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## Chronopharmacology and Chronopharmacotherapy- A Guide to better health

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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. This review focuses on chronopharmacotherapy of various diseases related to different human body systems, and also provides a molecular biological explanation for the influence of medications on the clock genes. Biological rhythms not only impact the pathophysiology of diseases, but the pharmacokinetics and pharmacodynamics of medications. Chronopharmacotherapy is the investigative science that elucidates the biological rhythm dependencies of medications.

**Keywords:** Chronopharmacology, chronopharmacotherapy, circadian rhythm, biological systems.

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## INTRODUCTION

### CHRONOPHARMACOLOGY

The investigation of the effects/side effects of drugs upon temporal changes in biological functions or symptoms of a disease as well as drug effects as a function of biologic timing.

### CHRONOPHARMACOTHERAPY

It 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 [1]. Circadian changes in the effects of various chemical agents have been documented: 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.

The major advantage of chronopharmacotherapy is 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. It reduces the unnecessary side effects of a drug and helps in caring out the treatment for only a particular or limited period of time.

### 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 the drug.

## 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, 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 effecting targeted body parts.

## STEPS INVOLVED IN EVALUATION OF CHRONOPHARMACOLOGY:

- I. Identification of its occurrence: its cause should be identified so as to know which type of variation is seen. This step also clarifies the point that whether the affect is due to biological clock or not.
- II. Determination of the parameter affected: the pharmacokinetic parameters which are affected need to be known. However, more than one parameter may be affected but a need arises to study for all the possible parameters.
- III. Mechanism of non-linearity: there are different types of variations because of which non-linearity in pharmacokinetic profile is seen. To implement chronopharmacotherapy it is necessary to first identify the mechanism and then take measures to solve it.

## 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.

### ***Cardiovascular system***

Most cardiovascular activities show a circadian rhythm, as do several electrophysiological phenomena [3]. Under the influence of both external stimuli and endogenous homeostatic mechanisms, cardiac electrophysiological properties change diurnally and enable the cardiovascular system to adapt to rest-exercise cycles. For example, when the case of blood pressure, both the systolic and diastolic pressures is taken, it seems that they are highest in the late afternoons and gradually decrease in the evenings to attain the lowest values at nights, which can be attributed to the circadian rhythms in the nervous and endocrine system.

Myocardial infarction (MI) occurs more frequently in the morning as a result of the concomitant unfavourable timing of several physiological parameters and/or biochemical conditions. However, little is known about the possible influence of this circadian pattern on prognosis.

During chronic oral treatment of hypertension patients with labetalol, an  $\alpha$ ,  $\beta$ -adrenergic receptor blocker drug, it was observed that the mean steady state levels in patients were almost twice those predicted from a single oral dose. Even most of the cardiac ischemic conditions and acute myocardial infarctions occur usually between morning and the noon.

### ***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 [4], especially in patients who already have compromised renal function. Theophylline causes an increase in the renal flow by increasing the clearance levels and thereby increases the urine flow and renal excretion. 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. The elimination of diazepam is slower with multiple dosing than following a single dose [5]. This change in clearance appears to be a consequence of the considerable accumulation of nor diazepam on the metabolism of diazepam.

### ***Gastrointestinal system***

The gastrointestinal motility, the intraluminal  $p^H$ , blood flow to 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 all the above mentioned factors are also influenced

by the time of the day [6]. 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:**

#### ***Cardiovascular diseases***

Cardiovascular functions such as heart rate and blood pressure show 24h variation [6]. 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 been shown to vary with time of the day, but whether these variations are due to the endogenous circadian clock, exogenous factors, such as the light dark circle, or an interaction between the two remains to be determined.

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. The blood pressure and the and essential (primary) hypertensive display highest values during daytime followed by a mighty drop and early morning rise [7]. In about 70% of forms of secondary hypertension, however this rhythmic pattern is abolished or even reversed exhibiting nightly peaks in blood pressure.

#### ***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 2am 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 uniphyl, 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 [8].

### **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. Eric zhang the first author of this study feels that it is very surprising that the “CRYPTOCHROME has a new function that no one has ever predicted since till date it was just supposed to be a just a key protein regulating the genes in a rhythmic way but now it is proved to have extra nuclear functions as well”. The additional function of the cryptochrome is the regulation of gluconeogenesis according to the diurnal activity and feeding levels. So modulating cryptochrome 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.

### **Cancer**

The tumour cells and the normal cells differ in their Chronobiological cycles. This fact is the basis for the chronopharmacotherapy of cancer [9]. 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]. For sufferers of allergic rhinitis, the major symptoms of sneezing, runny nose, and stuffy nose are typically worsened in the evenings.

### ***Immunological reactions***

In vivo immune responses vary with circadian rhythms including hypersensitivity reactions in the skin and lungs, acute graft rejection and humoral and cell antibody responsiveness. Circulating levels of immunoglobulin in normal animals and immune complexes in inflammatory states also vary with a predictable circadian pattern. Studies in the rat and in man have shown that the time of day at which an antigen is encountered has an influence on the expression of any subsequent cell-mediated immunity, when the responses measured after a fixed interval. This suggests that immune processes are modulated by intrinsic biological rhythms. The study in rats demonstrated a circadian rhythm in delayed hypersensitivity to oxazolone. The response is T cell-mediated although there are B cells and possible serum components [1-11].

### **CONCLUSION**

The major objective of this review is to inform biologists, clinicians, pharmaceutical scientists and other professionals the importance of biological clocks and chronopharmacology to human health and disease. Other purpose is to trigger further experimental and clinical research in the field of chronopharmacotherapy. However, the most important issue of this article is to motivate the investigation, and development of chronotherapeutics as a practical means of improving the outcomes and safety of medical treatment with the older or already well established active pharmaceutical ingredients. In addition, the discoveries of small compounds or new drug substances that act on the peripheral clock will help us to establish chronopharmacotherapeutic approaches to more appropriate extend.

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