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Chronotoxicity Studies in Pharmaceutical Science: A Comprehensive Review

Ulfet Gudul[1], Hananeh Kordbacheh[2, 3], Sonia Sanajou[4], Gonul Sahin[5*]

[1] Sinomart Plastic and Chemical Substance Company, ARGE Division, Gaziantep, Turkiye

[2] Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus via Mersin 10, Turkiye.

[3] Yeditepe University, Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul, Turkiye

[4] Istanbul Aydin University, Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul, Turkiye

[5] Kocaeli Health and Technology University, Faculty of Pharmacy, Izmit, Turkiye

Abstract

Chronotoxicity evaluates the time-dependent toxicity of xenobiotics together with an individual's circadian rhythm. Suprachiasmatic nuclei located in the hypothalamus regulate circadian rhythms in individuals. Circadian rhythms are important for human health, metabolic processes, inflammation, and various cancers. This comprehensive review aims to provide an overview of the literature on chronotoxicity, circadian pharmacokinetics, and chronoefficiency. Our literature search was conducted using databases including "Web of Science," "PubMed," and "Science Direct." We used the keywords "circadian rhythm dysregulation," "chronotoxicity of therapeutics," "chronotoxicity," and "time-dependent toxicity" for our literature search. Chronopharmacokinetics studies pharmacokinetic changes related to dosage time. Light plays an important role in circadian rhythm by stimulating ganglion cells. The stimulus is transferred to the suprachiasmatic nuclei and other parts of the brain that regulate the circadian rhythm. Evaluation of the risks and benefits of various therapeutic options requires detailed knowledge of the complex mechanisms that regulate circadian rhythms.

Keywords

Chronotoxicity, chronopharmacokinetic, chronotherapeutics, chronoefficacy, circadian rhythms.

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***Corresponding author:** Gonul Sahin **email:** sahingnl@gmail.com

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INTRODUCTION

Chronopharmacology is a scientific field that studies time-dependent physiological responses to drugs. In particular, it examines the influence of endogenous biological rhythms on the outcome of medical treatment. It has been proposed that chronotherapeutic methods can improve the efficacy of many drugs. For instance, chronotherapy is a successful treatment approach for various types of cancers. Chronotherapy improves the tolerability and antitumor efficacy of anticancer drugs in both experimental animals and patients with cancer. Since 2010, toxicologists and pharmacologists have increasingly focused on circadian rhythms, focusing on understanding their consequences (Ayyar et al., 2021).

Chronotoxicology is a subfield of chronopharmacology that focuses on the undesired and adverse effects of xenobiotics on living organisms in relation to their circadian rhythms. Circadian rhythm, known as the internal biological clock, is the cycle of physical, mental, and behavioral changes within organisms that naturally occurs in every 24 hours in response to the environment. Circadian rhythms are thought to be regulated and maintained by the "central clock" or "master clock" which is located in the suprachiasmatic nuclei (SCN) of hypothalamus (Koopman et al., 1989). The circadian timing system plays a crucial role in numerous biological processes and parameters, as depicted in Figure 1.

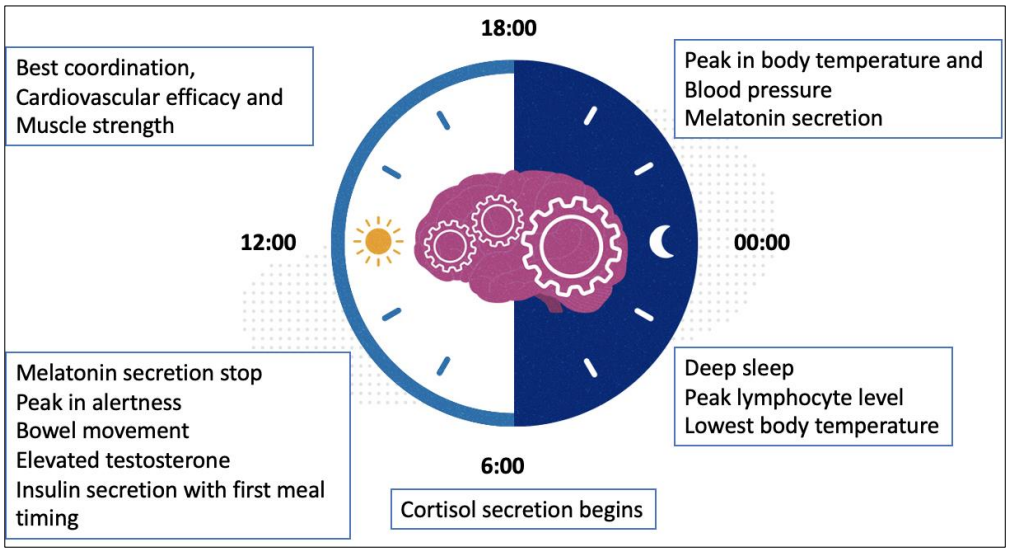

Figure 1: Biological process underlying circadian rhythm.

The importance of circadian rhythm in maintaining both systemic and tissue-level homeostasis, is well recognized. Disruption of the rhythm has direct consequence for human health, disorders, and diseases. In-depth studies on the daily patterns of cells

and tissues have uncovered significant effects of the circadian rhythm on how medicines and xenobiotics are processed and their consequences on the body (Ayyar et. al., 2021). For instance, metabolic syndrome, inflammation, and cancer are caused by disruptions in the circadian rhythm. Plants represent a crucial natural reservoir of diverse underexplored bioactive compounds. Therefore, the investigation of plant metabolites and their biological effects remains a focal point of scientific interest. The ultimate goal is to discover bioactive natural compounds and to advance the development of alternative, green, and sustainable technologies that can reduce or eliminate the reliance on hazardous substances in everyday life (Clairambault, 2007). In addition, circadian rhythm may change the severity of some diseases as listed below:

- Myocardial infarction and stroke incidence are high in the early morning due to a rapid rise in blood pressure (Mohd Azmi et al., 2021).
- Individuals with asthma are generally more susceptible to nocturnal exacerbations, primarily owing to the accumulation of inflammatory cells in the airways overnight (Mason et al., 2020).
- Rheumatic arthritis patients experience joint stiffness and pain in the morning or after a period of inactivity (Jacob et al., 2020).
- Patients with osteoarthritis experience pain in the afternoon, which could be due to decreased secretion of cortisol, an anti-inflammatory hormone, at night (Koyanagi, 2021).

Extensive investigations in mice and rats have been conducted to elucidate the complexities of circadian rhythm effects. Researchers have discovered notable differences in the regular physiological functions and harmful effects of drugs by subjecting laboratory animals to alternating periods of light and darkness lasting 12 hour each (Emmer et al., 2018). Within the 24 hour cycle, various biological processes such as cholesterol production and glucose homeostasis (Mason et al., 2020), oxidative stress levels (Budkowska et al., 2022), and cortisol equilibrium (Mohd Azmi et al., 2021), undergo variations. Recognizing that changes in circadian rhythms might affect how pharmaceuticals work in a person's body highlights the importance of considering individual variations in weekly, seasonal, and yearly circadian rhythms when assessing the balance between the risks and benefits of a therapeutic approach.

MATERIALS AND METHODS

A comprehensive and thorough search was performed on the Web of Science, PubMed, and ScienceDirect platforms to identify relevant papers. The search scope included studies that were published between 2014 and 2024, with a thorough examination of the chosen literature. To ensure the retrieval of publications closely linked to the research emphasis, a carefully selected set of keywords, such as "circadian rhythm dysregulation", "chronotoxicity of therapeutics", "chronotoxicity", and "dosage time-dependent toxicity", were used. Only publications written in English and available as full text were included in study, guaranteeing a meticulous and thorough examination of the pertinent scientific literature. Articles discussing chronotoxicity studies in cancer and cardiovascular diseases were targeted for this research.

Pharmacokinetic and Pharmacodynamic Base Chronotoxicity

Pharmacokinetic that deals with disposition process and fate of the drug is generally divided into four key components: Absorption, distribution, metabolism, and extraction (ADME). ADME describes what the body does to the drug. The four steps determine drug and metabolite concentrations in target tissues and organs, thereby effecting drug efficacy and toxicity (Okyar et al., 2024).

Pharmacokinetic behavior is influenced by various physiological factors including blood flow, gastric motility, enzyme activity, and renal function. Dosing time is also a variable that affects pharmacokinetics, that is referred to dosing time-dependent pharmacokinetics or chronopharmacokinetics (Koyanagi, 2021). Light plays a significant role in regulating the human circadian cycle via effectively synchronizing our internal clocks. When light reaches the eye, it predominantly stimulates the retinal ganglion cells which convert photon energy into an electrical signal. This vital information is subsequently transmitted directly to the suprachiasmatic nucleus neuron (SCN) and the other particular brain regions essential for controlling circadian elements such as sleep, alertness, and mood (Clairambault, 2007). The series of reactions entails the production of humoral, metabolic, and neurological signals, which act as messengers to synchronize the numerous internal clocks in the body. This synchronization results in a cohesive rhythmic arrangement of several cellular activities (Albrecht, 2020). SCN generates autonomous circadian rhythms through two interconnected molecular feedback loops in

circadian locomotor output cycles kaput (CLOCK) gene expression. These loops oscillate over about 24 hours to regulate their own expression. The positive loop is regulated by transcription factors, specifically brain and muscle ARNT-like protein 1 (BMAL1) and CLOCK. As a result of this activation, the period and cryptochrome genes (*per1*, *per2*, *cry1*, and *cry2*) are transcribed. Afterward, PER and CRY proteins gather in the cytoplasm, combining to create the PER/CRY heterodimer. The heterodimer then moves to the nucleus, where it reduces its own production by blocking Clock/Bmal1-mediated transcription. In addition, this complex transcriptional network has a far-reaching impact on the regulation of multiple genes found in different tissues, referred to as clock-controlled genes (CCGs), which are crucial for cellular physiology and metabolism (Korenčič et al., 2014). The dynamic characteristics of drug absorption and pharmacokinetics have been widely studied in animals and humans, and involve many medications (Ohdo, 2010).

Cytochrome (CYP)-mediated metabolic reactions can be either detoxification or bioactivation, where this metabolic pathway plays an essential role in determining drug chronotoxicity. Acetaminophen (APAP)-induced hepatotoxicity is primarily caused by the formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is mediated by CYP2E1 (Bielefeld et al., 2018). Studies revealed that the hepatotoxicity of APAP exhibits a strong circadian rhythm, with more severe toxicity occurring in the evening but milder toxicity in the morning in mice. This variation is attributed to the diurnal expression of CYP2E1, which is high in the nighttime and low in the daytime. Nutrient and drug transporters in the gastrointestinal tract exhibit a circadian rhythm, as documented by the circadian differences in the absorption of nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, indomethacin, and ketoprofen, which exhibit higher absorption after administration of the drug in the morning. The increased rate of absorption may be explained by daily variations in the gastric transit time and intestinal blood flow (Fernandez et al., 2011).

Propranolol, a β-blocker used to treat hypertension, exhibits a greater efficacy when administered in the morning. The lipophilic nature of propranolol may contribute to its rapid absorption in the morning, which is thought to be caused by daily changes in gastrointestinal physiological factors such as gastric pH and gastric emptying rate. Intestinal Abcc2, an ATP-binding cassette efflux transporter, is associated with circadian changes. The

absorption of chemotherapeutic agents, such as methotrexate (MTX), is typically higher when Abcc2 expression is low but lower when Abcc2 is high. Due to lower intestinal Abcc2 expression in dark phase, tissue accumulation and toxicity of MTX are higher than those in light phase. Numerous unwanted side effects such as hepatotoxicity and nephrotoxicity have been reported in patients treated with MTX (Jacob et al., 2020).

Limited research has been conducted on diurnal fluctuations in the dispersion of drugs in various tissues from the overall blood circulation. Circadian shifts can affect the transportation of small-molecule medications by causing diurnal changes in cardiac output and blood flow rates to organs, including the brain, liver, skin, and muscles (Bicker et al. 2020). Additionally, ion channels, transporters, and efflux pumps display diurnal fluctuations in tissue expression, possibly affecting the transport and removal of drug substrates. Protein binding in the plasma and tissue plays a crucial role in drug distribution (Ayyar et. al., 2021). Albumin and other plasma proteins show daily fluctuations in their presence in the bloodstream. These variations can modify the proportion of unbound drugs in the plasma, thereby affecting their distribution. The levels of lidocaine in the plasma exhibit a 2-fold variation based on the number of hours in a day, potentially because of the time-dependent changes in albumin concentrations influenced by the circadian rhythm (Bruguerolle et al., 1983).

The circadian timing system is essential for optimizing metabolism and energy expenditure, with fasting-feeding cycles and rest-activity rhythms serving as the significant timing signals. The system also significantly affects drug metabolism, namely circadian pharmacokinetics and pharmacodynamics, resulting in alterations in therapeutic effectiveness and toxicity (Erkekoglu and Baydar 2012; Levi et al., 2007). The liver is the primary organ responsible for drug biotransformation in the body. Factors that influence drug metabolism include the rate of blood flow in the liver, the activity of certain enzymes, and the binding of drugs to plasma proteins (Fernandez et al., 2011). Circadian rhythms are evident in the gene expression and activity of many enzymes that play a role in drug metabolism. Core clock genes regulate the transcription of several enzymes, and circadian fluctuations have been detected in almost all variables that affect hepatic metabolism (Sukumaran et al., 2010). Recent advancements in molecular biology techniques have revealed both the direct and indirect processes by which core clock genes regulate the transcription of circadian drug-metabolizing enzymes (Dong et al., 2020). Bmal1 and Clock induce circadian

rhythmicity in the expression of CYP2a4/5, Ugt1a1, Fmo5, and Sult1a1 by directly activating their transcription via binding to E-box elements in the promoter regions of these genes. Bmal1/Clock also indirectly controls the activity of drug-metabolizing enzymes, Bmal1, and the daily expression of CYP3a11 through Dbp and Hnf4α (Lin et al., 2019).

Drug excretion, whether in its original form or as metabolites, is the ultimate stage in the process of drug elimination. The kidney is the main organ responsible for the disposal of majority of medicines. However, many pharmaceuticals are also excreted through the bile and eliminated in the feces (Ayyar et al., 2021). Circadian rhythms are observed in all three processes involved in kidney excretion, namely glomerular filtration, tubular secretion, and tubular reabsorption. Research indicates that the glomerular filtration rate (GFR) exhibits a diurnal fluctuation, reaching its highest point during daylight hours and decreasing throughout the nighttime in humans (Koopman et al., 1989). The diurnal variation in renal clearance, mainly for medicines eliminated via glomerular filtration with minimal protein binding, depends on GFR variability and plasma protein binding fluctuations. The fluctuation in plasma protein binding over 24 hours can also impact the daily variations in renal excretion (Sukumaran et al., 2010). The kidneys have an inherent circadian timing system that regulates certain genes responsible for managing secretion/absorbtion of sodium ions, water balance, and the transport of nutrients and xenobiotics. Certain transporters in the proximal tubules of the kidney exhibit circadian cycle. The passive reabsorption of a drug is influenced by its lipophilicity, pKa, urine pH, and flow rate; all of which exhibit diurnal variations (Zuber et al., 2009).

Chronotoxicity of Therapeutic Drugs

Within the field of cancer, the use of a portable programmable pump is considered as a revolutionary method to improve the efficacy of cytotoxic medications delivered through systemic routes (Mak et al., 2020). This technique selectively delivers chemotherapy during the circadian rhythm, when healthy tissues are most sensitive, to minimize the dosage during periods of increased vulnerability.

An example of such an improved technique is the precise timing of the distribution of 5-fluorouracil (5-FU), a commonly used medication in the adjuvant, neoadjuvant, and metastatic therapy of many types of cancers, such as breast, esophageal, and colorectal cancers (Maeda et al. 2018) Interestingly, the injection of 5-FU specifically targets cancer cells but other cells in the body are also affected (Mohd Azmi et al., 2021). 5-FU causes

hematotoxicity depending on the time of administration. Administration of 5-FU at a dose of 300 mg/kg resulted in a significant and statistically measurable reduction in the average number of white blood cells (WBC) circulating in the bloodstream within a 24 hour timeframe, leading leukopenia. Mice treated with 5-FU at zeitgeber time (ZT) 5 and 21 showed maximum and minimum leukopenia, respectively (Bouali et al., 2023). Treatment with 5-FU near the daily awakening period leads to the least damage to the bone marrow and intestine. It enhances key genes' expression and enzymatic activities in the pyrimidine metabolic pathway, resulting in the greatest antitumor effect and the best survival. Moreover, for the optimal timing of effective cancer therapy, it is crucial to know the time of day when tumors reproducibly express proliferative targets relevant to DNA synthesis or cell division. Several chemotherapeutic drugs are toxic to both cancerous and healthy cells in the process of cell division. Furthermore, these drugs often exhibit cytotoxic effects at specific cell cycle stages. For example, drugs such as 5-FU and irinotecan are more effective against cells that are in the S phase (DNA synthesis) of cell division. The number of cells in the S and G2/M phases increased by approximately 50% during the second half of the dark period in the bone marrow tissue of mice, whereas G0/G1 cells were predominant during the light period. The optimal time for administering 5-FU, irinotecan, docetaxel, and gemcitabine in mice is during the early light period, when BCL2 expression (antiapoptotic) is high but proapoptotic BAX expression, is low. However, some anticancer drugs such as oxaliplatin which produces DNA cross links do not have phase specificity (Okyar et al., 2024).

Dihydropyrimidine dehydrogenase (DPYD) is a rate-limiting enzyme that detoxifies 5-FU. Several studies have revealed that the transcription and activity of DPYD reach its peak level during the midnight hours, which could impact the drug's tolerability when administered at these times (Cardinali et al., 2023).

Cisplatin is a highly effective chemotherapeutic agent that has ototoxicity as a notable side effect. Cisplatin has been shown to correlate with circadian timing, since it exhibits the highest efficacy as an antitumor agent and the lowest toxicity to the kidneys when administered during the active (dark) phase of the light-dark cycle in rodents. These findings suggest that administration of cisplatin during the active phase reduces the likelihood of ototoxicity in Fischer rats. This finding aligns with the reduced kidney toxicity observed in animals exposed to cisplatin during nighttime. The substantial differences in threshold shifts

between light and dark exposures suggest that the timing of exposure has a notable influence on susceptibility to cisplatin-induced hearing loss (Ma et al., 2023).

Oxaliplatin is one the therapeutics currently used for the treatment of colorectal cancer (Bruguerolle et al., 1983). It is widely used in combination with 5-FU and irinotecan. The combination therapy can cause hematological toxicity depending on the time of administration (Dulong et al., 2022). Preclinical studies on the chronotoxicity of oxaliplatin carried out on male mice, revealed diurnal patterns of hematological and intestinal toxicities. The most pronounced consequences were detected around ZT7, corresponding to the start of light in a 12-hour light/12-hour darkness cycle when the mice were exposed to these alternating cycles (Boughattas et al., 1994). The human cardiovascular system exhibits disting diurnal patterns over 24-hour cycles, including variations in the heart rate, blood pressure, circulating catecholamines, blood coagulation indicators, vascular endothelial function, and autonomic nervous system activity. Significantly, various cardiovascular systems undergo changes in the morning. Notably, these changes in the morning rhythm are linked to the development of Cardiovascular Disease (CVD) (Buurma et al., 2019).

Platelets are key role in arterial thrombosis, and aspirin prevents it by suppressing platelet function, with patients prescribed a maintenance dose of 75-325 mg daily. Despite lifestyle modifications and drug-based interventions, 10-33% of these patients experience relapse of cardiovascular events within 5 years, with the exact causes unknown but likely multifaceted (Buurma et al., 2019). Aspirin was administered orally. To decrease the fraction of uncontrolled platelets during the morning hours to 5%, one can align with the circadian cycle and consume aspirin before going to bed (Bonten et al., 2014; Krasińska et al., 2021).

Clopidogrel, a frequently given antiplatelet medication for stroke and heart attack, is metabolized by many CYP450 enzymes, including carboxylesterase 1 (CES1). A recent study revealed notable difficulties in achieving successful treatment results with clopidogrel, mainly due to drug resistance caused by differences in the expression of enzymes responsible for metabolizing the medication. Significantly, multiple instances of hepatotoxicity have been documented. Research suggests that clopidogrel has a strong diurnal pattern in its efficacy in wild-type mice, with a more powerful antiplatelet effect during the active phase (ZT 22) than during the resting period (ZT10). This is consistent with clinical observations showing improved effectiveness when clopidogrel is administered to humans in the morning.

Deletion of CLOCK increased the toxicity of clopidogrel and disturbed its daily cycle. In addition, the liver toxicity of clopidogrel is linked to daily variation in the expression of CES1D, which contributes to the complexity of its negative effects (Ma et al., 2023). Therefore, chronopharmacology and chronotoxicology are two important phenomena that significantly affect the fate of medicine (Kaur et al., 2013). Figure 2 provides an overview of various drugs that may be influenced by the phenomena.

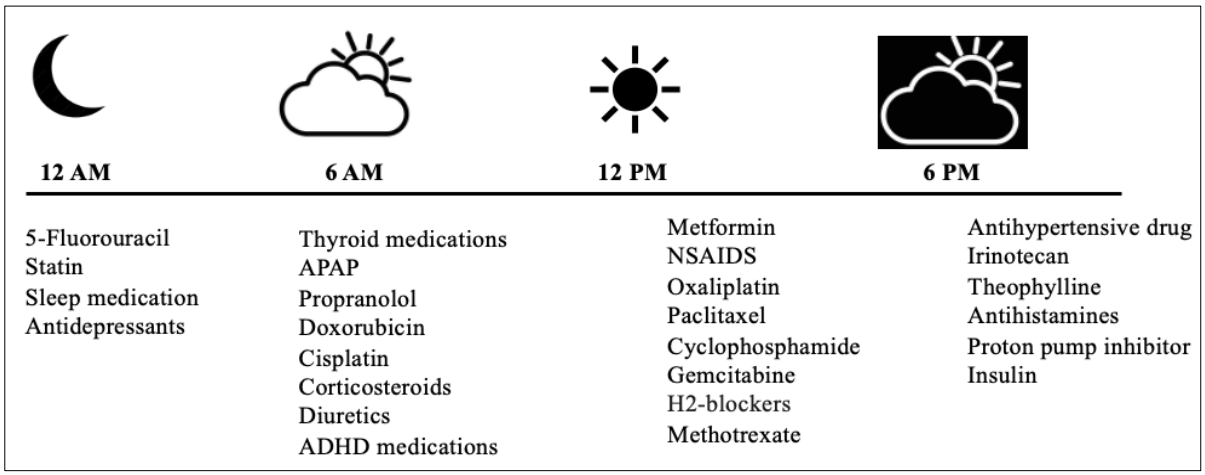

Figure 2: Certain medications whose efficacy and toxicity profiles are influenced at different times of the day.

CONCLUSION

The pharmacokinetic and pharmacodynamic characteristics of drugs show variations related to genetic predisposition, gender, and age of the individuals. The timing of drug administration has important effects on the efficacy and toxicity profiles of the drugs. Studying the regulation and dysregulation of chronotoxicity will help in the development of chronoefficient therapeutic options. Further research and the application of these findings could lead to more effective and safer pharmacotherapy regimens.

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