

**CHRONOPHARMACOLOGY: A TOOL FOR THERAPY OF DISEASES**

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ABSTRACT

Chronopharmacology is useful to solve problems of drug optimization, i.e. to enhance the desired efficiency or to reduce its undesired effects. In the human organism (among other animal species) the metabolic fate of a pharmacologic agent (as well as that of a nutrient) is not constant as a function of time. Thus, the Chronobiological approach of pharmacologic phenomena involves a lesser risk of errors and/or false information than the conventional homeostatic approach. Chronopharmacology is the study of the manner & extent to which the kinetics & dynamics of medication directly affected by endogenous biological rhythm & also how the dosing time of medications affects biological timekeeping & features (period, level, amplitude & phase) of biological rhythms. Chronopharmacotherapy is the investigative science that elucidates the biological rhythm dependencies of medication. It is useful to solve problems of drug optimization i.e. to enhance the desired efficiency or to reduce its undesired effects. So Chronopharmacologic approaches involve a lesser risk of errors and or false information than the conventional homeostatic approach. The effectiveness & toxicity of many drugs vary depending on dosing time associated with 24 hours rhythm of biochemical , physiological & behavioural process under the control of circadian clock such chronopharmacological phenomenon are influenced by not only the pharmacokinetics but also pharmacodynamics of medication. Now a day Chronopharmacological principle is used in the therapy of various diseases such as hypertension, myocardial infarction, angina pectoris, pulmonary embolism, diabetes etc.

Keywords: Chronopharmacotherapy, Circadian rhythm, hypertension, myocardial rhythm

INTRODUCTION

Many functions of the human body vary day by day and these types of variations cause the changes in both in disease state and in normal state.¹ Cardiovascular functions such as heart rate and blood pressure show 24 hours variation. The incidence of cardiovascular disease such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation since most of these disorders can induce fatal or severe outcomes. It is important to elucidate the precise mechanism of the onset of these diseases.² The dependence of our body functions in the certain diseased state depends on the circadian rhythm.¹The science dealing with the phenomenon of biological rhythmicity in living organism is called chronobiology. The branch dealing with the pharmacologic aspects of chronobiology is termed Chronopharmacology which may be subdivided into chronotherapy, chronopharmacokinetics and Chronotoxicity³

Circadian rhythm - 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 maker 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.⁴ 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.³ In the evening, when

less light enters in the eyes, the master clock triggers production of a hormone called melatonin which makes feel drowsy and helps stay in asleep. Circadian rhythm and their sensitivity to time may change as the age of the individual person increase.⁶

The 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 this 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.⁷

Chronotherapeutics: - Chronotherapeutics refers to a treatment method in which 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-through 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.⁸ One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated.⁹

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 caring out the treatment for only a particular or limited period of time⁷

Reason for Chronopharmacology

Auto induction:- A repetitive dose of a drug induces or increases enzymes responsible for its elimination, thereby increasing its clearance. This is called as auto induction. 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.

Auto inhibition:- It may occur during the metabolism of certain drugs. The metabolites formed from drug firstly increase in concentration and further inhibit metabolism of the parent drug. This phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition.

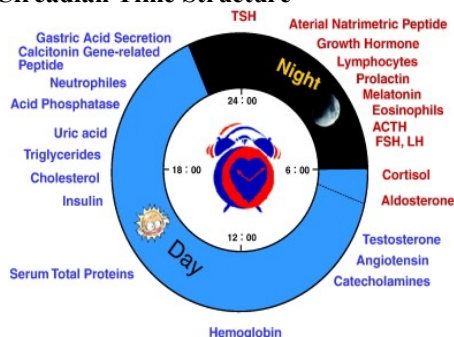
Need for Chronopharmacotherapy

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 led to diminished function of the organ. Thus the chronopharmacotherapy becomes a very important part of treatment of several diseases particularly those effecting targeted body parts¹⁰ 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 treatment¹¹

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 posses both an internal as well as external components. Rhythmicity has been detected for a numbers of physiological variables like pulse, temperature, blood pressure, hormonal secretion via diurnal variation in effects of insulin on blood glucose.¹²

Human Circadian Time Structure



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.¹³ 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- hours period).¹⁴ 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.¹⁵

Circadian rhythm in the pathogenesis of diseases- 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 A.M. 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 activity⁶ 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.¹⁶

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 documented¹⁷ 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 morning¹³

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.² 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.¹⁸ 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.¹⁹

Changing paradigm for targeting blood pressure control²⁰

Multiple daily dosing of medication



Once daily dosing of long acting medication

Evening dosing of long acting chronotherapeutics medication

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 fibrinolytic 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 fibrinolytic activity resulting in a hypercoagulable state that could elicit the morning onset of thromboembolic 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 thromboembolic 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.²

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.

BIOLOGICAL RHYTHMS OBSERVED IN VARIOUS BIOLOGICAL SYSTEMS

The basic physiological process governing the drug action the absorption the distribution the metabolism and the excretion are controlled by the following systems of the body. Hence it is important to know the circadian rhythms in these systems and their effect on drug action.

Urinary system- The urinary system which plays a pivotal role in the elimination of a drug has many instances of circadian rhythms altering either the clearance or the urinary flow causing nephrotoxicity. Amino glycosides can produce renal toxicity with chronic administration. Because these antibiotics are primarily eliminated by renal excretion, diminishing renal function with time may cause greater drug accumulation and more toxicity. There is clearly a need to monitor therapy to limit the duration of therapy, especially in patients who already have compromised renal function. Theophylline causes increase in the renal flow by increasing the clearance levels and thereby increase in the urine flow and renal excretion. Carbamazepine shows time dependence in its disposition.

Gastrointestinal system- The gastrointestinal motility, the intraluminal pH, blood flow to stomach and enzymatic action are not the only factors that influence the gastro intestinal absorption of the drug. It even depends on the circadian rhythms and all the above mentioned factors are also influenced by the time of the day. Most of the drugs we generally take are lipophilic and they are found to have more rate of absorption in early mornings rather than any hour of the day.

Hepatic system- The anti-depressant nartryptalline which is injected to significant presystemic hepatic metabolism accumulates in a highly predictable manner on multiple oral dosing. The clearance levels of acetaminophen are decreased due to the effect of circadian rhythms and thus resulting in the hepatotoxicity.

Diseases Showing Dependence on Biological Rhythms

Asthma-

Chronic airway inflammation and limitation of airflow in the airways characterize bronchial asthma, and attacks begin with paroxysms of coughing, wheezing, and dyspnoea. Chronopharmacological studies statistically show that the development of asthma symptoms and many types of bronchospastic attacks is clearly more common from midnight to early morning from 2 A.M. and 6am every day. Chronopharmacotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. Several drugs for asthma have been

developed based on chronopharmacology. One example is the bronchodilator uniphyll, a long-acting theophylline taken once a day in the evening causes theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours. Some studies have even proved that a single dose administered in those early hours is equally effective as four doses given in a day. In addition to bronchodilators, the inhaled glucocorticosteroid ciclesonide is now available with once-daily dosing, which also improves patient's compliance. Numerous investigations have demonstrated the usefulness of chronotherapy for asthma, especially for patients with nocturnal asthma.¹⁰

Diabetes- Biologists have found that a key protein that regulates the biological clocks of mammals also regulates glucose production in the liver and altering the levels of this protein can improve the health of diabetic mice. The additional function of the cytochrome is the regulation of gluconeogenesis according to the diurnal activity and feeding levels. So modulating cytochrome levels can also help decrease the diabetic effect on the patients.

Arthritis- Chronobiological patterns have been observed with arthritis pain. The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting NSAIDs like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes or averts their side effects. People with osteoarthritis, the most common form of the disease, tend to have less pain in the morning and more at night. For osteoarthritis sufferers, the optimal time for a non-steroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. The overall, back stiffness and pain were a problem throughout the 24 hours, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 and 09:00 than between noon and 15:00.¹⁰

Cancer- The tumour cells and the normal cells differ in their Chronobiological cycles. This fact is the basis for the chronopharmacotherapy of cancer. Based on study which suggested that the DNA synthesis in the normal human bone marrow cells has a peak around noon while the peak of DNA synthesis in lymphoma cells is near midnight, a s-phase active cytotoxic therapy at late nights was administered and it was found that there is a decrease in the tumour cell count with a little effect on normal cells.

Allergy- The allergic reactions both local and systemic are mediated through interactions of immune and inflammatory responses. Such responses during the day are usually coordinated by adrenocortical function and steroid release with high amplitude daily rhythms. Scientists now believe that the symptoms of allergic rhinitis, and even the skin testing results, can vary according to the time of day.¹⁰

New Techniques of Time Controlled Pulsatile Technology
Currently pharmaceutical companies have been focused on developing and commercializing PDDS that fulfil unmet medical needs in the treatment of various diseases. Recently developed technologies are SODAS® technology, IPDAS® technology, CODAS technology, CONTINR, OROSR, CEFORMR, DIFFUCAPSR, chronomodulating infusion pumps, TIMERx R and physico-chemical modification of API.
Spheroidal Oral Drug Absorption System (SODAS)- This technology is based on the production of controlled release beads and it is characterised by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. SODAS

can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give to a fast onset of action, which is maintained for 24 hrs. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day.²¹

Chronotherapeutics Oral Drug Absorption System (CODAS)-

The Chronotherapeutics oral drug absorption system (CODAS) is a multiparticulate system which is designed for bedtime drug dosing, incorporating a 4-5 hrs delay in drug delivery. This delay is introduced by the level of non enteric release – controlling polymer applied to drug loaded beads.¹³ This technology was designed to release its drug component after a prolonged period of time when administered. A good example is Verelan PM, which was designed to release verapamil approximately four to five hours after ingestion. This delay is introduced by the level of release –controlling polymer applied to the drug –loaded beads. The release controlling polymer is a combination of water-soluble and water –insoluble polymers. When fluid from the gastrointestinal tract contacts the polymer coat beads, the water-soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water-insoluble polymer continues to act as a barrier, maintaining the controlled-release of the drug. When taken at bed time, this controlled onset extended release delivery system enables a maximum Plasma concentration of verapamil in the morning hours, when blood pressure normally is high.²²

Contintr Technology- In this technology, molecular coordination complexes are formed between a cellulose polymer & a non polar aliphatic alcohol optionally substituted with a aliphatic group by solvating the polymer with a volatile polar solvent & reacting the solvated cellulose polymer directly with the aliphatic alcohol . This constitutes the complex having utility as matrix in controlled release formulations since it has a uniform porosity (Semi permeable matrix).²³

Chronomodulating Infusion Pumps- Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation , pH, magnetic fields, ultrasound, electronic field, temperature, light, & mechanical stimulation have been developed.²³

TIMERx Technology- The TIMERx Technology (hydrophilic system)²⁴ combines primarily Xanthan & Locust bean gums mixed with dextrose .The physical interaction between these components works to form a strong binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the timer x gum matrix which expands to form a gel & subsequently releases the active drug Substances.²³

CONCLUSION

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.

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