

Chronopharmacology - There Is a Clock for Treatment

¹Siraj Sundaran, ²M.G. Rajanandh, ³S. Sankar and ⁴K.P. Arun

¹Department of Pharmacy Practice, Devaki Amma Memorial College of Pharmacy,
Chelembra, Malappuram, Kerala, South India

²Department of Pharmacy Practice, Faculty of Pharmacy,
Sri Ramachandra University, Porur, Chennai-600 116, Tamil Nadu, South India

³Department of Pharmaceutical Chemistry,
J.S.S. College of Pharmacy, Rocklands, Ooty, Tamil Nadu, South India

⁴Department of Pharmacy Practice,
J.S.S. College of Pharmacy, Rocklands, Ooty, Tamil Nadu, South India

Abstract: Chronopharmacology involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. Rhythmicity has been detected in a number of physiological variables such as pulse, temperature, blood pressure and hormonal secretions like diurnal variation insulin effects on blood glucose. Biological rhythms are also found in blood pressure, heart rate, acute cardiovascular disease, episodes of dyspnoea in asthma, in hormonal pulses, in the organization of the immunological system and in the processes of cellular proliferation. 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. There are convincing scientific works to indicate that more attention should be given to the timing of drug administration. Auto-induction, auto-inhibition and food effects are considered to be the reasons of chronopharmacology. Circadian rhythm and its effects are very much observed in the pharmacokinetics and pharmacodynamic of drugs given to the patients. Nowadays prescribers are concerned with "when to prescribe it" which is an important strategy taken along with "what to prescribe". Chronopharmacology can certainly create a favorable condition for drug effects and safety and may therefore represent an important method of improving the treatment of many diseases.

Key words: Chronopharmacology • Rhythmicity • Dyspnoea

INTRODUCTION

Functions of the human body vary day today and these variations can lead to changes in both the disease state as well as a normal state. The dependence of our body functions in certain diseased condition is based on the circadian rhythm. The major periodic components of biological rhythms are found around 24 hours (Circadian), 30 days (Circamensual) and one year (Circannual) [1]. Circadian rhythms are found in all living organisms which include the plants and bacteria. History has long back accepted the fact that rhythmic physiology resulted in rhythmic disease symptoms.

Chronopharmacology is the science that deals with the optimizations of drug effect and the minimizations of adverse effects of timing medications in relation to biological rhythm. In simple words chronopharmacology is the science which is concerned with the biological rhythm dependencies of medications. The two major disciplines of chronopharmacology which are important in medical practice nowadays include the chronotherapeutics, which is the treatment in accordance with the body's biological rhythms that aids in optimizing therapeutic outcomes and minimize side effects and chronopharmacokinetics, which is the study of the absorption, distribution, metabolism and excretion of

drugs according to the time of days or year. According to the 1996 American Medical Association review, more consideration of chronotherapy in clinical trials is highly welcomed by the whole medical community and nearly 75% of the doctors are in favour of patient's circadian or daily rhythm oriented treatment. Rhythmicity has been detected in a number of physiological variables such as pulse, temperature, blood pressure and hormonal secretions like diurnal variation insulin effects on blood glucose. Biological rhythms are also found in blood pressure, heart rate, acute cardiovascular disease, episodes of dyspnoea in asthma, in hormonal pulses, in the organization of the immunological system and in the processes of cellular proliferation. Studies on chronopharmacology have already set goals to improve the understanding of periodic and predictable changes in both desired effects and tolerance of medication. This review might throw light to some of the basic concepts of chronopharmacology and how it can aid the medical professionals in the treatment approach [2, 3].

Reasons 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. A number of therapeutic consequences such as it may affect the time to achieve steady state and limits the use of information from a single dose to predict kinetics after repeated dose or continuous administration. An example of auto induction is with the administration of carbamazepine. Here either the oral bioavailability decreases or clearance increases with time due to repetitive oral administration [4].

Auto Inhibition: The metabolites formed from the drug initially increase in concentration and further inhibit metabolism of the parent drug. This phenomenon is also called as product inhibition or allosteric inhibition or feedback inhibition. Clarithromycin is an inhibitor of intestinal and hepatic CYP3A4 activity and thus gradually inhibits its own metabolism as well as that of co-administered drugs [5].

Food Effects: 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 of drug. It is a major cause of

circadian variations in the case of patients who tends to eat more in the evening than at breakfast. Usually when absorption is slowed by food, the rate of input into the liver and concentration of drug entering liver are lowered and prolonged and thus metabolism is lowered [6].

Steps Involved in the Evaluation of Chronopharmacology

Identification of its Occurrence: The reason for the change in drug effect should be identified to know the type of variation is present. This step helps to know whether the effect is due to biological rhythm or not.

Determination of the Parameter Affected:

The pharmacokinetic parameters which are affected are to be determined. In case more than one parameter is affected there is a need to study all the possible parameters.

Mechanism of Non-Linearity: To implement chronopharmacology it is necessary to first identify the mechanism by which non-linearity in pharmacokinetics is seen and then take steps to solve it [7, 8].

Circadian Regulation of Pharmacokinetics:

Circadian systems have been shown to influence drug absorption, distribution, metabolism and excretion. Each of which has a vital role in determining the drug level in blood. Therefore, time of drug administration in a day and the management of the peripheral molecular clocks in organs such as the gut, liver and drug target tissue can have a significant effect on drug levels and bioavailability.

Absorption: The absorption of orally administered drugs depends on factors such as physiology of the gastrointestinal tract (blood flow, pH, gastric emptying) and function of specific uptake and efflux pumps on epithelial cell surfaces. Studies have shown the existence of circadian clocks within the gut and the importance in the gut physiology. Lipophilic molecules are found to be absorbed less readily under acidic conditions. The production of the hormone ghrelin by oxyntic cells in the stomach is regulated by circadian clock genes and mediates circadian changes in activity prior to feeding. Oxyntic cells tune the circadian oscillation of the GI tract to food intake patterns rather than light. Other gut parameters such as gastric blood flow and motility are increased during daylight hours and decreased at night [9].

The absorption of many therapeutic agents is highly dependent on the specific transporter proteins in the gut. The circadian regulation of both physiologic parameters and the expression of specific proteins involved in drug absorption provide a mechanistic basis for understanding observed time-of-day effects on the absorption of many drugs. Circadian patterns of absorption are most pronounced in lipophilic drugs, where greater absorption occurs during the day than at night. An interesting observation made in the case of beta blockers was that the absorption of lipophilic beta blocker propranolol was greater in the morning, whereas the water-soluble beta blocker like atenolol showed no significant diurnal variation in absorption. Studies have shown that the absorption of most drugs is greater in the morning that parallels to the morning increases in gut perfusion and gastric pH [10].

Distribution: The volume of distribution of a drug is determined by its lipophilicity and plasma protein binding affinity. The degree of protein binding of several drugs, including the antiepileptic agents such as valproic acid and carbamazepine and the chemotherapeutic cisplatin, varies in a diurnal manner and correlates appropriately with changes in plasma albumin level. The binding capacity of the corticosteroid-binding globulin, transcortin, for prednisolone varies with time, maximum occurring at midnight and minimum in the morning. Variations in the free (active) fraction of drug have important implications for both the efficacy and side effect profile. The ability of a drug to cross membranes between different tissue compartments is also a determinant of drug distribution. Many water soluble agents require the expression of certain membrane-bound proteins (transporters or channels) to transit between tissue compartments and reach their receptors. A variety of drug transporters which are critical for drug distribution in tissues are regulated by circadian mechanisms [11].

Metabolism: Hepatic metabolism of drugs which are generally carried out by the cytochrome P (CYP) 450 family of monooxidases and conjugation process. Evidence has been accumulating recently regarding the circadian regulation for both the latter process and even for several non-CYP phase I enzymes. Circadian regulation of hepatic blood flow has been suggested to regulate drug metabolism, particularly for drug with a high extraction rate [12].

Excretion: Diurnal variations have been studied on the renal parameters that include glomerular filtration rate, renal plasma flow and urine output. Diurnal variation in the urinary excretion of several drugs has been observed. Circadian regulation of urinary pH could also contribute to variations in drug excretion, as many drugs become protonated at high pH which enhances excretion. In case of certain drugs such as amphetamine the urinary pH shows a diurnal variation [13].

Circadian Regulation of Pharmacodynamics: Circadian mechanisms regulate many factors which influence the efficacy of drugs aside from their metabolism. Rhythmic alterations in the expression of target receptors, transporters and enzymes, intracellular signaling systems and gene transcription all have been reported and have the potential to impact the efficacy of therapeutics. Several of the neurotransmitter systems, including serotonergic, cholinergic and dopaminergic nuclei plays critical role in the circadian rhythm. The circadian gene also regulates metabolic processes like insulin secretion, gluconeogenesis and fatty acid metabolism. Circadian regulations are therapeutic targets in case of old age related diseases [14].

Biological Rhythms in Common Diseases: The basic physiological process governing the drug action, such as absorption, distribution, metabolism and excretion is controlled by various organ systems of the body. Hence it is important to know the circadian rhythms in these systems and their effect on drug action.

Cardiovascular System: Like several electrophysiological phenomenon, cardiovascular activities show a circadian rhythm. Based on the influence of external stimuli and endogenous homeostatic mechanisms, the cardiac electrophysiological properties change diurnally and enable the cardiovascular system to adapt accordingly with the rest-exercise cycles. Cardiovascular functions such as heart rate and blood pressure show 24 hours variation. For example, in case of blood pressure is highest in the late afternoons and gradually decrease in the evenings to attain the lowest values at nights, which can be qualified to the circadian rhythms in the nervous and endocrine system. Essential/primary hypertensive display highest values during daytime followed by a mighty drop and early morning rise. In nearly 70% of

secondary hypertension this rhythmic pattern is abolished or even reversed exhibiting nightly peaks in blood pressure.

Myocardial infarction (MI) occurs more frequently in the morning as a result of the concomitant unfavorable timing of several physiological parameters and/or biochemical conditions. Even most of the cardiac ischemic conditions and acute myocardial infarctions occur usually between the morning and the noon. The activity of the several components of the vascular systems appears to be diurnally regulated. Endothelial cell activation, leukocyte and platelet interactions and lipoprotein metabolism all have been shown to vary with time of the day. In fact, the time of day of onset of platelet aggregability, nonfatal myocardial infarction and sudden cardiac death had prominent circadian rhythms with a primary peak in the morning and a secondary peak in the evening [15].

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.

Gastrointestinal System: The gastrointestinal motility, the intraluminal pH, blood flow to the stomach and enzymatic action are not the only factors that influence the gastrointestinal absorption of the drug. It even depends on the circadian rhythms and is 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 [16].

Respiratory System: 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 2AM and 6 AM every day. Chronopharmacotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. One example is the bronchodilator 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. Studies have also proved that a single dose administered in those early hours is equally effective as four doses given in a day [17].

Endocrinology: 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 diabetics [18].

Miscellaneous

Arthritis: Chronobiological patterns have been observed with arthritis pain. The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting non-steroidal anti-inflammatory drugs 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 [19].

Cancer: Based on the study, it was 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 administered at late nights was found to decrease the tumor cell count with a little effect on normal cells [20].

CONCLUSION

Ongoing research has begun to disclose the molecular mechanisms by which circadian genes regulate pharmacokinetic and pharmacodynamic processes. It is also becoming evident that drugs can influence the rhythmicity of circadian clocks, alter physiology and perhaps with unintended consequences. Ongoing investigation into mechanisms by which molecular clocks alter pharmacologic parameters, the consequences of these alterations of on drug efficacy and tolerability and possible methods to use circadian biology to our pharmacologic advantage is needed.

Chronopharmacology also grants new challenges for scientists and regulators. According to US Food and Drug Administration (USFDA), chronopharmacology clinical studies need more additional parameters which are not applied for other clinical trials, including drug administration time of the day; patient's normal habits and sleep pattern; biological factors which are time related like seasonal disorder.

Chronopharmacology is a developing science that gives much hope for better the effectiveness of drug therapy and reducing the incidence of toxic drug reaction. Nowadays prescribers are concerned with "when to prescribe it" which is an important strategy taken along with "what to prescribe". Chronopharmacology can certainly create a favorable condition for drug effects and safety and may therefore represent an important method of improving the treatment of many diseases.

REFERENCES

1. Deepa, A. and M. Kumar, 2000. Concept of chronopharmacology in ayurveda. *Ancient ScienLife.*, 19: 155-63.
2. Elsharkawy, A., A. Ramadan and M. Abdo, 2013. Vital role of chronopharmacology in cardiovascular therapy. *J. Scien. Innov. Res.*, 2: 176-86.
3. Maurya, K.K., B.C. Semwal, S. Neelam, V. Srivastava and K. Ruqasana, 2012. Chronopharmacology: a tool for therapy of diseases. *Int. Res. J. Pharm.*, 3: 128-32.
4. Koppiseti, V.S., N. Chandra and M.B. Raju, 2010. Vital role of chronopharmacology and chronopharmaco therapy in human life. *Int. J. Res. Pharm. Biomed. Sciences*, 1: 36-40.
5. Musiek, E.S., A. Garret and Fitz Gerald, 2013. Molecular clocks in pharmacology. *Hand b. Exp. Pharmacol.*, 217: 243-60.
6. Gupta, R., B.M. Gupta, V. Khajuria, N.K. Bhat and A. Gupta, 2013. Chronopharmacology: an Overview, 1: 6-9.
7. Lemmer, B., 1991. Circadianrhythms and drug delivery. *Int. J. Controlled Release.*, 16: 63-74.
8. Belanger, P.M., 1993. Chronopharmacology in drug research and therapy. *Adv. Drug Res.*, 24: 1-80.
9. Shigehiro, O., 2010. Chrono-Drug-Delivery Focused on Biological Clock: Intra-and Inter-Individual Variability of Molecular Clock. *Advanced Drug Delivery Reviews.*, 62: 946-55.
10. Pandit, V. and S. Suresh, 2009. Emerging role of biorhythms in optimizing treatment of disease. *IndianJ Novel Drug Delivery.*, 1 :2-10.
11. Koppiseti, V.S., H. Shree and Sunalatha, 2011. Chronopharmacology and chronopharmaco therapy a guide to better health. *Res. J. Pharma. Bio. Chem. Sci.*, 2: 266-72.
12. Evans, R.M. and C. Marain, 1996. Taking your medication: a question of timing. *Amer Med. Association*, pp: 3-8.
13. Srugulle, R. and B. Lemmer, 1993. Recent advances in chronopharmacokinetics: methodological problems. *Life Sci.*, 52: 1809-24.
14. Lemmer, B., 1994. Chronopharmacology: time, a key in drug treatment. *Ann. Biol. Clin.*, 52(1): 1-7.
15. Reinberg, A.E., 1991. Concepts of circadian chronopharmacology. *Ann. NY, Acad. Sci.*, 618: 102-15.
16. Staels, B., 2006. When the clock stops ticking, metabolic syndrome explodes, *Nat. Med.*, 12: 54-5.
17. Smolensky, M.H. and G.E.D 'Alonzo, 1993. Medical chronobiology: concepts and applications. *Am, Rev., Respir, Dis.*, 147: S2-19.
18. Youan, B.B.C., 2009. Chronopharmaceutics: Science and Technology for Biological Rhythm Guided Therapy and Prevention of Diseases, John Wiley and Sons, Hoboken, NJ, USA.
19. Youan, B.B.C., 2004. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. *J. Control Release.*, 98: 337-353.
20. Jha, N. and S. Bapat, 2004. Chronobiology and chronotherapeutics. *Kathmandu Univ. Med. J.*, 2: 384-88.