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Chronotherapeutics: Targeting the disease at its ideal time

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Chronotherapeutics is a branch of Pharmacotherapeutics, which follows the treatment approach of attacking the disease, when it is on peak level. Activities of some diseases are based on biological rhythms, which is a self-sustaining oscillation of endogenous origin. The best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun. Circadian rhythms are controlled by a master biological clock in a specific brain structure of the hypothalamus called the suprachiasmatic nuclei (SCN). Circadian rhythm can be observed in many diseases including asthma, hypertension, arthritis, diabetes mellitus and stroke. Chronopharmacokinetics includes the study of transition in drug absorption, distribution, metabolism and excretion based on time. The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablet and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity. Pulsatile drug delivery system is the most interesting time and site specific system designed for chronopharmacotherapy. The alteration of biological rhythm is a new concept for minimizing the adverse effects by optimizing the dosage schedule. Delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients.

Keyword: Biological rhythm, Chronopharmacokinetics, Chronotherapeutics, Circadian rhythm, Pulsatile drug Delivery system.

1. Introduction

Chronotherapeutics is a treatment approach 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 perception that there is an interdependent relationship between peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs [1]. Drug administration (dosing regimen) is synchronized with biological rhythms so as to maximize therapeutic effect. It involves the investigation of drug effects as a function of

biologic timing as well as the investigation of drug effects upon rhythm characteristics [2].

1.1 Biological rhythms:

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons [3]. A biological rhythm is a self-sustaining oscillation of endogenous origin. The spectrum of biological rhythms is broad as displayed in Table 1. Short-period rhythms of a second or so are uncommon; Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days [4]. Intermediate rhythms can be classified into three types:

1. **Ultradian rhythms**: with a period of shorter than 24 hours.
2. **Infradian rhythms:** with a frequency ranging from 28 hours to 6 days.
3. **Circadian rhythms:** "Circadian", is a Latin term coined by Franz Halberg, meaning "approximately one day". Human body appears to be genetically programmed to function on roughly a 24-hour cycle [5].

Finally, long-period rhythms show oscillations of roughly a week, month, and year [4].

The best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun [4]. The reasons behind this are:

- The efficacy and toxicity of many drugs vary depending upon the relationship between the dosing schedule and the 24 hour rhythms of biochemical, physiological and behavioral processes. Also several drugs cause alterations to 24 hours rhythms leading to illness and altered homeostatic regulation [6].
- Circadian rhythm regulates many body functions in humans, viz., metabolism, behavior, Physiology, sleep patterns, hormone production, etc [7].
- 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)

1.2 Molecular basis of circadian rhythms:

Circadian rhythms are controlled by a master biological clock in a specific brain structure of the hypothalamus called the suprachiasmatic nuclei (SCN). Apart from the SCN, the body has circadian oscillators in all brain regions and peripheral tissues. The SCN is synchronised daily by environmental signals – mainly light. Receiving information on lighting conditions directly from the retina, the SCN drives secretion of the pineal gland hormone melatonin as well as and many peripheral clocks, and their outputs modulate the SCN through feedback or feed-forward effects. Thus, in the body there is a hierarchy of interacting clocks. In all cells, the expression of many genes changes rhythmically over 24 hours. Specific circadian genes such as CLOCK, BMAL1, and PER are responsible for the main SCN clock working machinery as well as subsidiary clocks in other parts of the body [8,9] Activity of various components of the body at different time is represented in figure 1.

Table 1: Spectrum of biological rhythms [9]

Period	Major rhythmic components	Duration
Short	Pulsatiles	0.1 second to 1 second
Intermediate	Ultradian	0.5 hour to 24 hours
	Circadian	20 hours to 28 hours
	Infradian	28 hours to 6 days
Long	Circaseptan	~ 7 days
	Circamensual	~ 30 days
	Circannual	~ 1 year

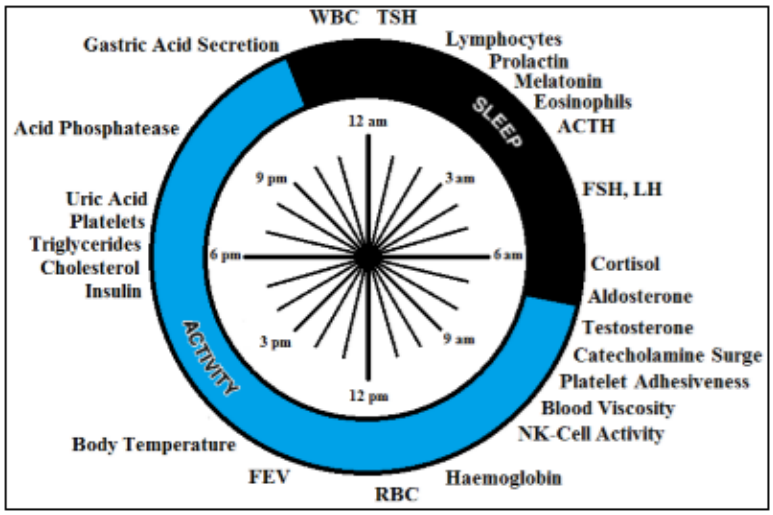

Fig 1: Shigehiro OHDO [4]

1.3 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.

1.3.1 Cardiovascular System:

Most cardiovascular activities show a circadian rhythm, as do several electrophysiological phenomenons. Under the influence of both external stimuli and endogenous homoeostatic mechanisms, cardiac electrophysiological properties change diurnally and enable the cardiovascular system adapt to rest-exercise cycles. Circadian rhythms followed by the diseases are given in the table 2.

Table 2: Rhythmic pattern of diseases

System	Disease or syndrome	Circadian Rhythmicity
Respiratory system	Asthma	Exacerbation more common during the sleep period & attacks after midnight or at early morning hours [10].
	Allergic Rhinitis	Worse in the morning/upon rising [10].
Circulatory system	Blood Coagulation	Even with constant heparin infusion rate, thromboplastin time and risk of bleeding vary significantly during the day[10].
Cardiovascular system	Congestive cardiac failure	Incidence of sudden heart failure higher in the morning after awakening [10].
	Hypertension	Blood pressure is the highest in the late afternoons and gradually decreases in the evenings to attain the lowest values at nights [2].
	Angina Pectoris	Chest pain and ECG changes more common in early morning [10].
	Myocardial Infarction	Incidence higher in the early morning [2, 10]
	Arrhythmias	Clear diurnal oscillations [3].
Musculoskeletal system	Rheumatoid Arthritis	Morning pain and more in night [10].
	Osteoarthritis	Symptoms worse in the middle/later portion of the day [10].
Endocrine system	Diabetes mellitus	Increased blood sugar level after meal [10].
	Hormone Secretion	Growth hormone and melatonin produced at night; testosterone and cortisol in morning hour [10].
Urinary system	Nephrotoxicity	Altered clearance or urinary flowbased on circadian rhythm [2].
	Hepatotoxicity	Altered hepatic clearance due to circadian rhythm [2].

Hepatic system	Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time [10].
Gastrointestinal system	Peptic ulcer disease	Acid secretion high in afternoon and at night [10].
Nervous system	Stroke	Incidence higher in the morning [10].
	Attention deficit syndrome	Increase Dopa level in afternoon [10].

1.3.2 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.

1.3.3 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 but depends on the circadian rhythms too [2]. It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at night. The timing of administration of ulcer medications has a significant impact on their therapeutic effect [1].

1.3.4 Hepatic system:
The overall aim of hepatic drug metabolism is to produce a more water soluble compound to facilitate the excretion of the drug in body fluids such as urine and bile, the primary routes of drug excretion [11]. Liver is also indulged in other functions such as hepatic cholesterol synthesis. During which a circadian rhythm occurs. However, this rhythm varies according to individuals. Indeed, there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis. Many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight; however the maximal production occurs early in the morning, i.e. 12 hour after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing [12].

1.3.5 Respiratory system:
It has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day. Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. The enhanced understanding of the chronobiological impact upon the pathology of asthma, and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care.[1] Thus, a smart drug delivery that is administrated before sleep and maintains high blood levels for longer period (from midnight to early morning, during which maximum intensity of the disease occurs) could be very much beneficial for proper management of nocturnal asthma [13].

1.3.6 Endocrine system:
Insulin is the most effective glucose-lowering agent, which stimulates glucose uptake in skeletal muscles, myocardium, and other tissues in order to control glucose homeostasis.[14] Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release [12].

1.3.7 Chemotherapy:
Antineoplastic drugs cause cytotoxic effects on healthy and diseased tissues. As would be expected, the biological rhythms of both healthy and tumor cells may influence the susceptibility of normal and malignant cells to these agents. It has been demonstrated that "susceptibility rhythms" to drugs may differ between healthy tissue and cancerous tissue. Therefore, the

"correct" timing of drug treatment may reduce host toxicity, increase maximum drug tolerance, and ultimately result in better tumor management. The pharmacologic and pharmacokinetic properties of the drug, rhythmic changes in DNA and RNA synthesis, RNA translational activity and mitotic activity may influence tumor cell susceptibility. It appears that the timing of drug administration in the treatment of cancer can have a significant impact upon treatment success [1].

1.4 Chronopharmacokinetics:

Chronopharmacokinetics entails the study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by various physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH may play a role in time-dependent variation of drug plasma concentration. Numerous chronopharmacokinetic studies have been conducted over the last 20 years. The results of these studies demonstrate that time of administration affects drug kinetics. Studies in man have been reported, particularly in relation to cardiovascular active drugs, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, anticancer drugs, psychotropic drugs, antibiotics and anti-asthmatic drugs. Most of the drugs seem to have a higher rate or extent of bioavailability when they are taken in the morning than when they are taken in the evening.

- Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration indicates that either oral bioavailability decreases or clearance increases with time. The latter has been shown to explain the observation caused by carbamazepine inducing its own metabolism [2].
- 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 [2].
- Anti-inflammatory drugs such as indomethacin and ketoprofen, have also shown that these drugs have a greater rate and/or extent of bioavailability when they are given in the morning than when they are given in the evening. Markedly higher ketoprofen plasma peaks were observed after administration at 07:00 than after administration at other times. Earlier and higher peak concentrations were obtained when indomethacin was given at 07:00 or 11:00 than at other times of the day or night. Better morning absorption has also been observed with controlled release indomethacin and ketoprofen formulations. The clinical relevance of such variations is that high plasma concentrations correlate with high incidence of adverse effects. It has been suggested that morning absorption for these drugs is better than night-time absorption. Greater blood flow of the gastrointestinal tract in the morning than in the evening may explain this phenomenon. Circadian changes in renal function, plasma protein binding or hepatic blood flow could also explain temporal variation in drug plasma levels [1].

Many variables are known to influence pharmacokinetics. In chronopharmacokinetic studies, it is important to strictly control the time of drug administration. When symptoms of the disease are circadian-dependent or drug used has a narrow therapeutic range, a chronophannacokinetic study should be performed. The studies should be conducted under controlled conditions, including fasting time, composition of meals and posture [1].

1.5 Pulsatile Drug Delivery System:

Chronotropic systems are based on the concept of chronopharmaceutics in which there is a transient release of certain amount of drug within a short period of time immediately after a predetermined off-release period. The chronotherapy of a

medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity [15].
Pulsatile drug delivery system is the most interesting time and site specific system. This system is designed for chronopharmacotherapy which is based on the circardian rhythm [16].

1.5.1 Ideal chronotherapeutic drug delivery system should:

- Be non-toxic within approved limits of use.
- Have a real-time and specific triggering biomarker for a given disease state.
- Have a feed- back control system (e.g. Self-regulated and adaptative capability to Circadian rhythm and individual patient to differentiate between awake – sleep status)
- Be biocompatible and biodegradable, especially for parenteral administration [17].

Pulsatile drug delivery system may be helpful for diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence. Dethlefsen and Repges reported sharp increase in asthmatic attacks during early morning hours. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis [10].

1.5.2 Advantages of Pulsatile Delivery:

- Extended daytime or night time activity.
- Reduced side effects
- Reduction in dose size dosage frequency.
- Improved patient compliance.
- Lower daily cost due to fewer dosage units are required by the patient in therapy.
- Biological tolerance
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific sites like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism [10, 18, 19].

2. Conclusion

The alteration of biological rhythm is a new concept of adverse effects, which can be minimized by optimizing the dosing schedule. Large-scale clinical trials have shown that the efficiency and safety of certain conventional (so called homeostatically formulated) medications can be improved by dosing them with reference to the circadian time structure. Delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients. We are sure that, with increase in technological advancement and better design parameters these hurdles can be conquered in the near future and more number of patients will be greatly benefited by these systems.

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4. Conflict Of Interest

All authors state that there is no conflict of interest.

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