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## REVIEW ON CHRONOPHARMACOLOGY

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### ABSTRACT

Chronopharmacology is the science that is of different types in the pharmacological activities of different treatment over organic timings and intrinsic balance. Chronotherapeutics is the science which increases the creativity and security of prescriptions stabilizing their fixations during the 24 h harmonizing with regular routine determinants of disease. Chronopharmacokinetics again manages time and expected changes in pharmacokinetic parameters of medicines. For example manages the examination of the brief changes in the assimilation, dissemination, digestion, and disposal because of the time of planning of the treatment. Circadian rhythms are especially remarkable in drugs. Biologic rhythms are the endogenous nature of circadian. Chronopharmaceutics is represented as a part of pharmaceutics gave to the plan and evaluation of medication prescribing structure that issued a bioactive specialist at a musicality that preferably coordinates the natural necessary condition of given disease treatment. The fresher treatment carrying structure that is structured with the chronopharmacological approach holds incredibly long for conveying better patient consideration regarding viability, resistance, and wellbeing parameters of the medication.

**Keywords:** Chronopharmaceutics, Chronopharmakokinetics, Circadian Rhythm.

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### I. INTRODUCTION

What is mean by Rhythm and Cycles?

Rhythm: Rhythm /Circadian Rhythm, the word circadian has been derived from the Latin word circa which means about and dies ,which means a day.

It is defined as the oscillations in the biological ,physiological and behavioral function of an organism with periodicity of 24 hrs.[1]

The circadium rhythm regulates many functions in the body /important behavior in all living organisms .[2]

It enables the organisms to maintain and restrict their activities according to the day and night time.[3]

Circadium rhythm and its sensitivity to time change with changes in the age of any individual.[4]

However, the human body also maintains the homeostasis by carrying out its normal functions according to the time cycle.[5]

For example; in the evening when the light intensity decreases in the eyes,the master clock stimulates the production of melatonin hormone responsible for generating a drowsiness feeling which helps in maintaining the sleep.[6]

#### Cycle/Biological Cycle:

All the living organisms ,including humans, plants, animals, fungi and other micro organisms have adopted a biological process that regulates at 24 hr. day-night cycle.

The biological cycle also called as circadian cycle regulates itself in every living organisms to carry out important biological funtions, like a sleep awakening cycle, blood pressure, hormone secretion, metabolism and many more .[7]

It is the daily cycle that is regulated in every living organisms characterized by rhythmic changes in all the chemical reactions and maintaining their homeostasis in the body along with the adaptation of biological functions .[8]

Chronobiology = Chronos + bio + logy

[with related to time ] [life] [study]

Chronopharmacology

Pharmacokinetic Pharmacodynamic

rhythm. The pharmacokinetic and Pharmacodynamic of drug with respect to time at which time period it will have high absorption, distribution, maximum efficacy is studied in chronopharmacology.

Circadian Rhythm changes in physical, mental or expressional activity in time cycle of 24 hrs. Deals with the correlation of drugs effect to the circadian.

Chronopharmacology is affected by – Light and Darkness. And controlled by small area in brain.

It will affect to human body; Sleep, Body Temperature, Hormones, Appetite.

Abnormality lead to ; Obesity, Diabetes, Depression, Bipolar disorder, Insomnia, Sexual behaviours.[9]

They are also called as the biological clock of the body. To change the activity of the body with respect to time.

Chronopharmacokinetics; study of changes in ADME based on the time of administration of drug ; Adsorption may be influenced by;

1. Gastrointestinal acidity
2. Gastrointestinal blood flow

Lipid soluble drugs are likely to be absorbed better in the morning and distribution will also be better.

Metabolism of drug by enzyme affected by Circadian Rhythm.

Chronopharmacodynamics ; study of how the effect of drugs are modified based on the time at which they are administered.

what will be effect of the time on the desirable effect of the drug.

Chronopharmaceutics;

Application of the circadian rhythm variation to the drug administration or matching the time of drug administration to the circadian rhythm to obtain better effect of drugs.

Comparative study of effect of drug at different time at which we get more desirable effect and less undesirable effect by giving the drug at different times.[10]

Effect and Applications:

- Morning = peak level of serum cholesterol, aldosterone, testosterone are found early in the morning. Glucocorticoids and Testosterone are administered in morning to mimic natural secretion.
- Mid -day = hematocrit [RBC's ratio with other cells is high during midday.]
- Evening = highest level of uric acid, cholesterol and insulin are seen during evening.[statins]
- Night = melatonin, prolactin, FSH are higher during night.
  - Ex; higher incidence of myocardial infarction and stroke at morning.
  - Symptoms of allergic rhinitis is worst in morning.[11]
- Uses:

Use in treatment of various diseases;

- Hypertension
- Bronchial asthma
- Peptic ulcer
- Myocardial infarction
- Arthritis
- Cerebrovascular accidents[12]

### **Circadian Hormones, Cellular Clocks, and the Control of Metabolism, Digestion, and Cardiac Function:**

Beyond the neurotransmitters whose circadian output is directly or indirectly regulated by the SCN, numerous other hormones show daytime regulation that remarkably regulates physiology and pharmacology. Melatonin, a circadian hormone of the pineal gland, holds various aspects of retinal and cardiovascular function and affects local clocks in diverse brain regions . Circadian regulation of the adrenal gland results in diurnal secretion of glucocorticoid hormone, which, in turn, strongly holds metabolism and in fact directly regulates 60% of the liver transcriptome .[13] Circadian regulation of gastrin, ghrelin, and somatostatin, as well as direct regulation by autonomous clocks within the gastrointestinal tract, mediate circadian rhythm. More generally, autonomous circadian clocks not only within the gastrointestinal tract but also in numerous other tissues have significant influences on physiology and metabolism. For example, abscission of clocks in pancreatic islets results in diabetes because of defects in the coupling of  $\beta$  cell stimulus to insulin secretion , and local clockwork

controls the expression of multiple ion channels and kinases in heart that influence cardiac function and triglyceride metabolism[14]. Recent transcriptome studies have identified widespread local circadian regulation not only in heart but also in skeletal muscle and fat, showing that clocks in these tissues directly regulate physiologynces on digestive function [15]

## II. CONCLUSION

The recent discovery that we have highlighted yield insight into the growing field of chronopharmacology and into the mechanistic basis for the variations in PK/PD that have been observed in a vast number of instances.

However, many important questions last unanswered. Most if not all of the circadian expression data at the genomic level on which these conclusions are based are available only for rodents.

Bearing in mind the fact that the expression and functional properties of drug-metabolizing enzymes and drug transporters are highly species specific , hypothesize of these results to humans is not a foregone conclusion. To translate research data to clinical application, significant progress in the characterization of circadian variations in protein expression and activity in humans is absolutely necessary.

Although there has been much more perception of the impact of the circadian clock on health, disease, and treatment in recent years, these findings have not translated to clinics or regulatory agencies on a broad scale. Entering the search term circadian on the ClinicalTrials.gov website yields a list of 205 related clinical trials. Twelve of these trials are cancer related, but none try to establish chronotherapeutic treatment regimens. The search term chronotherapy results in 14 hits. In disparity, the search term cancer produces 38,331 results. Similar results were obtained from the EU clinical trials register.

Given the fact that about 20% of the transcriptome, proteome, and metabolome are under clock control these results seem disproportionate. In the case of regulatory authorities, none of the chronobiological effects on PK/PD outlined here are mentioned in the guidelines published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This is surprising, especially considering that unexpected hepatotoxicity and cardiac side effects are the most common reasons for the withdrawal of marketed drugs.

Finally, the large proportion of physiology regulated by the circadian clock suggests that the clock itself might serve as a possible pharmaceutical target to increase efficacy and reduce side effects of existing drugs. For such treatments to be effective, more detailed knowledge will be required—not only of how clocks control physiology but also of how clocks in different organ systems contribute to different processes relevant to PK/PD.

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