Chronopharmacology: An Overview
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Abstract
The circadian clock imposes a rhythm on many metabolic pathways and may influence drug metabolism in a variety of ways. Circadian variation in the activity of many gastrointestinal, hepatic and renal processes could explain why the absorption, distribution, metabolism and excretion of drugs change as a function of the time of drug administration. Chronopharmacology utilizes rhythms of physiology to try to synchronize concentration and dosing of medications to increase their efficacy and safety.

Key Words
Chronopharmacology, Biological Clock, Circadian Rhythm

Introduction
Variation in the behavior has always attracted the Research workers. In 1729, French astronomer Jean Jacques d'Ortous de Mairan began his research on biological rhythm by observing changes in plants in relation to day and night. Pittendrigh in 1967 proposed that animals have an internal time keeping device, a circadian clock. Thus, emerging concepts "chronobiology - science of biological rhythms and biological time structure" and "circadian rhythm - oscillations in the biological, physiological and behavioural function of an organism with a periodicity of 24 hours" were incorporated in the medical terminology.

In early 1970s, 'chronopharmacology' became recognized as a scientific domain of investigation to understand the periodic and predictable changes in both, desired effects and tolerance of medication. It is defined as a science dealing with the optimization of drug effects and the minimization of adverse effects by timing medications in relation to the biological rhythm.[1] The rhythms that derive from the internal timing system and persist in the absence of environmental stimuli are called circadian from the Latin words circa (approximately) and dies (day). The circadian clock imposes a rhythm on many metabolic pathways and may influence drug metabolism in a variety of ways. Circadian variation in the activity of many gastrointestinal, hepatic and renal processes could explain why the absorption, distribution, metabolism and excretion of drugs change as a function of the time of drug administration. Chronopharmacology utilizes rhythms of physiology to try to synchronize concentration and dosing of medications to increase their efficacy and safety.

The clinical use of chronopharmacology in regulating both pharmacodynamics and pharmacokinetics is increasingly appreciated by the medical fraternity.[2]

Drug Absorption Distribution, Metabolism and Excretion
The absorption of a number of widely used drugs such as nitrates, benzodiazepines, calcium channel blockers, acetaminophen and antidepressants is found to be more rapid after oral administration in the morning compared to in the evening.[3-8] The rate of absorption is increased, the maximal plasma serum concentration is greater and
the time after administration needed to obtain maximal plasma levels is shorter when the drugs are taken at the beginning of the day. This difference in drug absorption at different times of the day is a result of diurnal changes in various aspects of physiology. Drug solubility and route of administration may influence the diurnal variability of drug absorption. Lipid-soluble drugs are more likely to show temporal variations in pharmacokinetics than do water-soluble drugs.\[^2\]

Time-dependent variation in drug binding to plasma proteins influences the distribution of drugs that are highly protein bound and have a small volume of distribution. The binding capacity of the plasma corticosteroid-binding globulin, transcortin, for prednisolone varies with time in humans, with maximum binding occurring at midnight and minimum at 8.00 o'clock in the morning. Drug distribution is also dependent on the permeability of membranes to drugs.\[^2,9\]

The liver is a major site of drug metabolism and oxidation and conjugation to endogenous substrates are the two main reactions in drug metabolism which change with time. The cytochrome P450 monooxygenase system is the main system responsible for drug oxidation. Protein levels of cytochrome P450 enzymes also describe circadian rhythms.\[^2\]

Diurnal rhythms have been described for glomerular filtration rate, effective renal plasma flow, tubular secretion, urine output and urinary excretion of electrolytes and many endogenous substances.\[^10\] These rhythms may result in different excretion rates for drugs at different times of the day. Diurnal variations in systemic blood pressure, the renin-angiotensin system and renal blood flow are responsible for time-dependent changes in renal hemodynamics.\[^2\]

**Molecular Basis of Circadian Clock**

The circadian system is organized in a hierarchical manner with a master clock located at the suprachiasmatic nucleus (SCN), which lies above the optic chiasm at the base of the hypothalamus. The SCN receives information about the day-night cycle through photic input via a direct retinal innervation, the retinohypothalamic tract.\[^11\] Neuropeptidergic signaling is responsible for interneuronal synchronization within the SCN.\[^12\] A second synchronizer of the SCN clockwork is melatonin, a hormone secreted by the pineal gland.\[^13,14\]

The master oscillator located at the SCN communicates day-night cycle phase information to the rest of the body. Through neuronal and humoral signals, the SCN sends this information to peripheral circadian clocks that exist in almost all cells of the body and synchronize them to the same phase.\[^15\]

The identification of the circadian clock at the molecular level makes possible the transition from observational studies of drug efficacy and toxicity at different times of the day to cause-effect studies that provide a link between the circadian clock and drug metabolism. When the circadian clock is disturbed, there is a change in drug effectiveness or toxicity.\[^2\]

**Timing of Drug Administration**

Many chronic and acute medical conditions exhibit prominent circadian patterns of symptom manifestation and severity. Among them, cardiovascular events, such as angina pectoris, ventricular arrhythmia, acute myocardial infarction, sudden cardiac death and thrombotic and hemorrhagic stroke, show strikingly higher frequency of appearance in the morning.\[^2,16-20\] The clinical severity of allergic rhinitis and bronchial asthma is most pronounced in early morning hours and timed administration of medications against them as been associated with sleep disturbances and melatonin has been suggested as a potential treatment.\[^21\]

However, comparative evaluations of chronopharmacological strategies have been few - in blood pressure and some forms of cancer - and even then only with evaluation of impact on surrogate variables rather than clinical outcomes.\[^2\]

The controlled-onset, extended-release calcium channel blocker verapamil was the first special drug-delivery medication specifically designed for the therapy of hypertension. The drug-delivery technology of this tablet delays the release of verapamil for ~4-5 hours following its recommended bedtime ingestion. Medication is released thereafter so the highest blood concentration is achieved in the morning around the time of awakening, with an elevated level sustained throughout diurnal activity.\[^22\]

Bedtime administration has proven to be more effective not only for calcium channel blockers but also for a number of other antihypertensive drugs such as angiotensin-converting enzyme inhibitors, alpha-adrenergic receptor antagonists and angiotensin II.
receptor blockers.\cite{23,24,25}

Circadian timing of drug delivery can play a significant role in anticancer therapeutic effectiveness and tolerability.\cite{26} The misalignment of circadian rhythms in physiology, endocrinology, metabolism and behavioural rhythms with the external environment is common among humans those work in night shifts or routinely travel across time zones. An increased incidence of breast cancer has been observed among female flight attendants.\cite{26,27} Also, increased risk of breast, colon, prostate and endometrial cancers has been associated with rotating or permanent night shift work.\cite{28,29,30} The relationship between the rest-activity cycle and cancer prognosis in humans has been investigated in patients with metastatic colorectal cancer. Patients with marked activity rhythms show a more favourable tumor response and survival rate and report a better quality of life.\cite{31}

Clinical studies for treatment of ovarian, renal, breast and liver cancers showed that controlling circadian timing of dosage often leads to decrease in drug toxicity.\cite{22,23,24,25} When 5-fluorouracil (5-FU) is delivered at the same rate over the course of the day by continuous intravenous infusion, the mean plasma 5-FU levels fluctuate, with the highest levels late at night and lowest levels at midday.\cite{32,33} The pharmacokinetics of 5-FU suggests that a chronomodulated delivery schedule would be most effective for cancer treatment, and numerous clinical trials have highlighted the benefits of chronotherapy of 5-FU, particularly in the treatment of colon cancer.\cite{34} Toxicity and efficacy of the platinum-based anticancer drugs cisplatin and oxaliplatin fluctuate with a diurnal rhythm, pointing towards a possible mechanism for these chronomodulated effects. Dosing of oxaliplatin during early to mid-night led to decreased toxicity and tumor growth as well as an increase in life span.\cite{26}

**Future Approach**

Now a day’s pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic and these drugs give hazardous problems in conventional and sustained release therapies. Pulsatile therapy is mainly applicable where sustained action is not required and drugs are toxic. Key point of development of this formulation is to find out circadian rhythm which will control the release of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. Many research trials are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors.\cite{35} Recently developed Spheroidal Oral Drug Absorption System (SODAS) technology is based on the production of controlled release beads and it is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. Chronotherapeutics Oral Drug Absorption System (CODAS) is a multiparticulate system which is designed for bedtime drug dosing, incorporating a 4-5 hours delay in drug delivery. The TIMERx Technology combines primarily Xanthan and Locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong binding gel in the presence of water.\cite{36}

**Conclusion**

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems. Thus designing of proper pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects.

**References**

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