at different times of the day, which significantly reduces intrinsic competitive disadvantage for the inferior competitor and such temporal portioning is achieved at least partly with the help of circadian clocks.<sup>5</sup> In the evening, when less light enters in the eyes, the master clock triggers production of a hormone called melatonin which makes feel drowsy & helps stay in asleep. Circadian rhythm and their sensitivity to time may change as the age of the individual person increase.<sup>6</sup>

Chronopharmacology is useful to solve problems of drugs optimization means to enhance the desired efficiency or to reduce its undesired effects. The chronopharmacologic approach involves a lesser risk of errors or false information than the

conventional homeostatic approach. Many seasonal psychopharmacological drugs are useful in seasonal affective disorders though diazepam has fewer adverse effects and other selected drugs like phenobarbitone and chlorpromazine also have many adverse effects because of which they are leaving the market even though their pharmacological actions are potent. The need of the hour is to design strategies to ameliorate the side effects which make them more acceptable if the pharmacology and adverse effects of these drugs is circadian time dependant, it can be modulated by altering the time of administration of drugs. Any dependence of these drugs on the circadian time may provide a clue to ameliorate the major drawback of drugs.<sup>7</sup>

**Chronopharmaceutics :-** It has been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy.

**Chronopharmacokinetics:-** It refers to rhythmic changes in drug bioavailability as well as excretion.

**Chronotherapeutics:-** Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between

the peak-to trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs takes into account predictable administration time dependent variation in the pharmacokinetics of drugs as well as the susceptibility due to temporal organization of physiochemical process and function of body as circadian and others rhythms.<sup>8</sup> One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated.<sup>9</sup>

**Chronopharmacotherapy: -** It is an area where the drug administration is synchronized with biological rhythms so as to maximize therapeutic effect. It involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. Circadian changes in the effect of various chemical agents have been documented such as histamine, sodium salicylate, acetylcholine, halothane, prostaglandin F<sub>2</sub>alpha, reserpine, Cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orciprenaline and SCH 1000 (the latter being bronchodilators), Indomethacin, lignocaine, ACTH, cortisol and various synthetic corticosteroids.

#### **Advantages of Chronopharmacotherapy –**

1. It prevents an overdosing of any class of drug.

2. It makes the utilization of the drug more appropriate and thus the value of a drug is increased.

3. It reduces the unnecessary side effects of a drug and helps in carrying out the treatment for only a particular or limited period of time.

### NEED FOR CHRONOPHARMACOTHERAPY

It is required to monitor therapy so as to limit the duration of therapy especially in cases where patients are already having compromised renal, cardiac and hepatic or any other function of the body. Any type of accumulation of drugs in these organs causes greater toxicity which may lead to diminished function of the organ. Thus the chronopharmacotherapy becomes a very important part of treatment of several diseases particularly those affecting targeted body parts.<sup>10</sup>

**Chronotherapeutics clinical studies overview –** Chronopharmaceutics also grants new challenges for scientists and regulators. According to FDA, chronotherapeutics clinical studies need more additional parameters which are not applied for other clinical trials including –

1. Drug administration time of the day.
2. Patient's normal habits & sleep patterns.
3. Biological factors which are time related, like seasonal disorder.

According to the 1996 American medical association review, more consideration of chronotherapy in clinical trials is highly welcomed by the whole medical community. The result of the survey showed that 75 percent of the doctors are in favour of patient's circadian or daily rhythm oriented treatment.<sup>11</sup>

### BIOLOGICAL RHYTHMS AND RHYTHMIC COMPONENTS:-

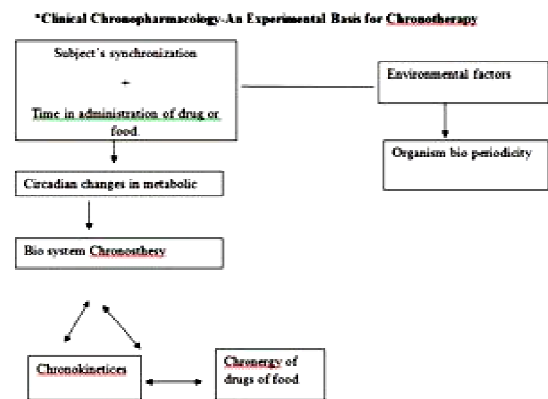
Circadian implies approximately a day, major periodic components of biological rhythms are found around 24 hours (circadian) and 30 days (Circamensual) and one year (Circannual). Circadian rhythms are found in all the organisms, infact the existence of circadian rhythms in living organisms was first established during a detailed study of leaf movement in plants more than 200 year ago. Biological rhythms possess both an internal as well as external components. Rhythmicity has been detected for a number of physiological variables like pulse, temperature, blood pressure, hormonal secretion via diurnal variation in effects of insulin on blood glucose.<sup>12</sup>

**Table-1 Biological Rhythms and Components:**

Period( $\tau$ )	Mark rhythmic components
Short period ( $\tau < 0.5$ h)	$S < \tau < 1$ S Pulsatile $\tau \sim \text{min.}$

2. Intermediate period $0.5 \text{ h} < \tau < 6$ days	Circadian $20 \text{ h} < \tau < 28 \text{ h}$ Ultradian $0.5 \text{ h} < \tau < 20 \text{ h}$
3. Long period	Infradian $28 \text{ h} < \tau < 6$ days Circamensual ( $\tau \sim 30$ days) Circaseptan ( $\tau \sim 7$ days) Circannual ( $\tau \sim 1$ year) [11].

Pharmacokinetics of drugs & Chronosthesy of various systems. It is also important to recognize the fact that plasma proteins undergo a circadian rhythm.

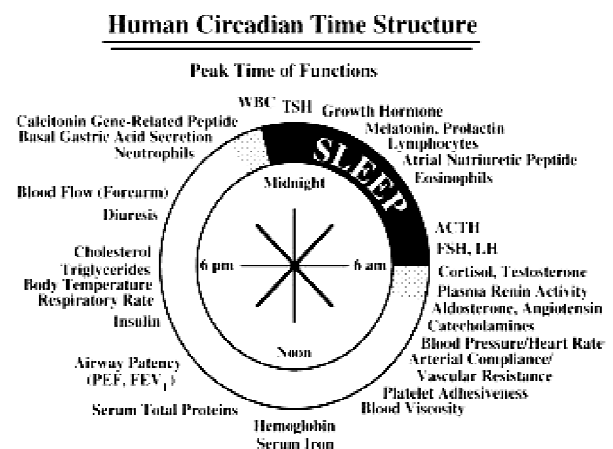


Rhythmicity has been observed in the efficiency and orientation of metabolic pathways and in the sensitivity of target systems to endogenous or exogenous chemical substances. The concepts of biological temporal structure have led to the development of Chronopharmacology and its practical significance is well illustrated in the form of chronotherapy i.e. “prescribing medicine at specified clock hours so as to achieve an optimization of therapeutic administration”. Thus Chronopharmacology involves both investigation of drugs effects as timing as well as investigation of medicines upon temporal structure, thus making it possible to enhance to desired and reduce the undesired effects of medicine.

**Chronosthesy:** - It refers to rhythmic variation detected in the systems. It also includes susceptible variations detected in parasites, bacteria, tumours.

**Chronergy-** The rhythmic changes in its effects and side effects, this depends on the

## HUMAN CIRCADIAN TIME STRUCTURE



The specific time that patients take their medication is very important as it has significant impact on treatment success. Optimal clinical outcome cannot be achieved if drugs plasma concentrations are constant. If symptoms of a disease display circadian variation, drugs release should also vary over time. Chronopharmaceutical drug delivery

system are gaining importance in the field of pharmaceutical technology as these system deliver right dose at specific time at a specific site. Various technologies such as time- controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for Chronopharmaceutical drug delivery.<sup>13</sup> Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24- hour period).<sup>14</sup> Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy and this brought a new approach to the development of drug delivery systems.<sup>15</sup>

**Circadian rhythm in the pathogenesis of CVS disease:-** From the various studies, it is formed that the many cardiovascular events including myocardial infarction, stroke and sudden death occur during the initial hours of morning activity between 6 AM and 12 noon. And this is much higher during this period that other timing during the day. BP rises rapidly in the early morning hours, the time when most individuals wake and begin their day. This rise in BP corresponds to increased secretion of catecholamine's and increased plasma rennin activity. Thus, vascular tone and total peripheral resistance increase in the

morning hours, and BP rises as a result. At the same time, heart rate increases in the late morning or early afternoon.<sup>16</sup>

**Chronotherapy of cardiovascular diseases: -** 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. Chronotherapeutics approach gives more accurate determination of the time when patients are at highest risk and in greatest need of therapy. For example – it has often been found that the blood pressure of 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. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening. For instance, capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Platelet agreeability is increased and fibrnolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. Blood Pressure is at its lowest during sleeping period and rises steeply during the early morning period. Many anti-hypertensive drugs do not control the early morning blood pressure, when given once daily early in the morning.<sup>13</sup>

## VARIOUS CARDIOVASCULAR DISEASES

### **Blood pressure (B.P) / Hypertension**

Blood Pressure is well known to exhibit 24 h variation with a peak in the morning. A number of factors influence diurnal variation of blood pressure which is internal factors such as the autonomic nervous system, vasoactive intestinal peptide, plasma cortisol, plasma rennin activity, aldosterone, plasma atrial natriuretic peptide. Both sympathetic activity and the rennin-angiotensin-aldosterone access peak in the early morning hours. In addition, b.p is affected by a variety of external factors including physical activity, emotional state, meal and sleep/wake routine. These extrinsic stimuli also affect the autonomic nervous system thus the 24 h variation in the B.P is representative of both endogenous diurnal rhythms and exogenous factors.<sup>2</sup> Blood pressure is characterized by a circadian rhythm, both in hypertensive and in normotensive subjects; this pattern is associated with lower B.P values during sleeping time and periods of minimal activity and higher B.P levels during wakefulness and mental and physical activity. Various, researchers reported that blood pressure changed depending on whether the subjects was sleeping, resting or working. Blood pressure fluctuates throughout the day and night. The duration of the fluctuations may be short, from seconds to minutes, or long from day to night and season to season. The most easily noted and significant blood pressure variations are the diurnal changes related to the sleep-wake cycle. The

pattern of blood pressure values obtained during the sleep-wake cycle from characteristic circadian rhythm. The Continuous monitoring of blood pressure throughout the day and night reveals a pattern with minimum values of systolic & diastolic pressure between midnight & 4 am. The pressure increases during waking hours remaining at a plateau for several hours & then reaching a maximum values early in the morning. This diurnal blood pressure fluctuation is altered in certain disease states, such as preeclampsia & chronic hypertension . Hypertension is a common chronic condition affecting up to 35% of human adults. This condition is an important risk factor for strokes, heart attacks and other vascular & renal disease. The Pharmacological treatment of high blood pressure reduces the incidence of these complications & prolonged life.

The treatment of hypertension not only includes the usual clinical goal of reducing mean blood pressure levels, but also the normalization of the entire blood pressure circadian pattern. The predictable day-night variation in the symptoms of chronic medical conditions, risk of severe life-threatening cardiovascular events & in medical conditions that are predisposing to serious disease presents the opportunity for a new i.e. chronotherapeutics treatment strategy that involves the delivery of medications so they are synchronized in time to biological need that varies according to the chronobiology of the targeted tissue. Currently



available, once daily extended release antihypertensive medication provide safe & effective B.P reduction over a 24 hours during interval but their static pattern of drug release may not tailored to suit daily physiologic B.P variations. Currently chronotherapeutics calcium channel blocker is available in market for the management of certain cardiovascular disease.<sup>3</sup>

**COMMON ONSET TIME OF CARDIOVASCULAR SYSTEM<sup>17</sup>**

Disease	Common onset time
Atrial fibrillation	Morning/night
Ventricular tachycardia/fibrillation	Morning
Acute coronary syndrome	Early morning
Pulmonary embolism	Early morning
Cerebral infraction	Morning
Subarachnoid haemorrhage	Day time

**Acute myocardial infraction (AMI) / pulmonary embolism (PE)**

It is well known that AMI or PE frequently occurs in the early morning. A number of physiological functions exhibit diurnal variation including BP, heart rate, coronary blood flow, platelet function,

blood coagulability and fibrnolytic activity. In the early morning, systemic BP & heart rate increases and augment the oxygen demand of the heart. In addition, the vascular tone of the coronary artery rises and coronary blood flow decreases in the morning. This increases in oxygen demand & decreases in oxygen supply exaggerate a mismatch of oxygen demand and supply in the morning. In addition, platelet function & blood coagulability also increases in the morning. A reduction in fibrnolytic activity resulting in a hypercoagulable state that could elicit the morning onset of thromboimbolic events. Accumulating evidences suggests that the autonomic nervous system plays a major role in the circadian variation of the onset of AMI. A morning increase in the frequency of ischemic episodes is absent in diabetic patients with autonomic nervous dysfunction. Patients receiving beta-blocker do not show morning increase in the incidence of angina, AMI & sudden death. Heart rate variability which reflects sympathetic/vagal balance is also associated with the onset of ischemic episode in the chronic stable angina. Platelets are not involved in the variation of AMI or thromboimbolic numbers & their aggregation activity possess circadian oscillation. Platelet activation in vivo is induced by catecholamine secreted from the sympathetic nervous system in a circadian fashion. However studies regarding platelet activation do not show clear circadian expression of any surface marker characteristic of

platelet activation, therefore it is unclear whether the internal clock system directly affects the circadian functions of platelets.<sup>2</sup>

### **Arrhythmia:**

A number of reports demonstrated the presence of circadian variation of cardiac arrhythmia. Evidences suggest that basic electrophysiological parameters have circadian variations. Atrial & ventricular refractory periods are strongly affected by the autonomic nervous system, in which sympathetic activity shortens it and parasympathetic activity elongates the period. Therefore fluctuations in the activity of autonomic nervous system within a day can be a major trigger of circadian onset of cardiac arrhythmia. Each parameter of ECG was analyzed as to whether it has diurnal variations. ECG, AV nodal function, QT interval, R&T wave voltage & QT interval have been shown to exhibit circadian variations. For the onset of cardiac arrhythmia paroxysmal atrial fibrillation is categorized into two types-

1. Vagatonic PAF- occurs at night.
2. Adrenergic PAF- occurs during day time.

There are several reports showing different results in term of peak paroxysmal supra ventricular tachycardia (PSVT) from morning to midnight. However they are consistent in that it is rare for PSVT to occur during the night time. Continuous halter monitoring of ECG revealed a 24 h variation

in the occurrence of ventricular premature beats with a peak between 6 am & 12 noon. The presence of a circadian onset of VPBs depends on left ventricular function. Only patient with a left ventricular ejection fraction greater than 30 % have a circadian variation of VPBs.<sup>2</sup>

### **CONCLUSION**

Chronopharmacology involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. Chronopharmacology certainly holds promise for the creation of the most favourable conditions for drug effects and safety and may therefore represent an important method of improving the treatment of many diseases. The goal of chronopharmacology is to optimize the therapeutic effect and control or reduce the adverse effects without altering the functioning of the drug in the body. Pharmacologic chronotherapy is a developing science that holds much hope for increasing the effectiveness of drug therapy and for reducing the incidence of toxic drug reaction. There is convincing scientific work to indicate that more attention should be given to the timing of drug administration. Most prescribers are currently more concerned with "what" to prescribe rather than "when" to prescribe it. Chronopharmacology certainly holds promise for the creation of the most favourable conditions for drug effects and safety

and may therefore represent an important method of improving the treatment of many diseases.

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