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CHRONOPHARMACOLOGY: THERAPEUTIC IMPLICATIONS AND EMERGING INSIGHTS

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Abstract

Chronopharmacology, explores how drug effects align with the body's natural rhythms. This field recognizes that factors like a drug's absorption, distribution, metabolism, and excretion (pharmacokinetics), as well as its overall effectiveness and potential toxicity, vary significantly based on administration time. The body's internal circadian clock, located in the suprachiasmatic nucleus (SCN) and influencing widespread physiological processes, plays a crucial role in these temporal variations. Understanding these rhythms are key to optimizing drug therapy for various conditions, including asthma, hypertension, and cancer, where chronotherapy can improve efficacy and reduce side effects by considering circadian-controlled drug metabolism and cellular processes. Despite growing awareness, translating this knowledge into widespread clinical practice and drug development remains a challenge, highlighting the need for more human-specific data and further research into the circadian clock as a therapeutic target.

Keywords: Circadian Rhythms, Chronopharmacology, Suprachiasmatic, Nucleus (SCN), Pharmacokinetics, Drug Metabolism.

Introduction

Chronopharmacology, formally recognized in the early 1970s [1,2], studies how drug effects change with the body's internal timing and rhythms [3]. This field aims to improve our understanding of predictable, cyclical changes in a drug's beneficial effects and tolerance, with dosing time adjustments considering circadian rhythm parameters like mean, period, amplitude, and phase [2]. Early on, it wasn't clear to pharmacologists that endogenous biological rhythms, not just external factors, controlled how drug effects and elimination varied [2]. Observing drug responses led to the idea, as early as 1814, that administration time could alter desired and undesired outcomes [3].

With chronological biology, it became vital to re-evaluate drug data based on when it was collected. An organism's body has many biological rhythms, meaning a drug's effect and fate can depend on its administration time. Chronopharmacology thus involves adjusting drug efficacy based on the hour, day, or month. It investigates temporal differences in drug activity, toxicity, and kinetics, and how drugs might change the organism's temporal structure [4]. Most drug data came from single or multiple doses, with effects typically assessed during the day. However, chronopharmacologic studies gather this by giving treatments at various times to uncover 24-hour circadian processes that greatly influence drug impact. This research has led to new concepts like temporal kinetics and sensitivity. Chronopharmacology aims to develop therapeutic strategies that maximize drug effects and minimize toxicity by designing regimens that account for the circadian rhythm system. Chronotherapeutics considers target tissue sensitivity and time-dependent pharmacokinetic changes due to rhythmic bodily processes [5].

The body's circadian rhythms are a key factor for medication timing. Disease onset (e.g., heart attacks, asthma attacks) isn't random over 24 hours, meaning drug effects and pharmacokinetics can also show significant daily variations. This confirms circadian rhythms are a crucial basis for drug therapy, especially when assessing

drug delivery systems and pharmacokinetics [6]. Circadian rhythms of sensitivity are increasingly understood in humans and animals, with more functions linked to these rhythms as research progresses [7]. In mammals, the circadian system drives sleep-wake behavior, hormonal secretion, and metabolism, responding to daily environmental changes like light-dark cycles, food intake, and medication [8]. Research shows regular changes in biological sensitivity and response to various physical and chemical factors are noteworthy (Reinberg, 1976). Pharmacological facts concerning human circadian rhythms are well-documented, with studies extending beyond 24 hours to cover months or even a year (Reinberg, A, 1976). Three new concepts should be taken in consideration in order to understand the chronopharmacologic findings,

a) The chronokinetics of a drug, defined as both rhythmic (circadian) changes in the drug bioavailability (and/or pharmacokinetic effects) and its excretion (urinary, among others)
b) The chronesthesy of a bio system to a drug, or the circadian change in the susceptibility of any bio system to a drug (including organ systems, tumors, parasites, etc.)
c) The chronergy of a drug, or the rhythmic change in the overall effects and the effectiveness of a drug (Tahara, 2014).

One of the goals of chronic pharmacology is to overcome the problems of drug optimization, that is, to support the desired effect of corticosteroid or other drugs, or the undesirable effect [4]. In the human organism, among other animal species, the result of drug and nutrient metabolism is not fixed as a function of biological time. As the fact that metabolic pathways are not permanently open, or with continuous 24 hours, among other biological cyclic domains. Thus, the biological chronological approach with respect to pharmacological phenomena provides greater safety from errors compared to the traditional approach to treatment [4]. The knowledge of interactions between circadian clock and drugs should be very useful for clinical practice [9].

Biological rhythms and Chronobiology

Cyclic biological rhythms in the physiological and biochemical processes of most animals, including humans can be observed.. For example, when looking at plasma cortisol concentrations. Blood levels van be noticed to be different over a maximum 24 hour period, called the end phase, falling at 07:00 in humans, resting at night, and daily activity. This point is of particular importance because the rhythm may be reversed if the activity occurs at night [10,11].

This difference, which is characterized by a period of about 24 hours, represents a circadian rhythm: a sinusoidal curve may often model such a difference, and thus can be characterized by the usual parameters of this sine function (for example, period, amplitude, mean value, and phase, Also called metaphase). Specific statistical methods such as singular or custom cosinor, Fourier analysis, etc., as well as classical methods (such as analysis of variance) can be used to document statistical significance and detect rhythm [10, 11].

Most circadian rhythms are genetically determined according to an assessment of their stability under constant conditions such as continuous light or darkness (eg, free-running conditions). In mammals, circadian rhythms are controlled by an internal clock located in the hypothalamus in the suprachiasmatic nucleus (SCN). Clock genes such as Per 1, Per 2, Per 3, Cry 1, Cry 2, Clock, B mal1, Tim, etc., are coding for the synthesis of proteins involved in regulatory loops of the SCN. For example, peripheral clocks have also been described in the gut or in the liver.

Temporal differences in the light/dark cycle, rest/activity, fasting/eating as well as any other environmental conditions that give temporal cues, known as 'synchronisers', give the organism temporal markers and thus may influence circadian rhythms. Thus, the phase shift in the synchronization mode is followed by the same phase shift of the studied rhythm. Synchronizers do not create rhythms but may affect them. When suppressed, (eg, in free-running conditions) the rhythm generally remains observable but has a 'normal' period of more than 24 hours justifying the qualification of 'circadian clock' which means about 24 hours and not exactly 24 h , (eg, nycthemeral). Thus, synchronizers are responsible for resetting the time of circadian rhythms resulting in a better adaptation of the organism to its environment.

In many pathophysiological, social and environmental changes (eg, jet lag, shift work, illness, etc.), these rhythms can be altered or suppressed.

Medications may also alter circadian rhythms as documented in chronopharmacology studies. Chronopharmacology studies the effect of the moment of drug administration on its response according to the temporal structure of the receiving organism as well as drug-induced changes in circadian rhythms. The drug may determine a different response from a qualitative or quantitative point of view (temporal pharmacodynamics) and/or a different plasma profile (pharmacokinetics) [12,13].

Biological Rhythms

There are four biological rhythms

Circadian Rhythms: A 24-hour cycle that includes physiological and behavioral rhythms such as sleep.

Diurnal Rhythms: The circadian rhythm is synchronized with day and night.

Ultradian Rhythms: circadian rhythms with a shorter duration and higher frequency than circadian rhythms.

Infradian Rhythms: biological rhythms lasting more than 24 hours, such as the menstrual cycle [14]. The circadian clock plays a physical, mental, and behavioral role that responds to light and darkness. This watch helps in

organizing the functions that includesleep schedule, appetite, body temperature, hormone levels, alertness, daily performance, blood pressure, reaction times [1].

Biological Rhythm Disorders

Disorders may occur when normal biological rhythms are disturbed. These disorders include:

Sleep disturbances: the body is "wired" to sleep at night. Disruptions in the body's natural systems can affect sleep, including insomnia.

Jet Lag: disruption of circadian rhythms when traveling across time zones or overnight.

Mood Disorders: Lack of exposure to sunlight can lead to conditions such as depression, bipolar disorder, and seasonal affective disorder (SAD).

Shift Work Disorders: When a person works outside the normal work day, it causes changes in typical circadian rhythms [15]

Cicadian Rhythm

Rhythmic variations in various physiological, biochemical and behavioral factors occur in all living organisms including humans. These differences improve energy use by prioritizing certain body functions at certain times of the day and conserving energy at other times. The circadian rhythm, which has a cycle length of about 24 hours, regulates many functions in humans. Central and peripheral biological clocks are involved in regulating the circadian rhythm in response to environmental cues such as sunlight and nutrition called zeitgebers. The melatonin-pituitary-adrenal (HPA) axis plays key roles in regulating circadian balance.

Chronopharmacology refers to the study of the biological rhythm dependencies of drugs to improve drug therapy by choosing the appropriate time to give a drug, which is associated with maximum efficacy and least adverse effects. Differences in the circadian clock have also been observed in various diseases such as hypertension, myocardial infarction, bronchial asthma and cancer.

Chronopharma chemotherapy strategies have been implemented in improving the timing of drug administration in many diseases showing circadian changes. Innovative chronic drug delivery systems have also been developed to circumvent the need to administer medications at odd times. However, interindividual, interspecific differences, high cost of drug trials incorporating chronopharmacological approaches, and the lack of a reliable biomarker to guide chronological drug therapy are major limitations in this field and require further research [16].

Role of Circadian Clocks in Circadian Regulation

- Circadian clocks are present in almost all cells of our bodies.
- The main objective of the • circadian clock is to improve the metabolism and use of energy to maintain life processes in the organism.
- They regulate homeostasis such as the sleep-wake cycle, appetite, hormone levels and other bodily functions with a 24-hour cycle.
- There are two types of circadian clocks, the central/master clock (found in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus) and the peripheral/dependent clocks found in all other cells of the body.
- They are organized in a hierarchical manner where the central clock controls the peripheral clocks.
- Both clocks contain molecular oscillators that are regulated by environmental signals called zeitgebers. Some examples of zeitgebers are light, food, activity, and others.
- Central and periphery clocks are synchronized by different environmental signals or zeitgebers. (16)
- Sunlight is the main regulator of the central clock. Sunlight falls on the retina, and the signal is transmitted to the feeder subnetwork via the sham retinal canal.
- Terminal clocks are regulated by direct and indirect signals from SCN. Direct signals are transmitted by neural networks (activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis) and through hormonal signals (eg, cortisol). Indirect signals are relayed by the SCN on peripheral clocks by inducing changes in body temperature and feeding behaviour..
- Various transcription factors are involved in regulating the circadian clock. Important transcription factors are CLOCK, BMAL1, and NPAS2 (15,16)

Role of Melatonin in Circadian Regulation

- The SCN contains the MT1 and MT2 melatonin receptors.
- Melatonin is released from the pineal gland during the dark phase of the light/dark cycle and acts on its receptors in the SCN to align the phase with the external light/dark cycle.
- The external administration of melatonin in the morning changes the intrinsic clock by phase, while the evening administration synchronizes the internal clock according to thelight/dark cycle.

Role of Hypothalamo-Pituitary-Adrenal (HPA) Axis in CircadianRegulation

- The HPA axis plays a key role in synchronizing the peripheral clocks and the central clock.
- The SCN communicates with the anterior pituitary gland, which leads to the regular secretion of adrenocorticotropic hormone (ACTH) and thus the release of cortisol from the adrenal glands.
- Peripheral clocks contain glucocorticoid receptors (GCRs), and their activation can alter the transcription of genes in them, synchronizing them with the central clock. However, central clock lacks GCRs, and thus it is devoid of alteration due to cortisol levels [15,16].

- Pharmacokinetic parameters such as drug absorption, distribution, metabolism, and excretion show daily changes.
- Chronopharmacokinetic information can be used to choose the appropriate timing of drug administration to improve drug therapy.

Circadian rhythms in absorption

- Parameters regulating drug absorption and bioavailability such as gastric acid secretion, gastric motility, gastric emptying time, and gastrointestinal blood flow show circadian changes.
- Most lipophilic drugs are absorbed better in the morning than in the evening due to improved blood flow to the digestive system and faster gastric emptying time in the morning [17].

Circadian Rhythms in Distribution

- The drug distribution depends on body size, body composition, blood flow, protein binding, and membrane permeability, which mainly blood flow and protein binding have been shown to have daily variability.
- Blood flow is regulated by the activities of the autonomic nervous system with a more diffuse daily influence of the sympathetic system. Hence, blood flow
- It increases during the day due to predominant sympathetic activity and decreases at night due to decreased sympathetic activity
- Levels of plasma proteins such as albumin and globulin produced by the liver show changes during the day and night due to circadian changes in liver activities. Their blood levels are very low during the night, increase during the day, and reach a very high value during the afternoon [17].

Circadian Rhythms in Metabolism

- Hepatic drug metabolism depends on the activity of metabolic enzymes and/or hepatic blood flow, both of which show circadian changes.
- All stages of drug metabolism are subject to daily control.
- Both microsomal and non-microsomal enzymes show circadian changes.
- The daily variation in hepatic blood flow affects the metabolism of drugs such as propranolol.
- Oxidative microsomal reactions reach their maximum activity during the day and least at night. Conversely, sulfate conjugation reactions are faster during the night than during the day

Circadian Rhythms in Excretion

- Renal excretion depends on renal blood flow, glomerular filtration rate (GFR), tubular secretion, and urine pH [3].
- Glomerular filtration rate (GFR) is highest during the middle of the day and lowest at night.
- Urine pH is acidic in the evening and alkaline in the morning [17].

Chronobiological Implications for Drug Treatment

To what extent has the knowledge presented above translated into effective drug interventions? The most obvious examples of successful chronotherapy are those with obvious symptoms that depend on the time of day. Treatment of bronchial asthma has been adjusted to show maximum plasma levels at the time of the highest incidence of dyspnea, thus relieving symptoms more effectively. Similarly, blood pressure shows a sharp peak in the early morning, importantly coincides with the peak of cardiovascular events, and extends through the night. This difference is seen in both healthy blood pressure levels and patients with essential hypertension. For example, the L-type calcium channel blocker verapamil uses an extended-release formula to obtain therapeutically effective plasma levels in the early morning after oral administration before bed. In addition, such delayed-release drugs were useful for hypertensive patients who do not show a nocturnal decrease in blood pressure, the so-called "non-dippers". Not dipping is a risk factor for congestive heart failure even in clinically normal pressure subjects [18].

Circadian rhythms have been documented throughout the plant and animal kingdoms at every level of eukaryotic organization. Circadian rhythms are intrinsic in nature, driven by oscillators or clocks, and persisted in free-running conditions (such as constant darkness). Genes that express the circadian clock have been identified in different species. An important feature of endogenous circadian rhythms is their anticipatory character.

The rhythm inherent in all living systems, allows them to adapt more easily and survive better under changing environmental conditions 24 hours a day as well as during changing seasons. With this in mind, it is easy to imagine that not only the right amount of the right substance must be in the right place, but that it must also happen at the right time. Also in humans almost all body functions including those that influence pharmacokinetic parameters such as drug absorption and distribution, drug metabolism and renal elimination show significant daily variations. The appearance and symptoms of diseases such as coronary infarction, angina pectoris, stroke and ventricular tachycardia depend on the biological stage.

As mentioned above, not only PK/PD parameters are modulated by time-of–day, but also drug metabolism. For example, Over-the-counter acetaminophen (analgesic N-acetyl-para-aminophenol, APAP) is a leading cause of drug-induced liver failure in the United States.

- APAP is metabolized exclusively by the CYP P450 system of the liver, and toxicity depends on the

production of N-acetyl-p-benzoquinone imine (NAPQI) by CYP2E1.

- The toxicity of APAP is dependent on the time of day, but hepatic clock resection in mice impairs this rhythm [19].

Cancer

While the chronological treatment approach to the above examples relies on relatively few well-established variables, in the case of chemotherapy and associated cancer treatments, predictions for optimal treatment schedules become very complex. On the one hand, chemotherapy drugs must be given in doses high enough to be toxic to cancer, but on the other hand, the dose must be low enough to prevent serious damage to healthy tissues or organs. This means that the pharmacokinetics and dynamics operate within a narrow therapeutic range. Under these preconditions, the differences introduced by the circadian system at multiple levels can be crucial. Further complicating the matter is the possibility that healthy tissue contains not only a clock but also a tumor.

In vivo, this has been shown to measure p32 incorporation into terminal breast cancer tumors. These results are in line with the most recent in vitro data from various human and murine tumor cell lines such as human U2 osteosarcoma. This is an important factor because most cancer drugs are toxic only to dividing cells or have a particularly effective mechanism of action in one phase of the cell cycle, which is at least in healthy tissue surrounded by clock [20].

Irinotecan

The topoisomerase inhibitor (irinotecan) is most effective in the S phase, while alkylating agents cross DNA at any stage of the cell cycle. In the case of an arrhythmic tumor, as in the mouse exocytic osteosarcoma model, other interesting complications emerged [18].

Seliciclib

Seliciclib, a cyclin-dependent kinase inhibitor, appears to stimulate circadian gene expression in tumors and may additionally slow tumor progression through this mode of action. Given the known disruption of circadian behavior in many human cancers, additional efficacy without harm can be achieved by this type of clock resynchronization.

Overall, in several different experimental rodent models, efficacy and side effects of anticancer therapies have been shown to vary up to 10-fold depending on the time of day. However, these parameters are form and drug specific, and it is common for efficacy to depend on mechanism of action, metabolism, and toxicity, and the best treatment schedule should take into account all of these parameters [19].

The therapeutic index of the alkylating agent cyclophosphamide, for example

It is significantly better if the compound is administered during the first part of the active dark phase. This rhythm has been suggested to be dependent on CLOCK: BMAL1 binding in B cells, changes in CYP P450 enzyme activity and most importantly an increase in reduced glutathione such as cisplatin.

- In contrast, the first, rate-limited step of 5-fluorouracil metabolism depends on the availability of dihydropyrimidine dihydrogenase (DPD), some metabolites 5-FU and then inhibits the activity and de novo synthesis of thymidylate synthase (TS), which is important for acid synthesis Nuclear (20).
- DPD and TS expression is high and low, respectively, during the first part of the light phase. Therefore, 5-FU shows the best tolerance and efficacy 180° out of phase with cyclophosphamide and most other alkylating agents.
- Leucovorin (LV) is a TS inhibitor and is often co-administered with 5-FU. This adds to the efficacy of 5-FU and intriguingly changes the ratio of DPD to TS in the same direction as observed at the optimal time of day selected in animal experiments.

Conclusion

Recent insights show chronopharmacology is growing, explaining PK/PD differences, but human data on daily protein expression is still needed to bridge the gap from rodent studies to clinical use. Despite increasing awareness of the circadian clock's impact on health and treatment, this hasn't broadly translated into clinical trials or regulatory practices, disproportionate to the vast physiological regulation by the clock. This suggests the circadian clock itself could be a drug target, though more detailed knowledge is needed on how clocks in various organs influence PK/PD for effective therapies.

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Author Contribution

Zainab Alebady\ Biological rhythms and chronobiology
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