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IMPORTANCE OF CHRONOPHARMACOLOGY IN LIFESTYLE

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ABSTRACT

Chronopharmacology, is to achieve the highest level of individualization, ensuring both maximum effectiveness and patient safety. To achieve this, a variety of factors must be considered, all of which contribute to the uniqueness of each patient's treatment. These factors include, but are not limited to, the patient's age, sex, comorbidities, specific physiological conditions (such as pregnancy, lactation, or extreme age), polypharmacy, and polypragmasia (especially with respect to the risk of drug interactions), as well as the patient's phenotypic response to medications, which may include genotyping. Additionally, individualized therapy can be supported through Therapeutic Drug Monitoring (TDM), which tracks the concentration of certain drugs in the blood. Another important yet often overlooked factor in pharmacotherapy is chronopharmacology, which indirectly affects the interpretation of drug concentrations in TDM. This paper offers a concise summary of chronopharmacology, with a focus on chronopharmacokinetics, and discusses its importance in the clinical interpretation of drug concentrations obtained through the TDM process.

Keywords: chronopharmacology; circadian rhythm; therapeutic drug monitoring; chronopharmacokinetics.

1. INTRODUCTION

Identificatiion of Chronopharmacology and Review with Objective.

Chronopharmacology is a scientific discipline that examines how biological rhythms influence the effectiveness of pharmacotherapy. It explores the relationship between the timing of drug administration and its therapeutic outcomes, and it plays a crucial role in optimizing pharmacotherapy to ensure maximum efficacy and safety. At present, the personalization of treatment for individual patients typically involves the prescribing physician considering factors such as age, gender, and specific physiological and pathological conditions (e.g., the presence of coexisting diseases) to anticipate potential drug interactions, particularly in cases of polypharmacy. Additionally, pharmacogenetic profiling, which can be determined through phenotypic responses to medications or direct genetic testing, helps guide treatment decisions. Pharmacists also contribute to personalized pharmacotherapy through services like pharmaceutical care and medicine use reviews (MUR), supporting the customization of treatment plans. The ideal approach is to implement personalized pharmacotherapy that takes into account the patient's unique characteristics, alongside a clear understanding of the disease's underlying mechanisms. Other important factors in individualizing and personalizing pharmacotherapy include the use of Therapeutic Drug Monitoring (TDM) to track blood drug concentrations, as well as considering the impact of biological rhythms on the drug's pharmacokinetics (how the body absorbs, distributes, metabolizes, and excretes the drug) and pharmacodynamics (how the drug affects the body). However, challenges remain in fully integrating these factors into clinical practice.

2. AIM OF THE REVIEW

The aim of this brief narrative is to outline the key chronopharmacological concerns and highlight how biological rhythms may influence the guidelines for conducting therapeutic drug monitoring.

Chronopharmacology—A Brief Theoretical Overview

2.1 A Short Historical Review and Present Status in Pharmacology.

Chronopharmacology utilizes knowledge of biological rhythms to develop optimal pharmacotherapeutic approaches. A fundamental physiological characteristic of living organisms is the rhythmic nature of biological processes, which vary over time rather than remaining constant. These rhythms manifest at systemic, organ, and cellular levels and are driven by internal "biological clocks." These self-sustaining oscillations are characterized by regularity and reflect the body's adaptive ability to synchronize its biological and behavioral functions with the changing and predictable conditions of the external environment, thereby maintaining homeostasis. The cyclic nature of physiological processes recognized by chronopharmacology has been noted for centuries. In 1814, French researcher Julien Joseph Virey contributed further by noting that the effectiveness of medications varied depending on the time of day they were administered. Over time, research into biological rhythms expanded to include studies on heart rate variability (HRV), body temperature fluctuations, respiratory patterns, pain perception, and the exacerbation of psychiatric disorders A significant milestone in the study of biological rhythms in physiology and pharmacology was reached in 2017 when the Nobel Prize in Physiology or Medicine was awarded to Jeffrey C. Hall, Michael Rosbash, and Michael W. A significant milestone in

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the study of biological rhythms in physiology and pharmacology was reached in 2017 when the Nobel Prize in Physiology or Medicine was awarded to Jeffrey C. Young for his groundbreaking research on the molecular mechanisms of the biological clock. Their research, conducted in fruit flies, demonstrated how specific proteins accumulate at night and degrade during the day, helping to explain how the body's internal clock adapts to daily rhythms. The Nobel Assembly at the Karolinska Institute highlighted the importance of these discoveries, which elucidated how the internal biological clock helps living organisms, including humans, anticipate and adapt to the regular patterns of day and night. These findings underscored the importance of chronobiology and its relevance to the development of chronopharmacology. Despite this, the practical application of chronopharmacology in pharmacological treatment and therapeutic drug monitoring (TDM) remains limited. . A PubMed search conducted on July 15, 2021, using the term "chronopharmacology" returned just 399 articles, with only 128 published in the past decade. Many of these studies date back to the 1980s and 1990s. A combined search with terms like "chronopharmacology" or "chronopharmacokinetics" and "therapeutic drug monitoring" yielded only 12 results, including two from the past 10 years. These figures suggest that the significance of biological rhythms in clinical pharmacology is often overlooked and must be more widely acknowledged, particularly when developing TDM guidelines.

3.2 Characteristics of Biological Rhythms: Examples of Physiological Phenomena and Pathophysiological Conditions with a Chronobiological Basis.

Biological rhythms are characterized by several key features: period, which is the duration of one full cycle; mean value (mesor), representing the average level of the rhythm; amplitude, The mesor, which represents the average value, the acrophase, which is the time at which the maximum value occurs during a cycle, and the nadir, which refers to the time when the rhythm reaches its minimum value.Based on the period, biological rhythms can be classified into three main types: Ultradian rhythms, with cycles that are shorter than 24 hours, ranging from seconds to hours. These include rapid oscillations seen in electroencephalographic (EEG) recordings, heart rate, and respiratory rate, as well as the basic sleep stage transition cycle, which typically lasts a few hours. Circadian rhythms, derived from the Latin words "circa" meaning "around" and "dies" meaning "day," are biological cycles with a duration of approximately 24 hours. These rhythms are fundamental to regulating various physiological processes, aligning them with the Earth's day-night cycle. Examples include the sleep-wake cycle, fluctuations in body temperature, hormone secretion patterns, and the regulation of blood pressure.

These rhythms are largely governed by the light-dark cycle (photoperiodism) and regulate key physiological functions, including the sleep-wake cycle, core body temperature, secretion of various hormones, fluctuations in arterial blood pressure, and immune system efficiency. These rhythms can occur on a weekly, monthly, or even seasonal basis. Examples include menstrual cycles and seasonal variations in mood and behavior. The physiological and pathophysiological processes influenced by circadian rhythms are particularly noticeable and can impact a wide range of bodily functions, from hormone secretion to cardiovascular and immune responses. These rhythms are illustrated in Figure 1.



Figure 1. physiological and pathophysiological phenomena that follow a circadian rhythm

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It is also important to note that the pathophysiology of many conditions, such as bronchial asthma, peptic ulcer disease, rheumatic disorders, and depression, is closely linked to disruptions in endogenous biological rhythms. Additionally, certain diseases show a higher risk of onset at specific times of day. For example, cardiovascular events like sudden cardiac death, myocardial infarction, and stroke are more likely to occur in the morning, while exacerbations of peptic ulcer disease can also be more frequent at certain times, reflecting the influence of circadian rhythms on disease progression.

3.3 The Regulation of Biological Rhythms: Genes Involved in Controlling the Biological Clock.

The circulatory system, along with various physiological functions such as behavior, hormone levels, sleep, body temperature, and metabolism, is regulated by the biological clock. The suprachiasmatic nucleus (SCN) is the central "biological clock," or primary oscillator, that coordinates the activity of other peripheral oscillators in the body. Located bilaterally in the anterior part of the hypothalamus, just above the optic chiasm, the SCN plays a critical role in synchronizing biological rhythms. The activity of the SCN is primarily influenced by light, with incoming signals modulating its function. The SCN receives afferent information through the retinohypothalamic tract, which originates from photosensitive retinal ganglion cells, as well as from other tracts, including the geniculo-hypothalamic tract and pathways from the reticular formation, septum, hippocampus, and limbic system. These afferent signals help regulate the SCN's cyclic activity, which autonomously generates rhythmic patterns. Efferent impulses from the SCN are transmitted to external oscillators-target structures in the autonomic, endocrine, and immune systems. These systems further adjust the functioning of various body systems, aligning them with the rhythmic changes of the external environment, particularly the day-night cycle. One of the most important pathways is the retino-hypothalamic tract, which is involved in the regulation of melatonin secretion from the pineal gland. Light exposure inhibits melatonin production, while its secretion increases in darkness. Melatonin receptors are present in various peripheral tissues, where the hormone exerts its effects, modulating physiological functions. Another critical pathway is the tract connecting the SCN to the periventricular nucleus of the hypothalamus. This connection links the SCN to neurosecretory cells that secrete corticotropin-releasing hormone (CRH), which is involved in the hypothalamic-pituitary-adrenal (HPA) axis and helps regulate the secretion of hormones from the adrenal glands, as well as other endocrine functions. These connections between the SCN and various bodily systems highlight the integrated role of the biological clock in maintaining physiological rhythms and homeostasis.

One of the most important pathways involved in this process is the retino-hypothalamic tract, which influences the secretion of melatonin from the pineal gland. Light exposure inhibits melatonin secretion, while darkness triggers its release. Melatonin receptors are present in various peripheral tissues, allowing the hormone to exert a wide range of effects, modulating physiological functions. Another key tract connects the SCN to the periventricular nucleus of the hypothalamus. This pathway links the SCN to neurosecretory cells that release corticotropin-releasing hormone (CRH), which plays a crucial role in the hypothalamic-pituitary-adrenal (HPA) axis, regulating the release of hormones from the adrenal glands and other endocrine glands. Together, these mechanisms help align bodily functions with the predictable environmental changes that occur throughout the day and night. At the molecular level, the cyclic changes in the SCN's physiological activity are driven by oscillations in the expression of specific genes, their transcription factors, and the proteins they produce, which create negative feedback loops that regulate neuroendocrine output. The key genes involved in regulating the biological clock include Clock (Circadian Locomotor Output Cycles Kaput) and Bmall (Brain-muscle Arnt Like-1). These genes are transcribed and translated early in the day, producing CLOCK and BMAL1 proteins. These proteins then form a heterodimer and translocate to the cell nucleus, where they bind to the promoter regions of target genes such as Per1, Per2, and Per3 (Period), and Cry1 and Cry2 (Cryptochrome). The proteins encoded by these target genes are part of the negative feedback mechanism that regulates the clock. As the day progresses, PER and CRY proteins accumulate in the cytoplasm and eventually move into the nucleus, where they act as repressive transcription factors, inhibiting the CLOCK-BMAL1 complex. This repression reduces the transcription of Clock and Bmall, contributing to the rhythmic nature of the biological clock. At night, the PER and CRY proteins are degraded, which releases the inhibition on CLOCK and BMAL1, thereby restarting the cycle and initiating a new round of transcription and translation. This molecular mechanism, which helps synchronize the body's internal processes with the changing light-dark environment, was foundational to the understanding of circadian rhythms and led to the 2017 Nobel Prize in Physiology or Medicine being awarded to researchers Jeffrey C. Hall, Michael Rosbash, and Michael W. Young for their discovery of the genes and proteins that govern the biological clock and adapt organisms to cyclic environmental changes.

3.4. The Impact of Biological Rhythms on Pharmacology of Selected Diseases.

The most well-documented circadian rhythms include the variability in arterial blood pressure (BP), which exhibits a predictable pattern in both normotensive individuals and those with primary arterial hypertension. BP and heart rate

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(HR) typically decrease at night and increase in the morning, reflecting the body's preparation for daytime activity. This rhythm is primarily driven by the cyclic increase in morning activity of the sympathetic nervous system, along with elevated plasma renin activity and the secretion of pressor hormones that increase peripheral vascular resistance and enhance the automaticity of the heart's electrical conduction system. As a result, blood pressure peaks in the late morning and early afternoon, then declines in the evening, reaching its lowest point between 8 p.m. and 2 a.m. Additionally, fibrinolytic activity in the plasma is lower in the morning, which is associated with an increased risk of thrombus formation. This makes the early morning period (3–4 hours after waking) particularly dangerous, as it coincides with a higher likelihood of cardiovascular events such as acute coronary syndromes or strokes. Interestingly, the endothelium also exhibits cyclic activity, with maximal nitric oxide secretion in the morning and during the day. This serves as a physiological countermeasure to excessive blood pressure increases, helping to maintain vascular homeostasis.

In contrast, the evening and night are periods dominated by the parasympathetic nervous system, which leads to a reduction in pressor hormones and decreased activity of the renin-angiotensin-aldosterone (RAA) system, resulting in lower blood pressure and heart rate . Clinically, these circadian patterns can be used to categorize patients with hypertension into two distinct groups: "dippers" and "nondippers".

- Dippers are patients whose systolic and diastolic blood pressure drops by 10-20% at night compared to daytime values.
- Nondippers fail to show this expected dip, maintaining higher levels of BP throughout the night.
- Extreme dippers, on the other hand, experience a greater-than-20% drop in BP overnight, which can increase the risk of orthostatic hypotension and other ischemic complications, such as optic nerve damage.

The phenomenon of "morning surge", which refers to a significant rise in BP within the first few hours after waking up, is also clinically significant. Research has shown a positive correlation between the morning surge and the risk of cardiovascular events and complications in primary hypertension. This surge is typically measured by comparing the mean systolic BP (SBP) in the two hours after waking to the three lowest SBP readings during the night. A pathological morning surge is defined as an increase of \geq 50 mm Hg in systolic pressure and/or \geq 22 mm Hg in diastolic pressure compared to the lowest nocturnal values. Chronopharmacology plays a crucial role in managing hypertension, emphasizing the importance of synchronizing the timing of antihypertensive drug administration with the natural fluctuations of BP throughout the day. This approach can improve both the effectiveness and safety of treatment, particularly when tailoring therapy to specific chronotypes, such as dippers, nondippers, or morning surge patients.

Chronopharmacotherapy is a key approach in managing primary hypertension, as it involves aligning the administration of antihypertensive medications with the body's natural circadian rhythms to improve treatment efficacy and safety. Since blood pressure exhibits daily fluctuations, with peak values occurring in the early morning and lowest values during sleep, chronopharmacotherapy aims to synchronize drug concentrations with these fluctuations. For instance, antihypertensive drugs are typically administered at higher doses in the early-morning post-awakening period, when blood pressure is highest, and at lower doses during sleep, when blood pressure naturally drops.

However, the optimal timing for drug administration may vary depending on the patient's circadian profile—whether they are "dippers," "nondippers," or have a "morning surge." Clinical research supports that different chronotypes may respond better to medications administered at specific times of day. For example:

- RAA (Renin-Angiotensin-Aldosterone) system inhibitors, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, are most effective when taken at night. This timing improves blood pressure control in nondipper patients (those whose blood pressure does not exhibit the expected nighttime dip).
- Thiazide diuretics, when administered in the evening, have been shown to be more effective for controlling blood pressure in monotherapy.
- Beta-adrenolytic drugs should be taken in the morning, as they work most effectively during periods of higher catecholamine activity and adrenergic receptor expression.

Interestingly, dihydropyridine calcium channel blockers do not show a clear dependency on the timing of administration, likely due to their long half-life, which makes them effective regardless of the time of day. A further application of chronobiology in medicine is in the treatment of insomnia, particularly through the use of melatonin and melatonin receptor agonists. As mentioned, melatonin is a hormone synthesized by the pineal gland in response to signals from the suprachiasmatic nucleus (SCN), the body's central biological clock. Melatonin levels naturally increase in the evening as darkness approaches, signaling to the body that it is time to prepare for sleep. This increase is a key part of the body's circadian rhythm, which regulates the sleep-wake cycle. Melatonin continues to rise during the night, peaking in the middle of the sleep period, and then gradually declines as dawn approaches, signaling the body to wake up. This rise in

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melatonin helps to facilitate sleep onset and supports the synchronization of the circadian rhythm, which is why melatonin and its receptor agonists are effective treatments for insomnia and other circadian rhythm disorders. Several melatonin receptor agonists are used for sleep induction in conditions like delayed sleep phase disorder:

- Ramelteon and tasimelteon are used in the treatment of insomnia, particularly for helping patients who have difficulty falling asleep. These drugs are commonly prescribed in European countries, Japan, and the USA.
- Agomelatine, an antidepressant that modulates melatonin receptors, has also been shown to improve circadian rhythms, making it useful in conditions like dementia and depression, where 24-hour sleep-wake patterns are disturbed.

In sum, chronopharmacotherapy applies the principles of circadian biology to optimize the timing of drug administration for the treatment of various conditions, enhancing therapeutic outcomes and minimizing side effects. This approach recognizes the inherent daily fluctuations in bodily functions and seeks to align treatment with those natural rhythms, leading to more personalized and effective care.

Chronopharmacokinetics – The Impact of Biological Cycles on Pharmacokinetic Processes

As noted earlier, biological rhythms significantly influence the pharmacokinetic properties of drugs in the body. Chronopharmacokinetics (chronoPK) explores the relationship between these endogenous biological rhythms and the ADME (Absorption, Distribution, Metabolism, Excretion) processes that govern drug metabolism. Since pharmacokinetics precedes the final pharmacological effect of a drug, chronoPK indirectly affects the pharmacodynamics of drugs and their concentration in the bloodstream, which is typically assessed through therapeutic drug monitoring (TDM). In this way, an understanding of pharmacokinetics also enables the concept of chronoTDM, which considers the timing of drug administration in relation to circadian rhythms to optimize drug efficacy and safety. The circadian rhythm of the gastrointestinal tract plays a crucial role in determining the pharmacological effects of orally administered drugs. This rhythm influences a range of gastrointestinal processes, such as cell proliferation, motility, digestion, absorption, electrolyte balance, and even intestinal barrier integrity and microbiota composition. Drug absorption, in particular, depends on a combination of the drug's physicochemical properties (e.g., molecular mass, lipophilicity), physiological factors (e.g., gastric pH, blood flow, motility), and any underlying pathophysiological conditions. Gastric pH, which plays a crucial role in drug ionization and solubility, exhibits a circadian pattern, with peak acid secretion occurring typically just before midnight. For drugs that are transported across biological membranes via active transport rather than passive diffusion, bioavailability is influenced by the activity of membrane transport proteins, such as P-glycoprotein (P-gp), ABCB1, MDR1, BCRP, and MRP. These proteins are subject to circadian regulation, with their expression and transport functions fluctuating over the course of the day. For example, the Bmall gene regulates the cyclic expression of the MRP2 protein, in part through the activation of DBP (a protein that activates MRP2) and the repressor protein E4BP4. Similarly, the activity of other transport proteins like BCRP and MDR1 is influenced by transcription factors (e.g., ATF4) that follow circadian rhythms.

In general, drug absorption is more efficient during the daytime, especially in the morning and early afternoon. This is due to increased visceral blood flow (secondary to higher cardiac output) and accelerated gastrointestinal motility at these times. Lipophilic drugs, in particular, are absorbed more quickly in the morning, resulting in higher C max (peak concentration) and shorter T max (time to reach peak concentration) when taken during this time .For example, studies have shown that morning administration of NSAIDs like diclofenac, indomethacin, and ketoprofen leads to a significant increase in C max values by approximately 32%, 52%, and 50%, respectively. Similar findings have been reported for other drugs, including digoxin, nifedipine, propranolol, verapamil, terbutaline, and diazepam-these drugs achieve higher C max values when administered in the morning compared to the evening. Other routes of drug administration also show circadian-dependent variations in bioavailability. For instance, transcutaneous administration of melatonin in rats leads to higher bioavailability (both AUC and C max) when administered during the animals' dark phase, a time when they have lower light exposure. Similarly, subcutaneous administration of caffeine in animals results in greater bioavailability (increased AUC and C max) when administered during the early part of the night phase compared to the light phase. These findings emphasize the significance of chronopharmacokinetics in enhancing drug therapy by synchronizing the timing of drug administration with the body's natural circadian rhythms. This approach not only enhances the efficacy of treatments but also minimizes side effects by taking advantage of the body's peak absorption and metabolic windows.

The distribution of drugs in the body is also influenced by circadian rhythms, with key factors such as blood flow, drug binding to plasma proteins and tissues, and physiological fluctuations all playing a role. Blood flow to both central and peripheral compartments is higher during periods of daytime activity, enhancing the distribution of drugs during these times. Additionally, binding to plasma proteins such as albumin and alpha-1-acid glycoprotein varies throughout the

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day. For example, corticosteroid-binding transcortin has the lowest binding capacity for both endogenous and exogenous steroids in the early morning (around 4 a.m.) and the highest capacity in the late afternoon (around 5 p.m.. Similarly, the concentrations of albumin and alpha-1-acid glycoprotein peak in the afternoon and are lowest at night, suggesting that the free fraction of drugs may be higher during the nighttime hours, potentially influencing drug availability and action. However, the clinical significance of these circadian fluctuations in protein binding has not been fully explored Drug metabolism is also subject to circadian rhythms, with fluctuations observed in the processes of biotransformation, conjugation, and elimination. The liver is the primary site of drug metabolism, although extrahepatic tissues, such as the kidneys and lungs, also contribute. Metabolism occurs in three phases: phase I involves oxidation, reduction, and hydrolysis reactions; phase II involves conjugation with hydrophilic molecules to increase solubility; and phase III transports metabolites out of cells and into body fluids like bile and urine . Hepatic clearance of drugs depends on factors such as hepatic blood flow, intrinsic clearance (enzymatic activity), and the fraction of the drug that is unbound, as only the free drug is metabolized. Circadian variability in hepatic blood flow and protein binding influences the rate of metabolism, particularly for drugs with high intrinsic clearance, where blood flow becomes the limiting factor. For drugs with low intrinsic clearance, the primary factors affecting metabolism are protein binding and the activity of hepatic enzymes.Circadian fluctuations also impact the activity of drug-metabolizing enzymes in the liver. For instance, enzymes in phase I of biotransformation, such as CYP2B10, CYP2E1, and CYP2A4, show heightened activity during the day and reduced activity at night. In contrast, enzymes involved in phase II, such as UDP-glucuronosyltransferase and sulfotransferases, exhibit peak activity at night. This rhythmic fluctuation is partly regulated by xenobiotic receptors, including the constitutive androstane receptor (CAR) and pregnane X receptor (PXR), which mediate the induction of metabolic enzymes in response to the presence of xenobiotics, such as drugs. These receptors are activated by xenobiotics and translocate to the cell nucleus, where they trigger gene transcription for phase I and II enzymes. The cyclic expression of drug-metabolizing enzymes is also influenced by transcription factors in the PARbZip family, such as the D-site-binding protein (DBP) and the hepatic leukemia factor (HLF). These factors bind to the promoter regions of genes encoding metabolic enzymes, controlling their circadian expression. In studies with mice deprived of PARbZip factors, there was a notable reduction in the expression of phase I and II enzymes, and no circadian fluctuations in enzyme activity were observed. This suggests that these transcription factors play a critical role in maintaining the circadian rhythm of drug metabolism. However, the final activity of these enzymes also depends on post-translational modifications, which further regulate their function. The excretion of drugs and their metabolites also follows circadian rhythms, with significant variability in how substances are eliminated from the body over a 24-hour period. Most drugs are primarily excreted via the kidneys, though some are also eliminated through the bile into the gastrointestinal system, where they may be reabsorbed into the liver through the hepatic portal system. Bile formation involves the secretion of bile salts and organic anions, including drug metabolites, through specialized transporters like ABCB11, ABCC2, and MRP2. Additionally, cationic drug metabolites are excreted into the bile via MDR1 (ABCB1). The activity of these transport systems is subject to circadian changes, which has been indirectly demonstrated through studies on the circadian variation in the excretion of ampicillin in rats, where the drug is predominantly secreted into the bile. In animal studies, bile secretion has been shown to follow a clear circadian rhythm, particularly in rats exposed to a light/dark cycle. The bile flow peaks at the end of the light phase and decreases during the dark phase, with higher lipid concentrations observed in the bile towards the end of the light exposure period. This rhythm reflects the natural variation in bile secretion, which is influenced by the circadian clock. For drugs that are primarily eliminated via the kidneys, factors such as renal blood flow (RBF), glomerular filtration rate (GFR), tubular secretion and reabsorption, urine flow, and urine pH are all important determinants of excretion. RBF is a critical factor in determining GFR, with around 20% of RBF contributing to urine production. Circadian fluctuations in these parameters have been documented, with GFR typically peaking during the daytime and declining at night. This means that for drugs that are minimally bound to plasma proteins and rely on glomerular filtration for elimination, the circadian rhythm of GFR plays a key role in regulating their excretion. The oscillations in GFR are closely tied to changes in RBF, which are themselves influenced by circadian rhythms in arterial blood pressure and cardiac output, reaching a peak during the active phase of the day. Interestingly, GFR rhythms are not entirely dependent on changes in RBF. Research has shown that GFR maintains its circadian fluctuations even in bedridden patients or individuals with kidney transplants, suggesting that intrinsic renal mechanisms also contribute to this rhythm. In clinical practice, this circadian variation in renal clearance is significant. For instance, gentamicin, a nephrotoxic drug, is less toxic when administered in the early morning or early afternoon due to better renal elimination, compared to when it is given in the evening or at night.

Experimental studies in mice have also demonstrated chronopharmacokinetic variations for drugs like valproic acid. When administered intraperitoneally during the active (dark) phase, valproic acid achieves higher plasma concentrations (Cmax) and greater area under the curve (AUC) values, indicating increased absorption and systemic exposure. In

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contrast, when administered during the light (rest) phase, the drug's plasma concentrations and AUC are significantly lower. These studies also showed that the optimal tolerance for valproic acid in animals, as indicated by survival rates, occurred when the drug was administered during the latter half of the light-rest phase, which is roughly analogous to the second half of the night in humans. The pH of urine plays an important role in the excretion of drugs by the kidneys, as it influences the ionization of compounds dissolved in urine. Physiologically, urine pH ranges from 4 to 8, a process regulated by mechanisms that control the secretion and reabsorption of bicarbonate and hydrogen ions. The sodiumproton exchanger 3 (NHE3), located in the proximal tubules, is the primary protein involved in renal hydrogen ion secretion. During the early morning hours, after a period of rest, urine typically becomes more acidic, which indirectly affects the ionization of drugs, particularly acidic compounds, by increasing their reabsorption into the bloodstream. When the urine pH is low, acidic drugs and their metabolites remain in a non-ionized form, facilitating their passive reabsorption and reducing their renal clearance. Other renal transport processes, including secretion and reabsorption, also exhibit circadian patterns, much like the transport mechanisms involved in bile secretion. Polar and water-soluble drug metabolites are actively transported into the urine by various transporters, including those from the ATP-binding cassette (ABC) and solute carrier (SLC) families, located in both the apical and basolateral membranes of renal tubule cells. These transport processes predominantly occur in the proximal tubules of the nephron, where there is a preference for the transport of organic anions. Experimental studies have shown that mice lacking PARbZip transcription factors exhibit not only disruptions in hepatic cytochrome enzyme activity but also reduced expression of renal tubular transporters, such as MRP4 (ABCC4) and OAT2 (SLC22A7), further supporting the circadian regulation of these transport systems.

Therapeutic Drug Monitoring—Basic Assumptions and Rules

An essential approach for personalizing treatment and enhancing its effectiveness and safety is Therapeutic Drug Monitoring (TDM). TDM involves measuring the concentration of a drug (and possibly its pharmacologically active metabolites) in bodily fluids, typically blood, plasma, or serum, although sometimes saliva or capillary blood in young children may also be used. The results are then clinically interpreted in the context of the patient's unique physiological and pathophysiological conditions, enabling individualized dosage adjustments. It's important to note that "measuring drug concentration in blood" is not synonymous with "therapeutic drug monitoring." Simply measuring drug levels in isolation, without interpreting the results in the broader clinical context, offers little value in optimizing therapy. For example, a measured concentration of digoxin must be assessed alongside other relevant clinical parameters, such as creatinine, calcium, and potassium levels, acid-base balance, and the patient's other medications. The fundamental concept of TDM relies on the established relationship between drug concentration in the blood and its pharmacodynamic effects. Since it's not feasible to measure drug concentrations directly at the receptor or effect site, blood concentration serves as a surrogate marker. The origins of TDM trace back to the 1960s, when research first demonstrated a correlation between plasma phenytoin levels and seizure control, as well as between lithium plasma concentrations and its thymoleptic (mood-stabilizing) effects. Over time, TDM has evolved, particularly with advances in analytical techniques used to measure drug concentrations. For many drugs, TDM may not be necessary, as their pharmacodynamic effects can be easily evaluated clinically-for example, through measurements of temperature, blood pressure, heart rate, blood glucose, lipid profiles, or urine volume. However, TDM is particularly beneficial for drugs with difficult-to-assess endpoints, such as antiarrhythmic drugs (which can themselves cause arrhythmias), antiepileptic drugs, mood-stabilizing medications (e.g., antidepressants), immunosuppressive drugs, or drugs exhibiting nonlinear pharmacokinetics or high individual variability. It is also valuable for drugs with a narrow therapeutic index, where slight variations in concentration can result in toxic effects or therapeutic failure. In such cases, TDM can help optimize therapy by ensuring the drug remains within the therapeutic range, anticipating and mitigating toxic effects, identifying potential drug interactions, and addressing issues related to patient adherence (compliance). Additionally, TDM can be used to investigate the causes of treatment failure, such as insufficient dosage, non-compliance, or inadequate drug absorption. In routine clinical practice, TDM is typically applied to drugs that meet specific criteria, such as a narrow therapeutic index or known pharmacokinetic variability, and are commonly used in clinical settings.

The timing of blood sampling is crucial in the Therapeutic Drug Monitoring (TDM) process. To ensure reliable results, samples must be collected during the elimination phase of the drug's pharmacokinetic cycle. If blood is drawn too early, while the absorption and distribution phases are still underway, the drug concentration measured may not reflect steady-state levels, leading to inaccurate results. For oral medications, it is recommended that blood samples be taken no earlier than 2 hours after drug administration, with the possibility that food intake may delay absorption further. For drugs with slower distribution phases (e.g., digoxin), sampling should be delayed by up to 6 hours. In practice, TDM is typically performed before the next scheduled dose is administered, and this sample concentration is referred to as C trough. This measurement represents the drug concentration at the end of the dosing interval, just before the next dose is taken.

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In certain clinical situations, the peak concentration (C max) of a drug may also be of clinical importance. For example, aminoglycosides and vancomycin, antibiotics whose efficacy depends on the C max relative to the minimum inhibitory concentration (MIC), require careful monitoring of C max to ensure therapeutic effectiveness. The general rationale for C max monitoring is in the treatment of patients with severe infections, where the goal is to achieve a concentration sufficient to kill the pathogen. The ratio of C max to MIC (C max/MIC) determines the effectiveness of the antibiotic. If the C max exceeds the MIC, the drug is more likely to be effective.

Peak concentrations are typically measured at different times depending on the route of drug administration:

- IV injections/infusions: about 15-30 minutes after administration
- IM injections: about 30 minutes to 1 hour after administration
- Oral drugs: around 1 hour post-administration

C max is also important for drugs used in high-dose treatment regimens, particularly to minimize the risk of dosedependent serious adverse drug reactions. Once a drug reaches a steady state—which generally occurs after 4-5 halflives of the drug—blood samples should be collected for TDM. However, for drugs with a long half-life, TDM can be performed at any point if there is concern about drug overdose, especially in patients with compromised liver or kidney function. If signs of toxicity are present, it's important to collect a blood sample as soon as possible for analysis, to guide appropriate intervention. In summary, Critical to the success of TDM is the timing of blood sampling. By following established protocols for when and how to sample, clinicians can obtain reliable drug concentration data, ensuring that therapeutic levels are maintained while avoiding toxicity, and ultimately optimizing patient care.

It is important to emphasize that the timing of sampling in Therapeutic Drug Monitoring (TDM) depends primarily on the specific purpose of monitoring the drug and is closely linked to evaluating its safety and efficacy at any given moment. The pharmacokinetics of the drug—how the body absorbs, distributes, metabolizes, and eliminates the drug—and the pharmacodynamics—the drug's effects on the body—must not be considered in isolation. Both factors must be interpreted together, along with the patient's clinical condition, to properly assess the drug's effectiveness and potential risks.Furthermore, the role of TDM in determining the pharmacokinetic parameters is significant, and this process must consider the circadian variability in these parameters. Common pharmacokinetic parameters, such as clearance, volume of distribution (Vd), half-life, and bioavailability, can be influenced by the time of day and other factors. These parameters help describe how the drug moves through and is eliminated from the body:

- Clearance refers to the body's ability to eliminate a drug, typically through the kidneys or liver.
- The volume of distribution (Vd) represents the estimated volume in which a drug is dispersed, reflecting how widely the drug distributes throughout the body.
- The half-life refers to the time required for the concentration of the drug in the bloodstream to reduce by 50% following distribution.
- Bioavailability refers to the proportion of a drug that enters the systemic circulation intact after it has been administered. It is a key pharmacokinetic parameter, as it determines how much of the drug is available to exert its therapeutic effects once it reaches the bloodstream.

Therefore, TDM not only allows for the precise monitoring of drug levels but also helps account for the potential circadian variability in pharmacokinetic parameters. By considering these fluctuations, TDM can provide a more accurate and personalized understanding of drug behavior, which in turn helps optimize treatment strategies and improve patient outcomes.

Chronopharmacology and Conducting a Therapeutical Drug Monitoring

The interpretation of Therapeutic Drug Monitoring (TDM) results is a complex process that requires careful consideration of both the drug's pharmacokinetic properties and the individual patient's physiological and pathophysiological conditions. The circadian rhythm (chronoPK) plays a key role in influencing drug concentrations at different times of the day, and this must be factored into the TDM process.

Key Points in Interpreting TDM Results:

- 1. Circadian Influence:
- As highlighted in the theoretical framework of TDM, drug concentrations can fluctuate over the course of the day, in line with the body's natural circadian rhythm. Therefore, samples taken during the day may show different drug concentrations than those taken at night. This makes the timing of blood sample collection critical to interpreting the results accurately.
- 2. Physiological and Pathophysiological Factors:



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- The interpretation of drug concentrations should also consider factors like liver and kidney function, the presence of other medications, and the patient's overall health status. For example, kidney or liver dysfunction can alter the clearance rates of drugs, leading to elevated drug levels even if the prescribed dose remains unchanged.
- 3. Clinical Relevance of Chronopharmacokinetics (chronoPK):
- As demonstrated by various studies, chronoPK variability can affect the pharmacokinetics of certain drugs. This can influence parameters like absorption rates, distribution, and elimination. The time of day when a drug is administered, or when a blood sample is taken, can impact the resulting drug concentration, which may require adjusting the timing of the sampling or the dosage.

Examples of Chronopharmacokinetics in Common Drugs:

- 1. Valproic Acid (VPA):
- Urinary Excretion: Studies have shown circadian fluctuations in the concentration of VPA and its metabolites in the urine, with peak levels observed between 2 and 6 a.m., and lower levels in the afternoon and evening.
- Plasma Concentration: Clinical studies involving oral administration of VPA showed increased C max (maximum plasma concentration) and a shorter t-lag (time to reach peak concentration) in the morning compared to the evening. This indicates that timing of blood sample collection is crucial to account for the circadian variations in drug levels and metabolic activity.
- 2. Diazepam:
- A study on diazepam showed that morning administration resulted in higher blood concentrations (including C max and T max) compared to evening administration, indicating that chronopharmacokinetics could play a role in the variability of diazepam's effectiveness and side effects.
- 3. Carbamazepine:
- For carbamazepine, an experimental study in rodents demonstrated that drug concentration was higher when administered around noon as opposed to the morning, with both C max and C min values being significantly different depending on the time of administration. Furthermore, clinical studies showed that the timing of meals (such as breakfast) could influence the drug's absorption, with higher C max values and shorter T max observed when carbamazepine was taken after breakfast.

The chronopharmacokinetic (chronoPK) variability of drugs is a critical aspect of Therapeutic Drug Monitoring (TDM), influencing drug concentrations depending on the time of administration. This is particularly important for drugs with narrow therapeutic windows, such as digoxin, a commonly monitored drug in TDM. Several studies have demonstrated circadian fluctuations in the pharmacokinetics of digoxin, underscoring the need to consider the timing of drug administration when interpreting TDM results.

Chronopharmacokinetics of Digoxin

Digoxin is a cardiac glycoside used primarily in the treatment of congestive heart failure and atrial fibrillation. It is known to exhibit significant circadian fluctuations in its pharmacokinetics, including C max (maximum plasma concentration), T max (time to reach C max), AUC (area under the concentration-time curve), and elimination half-life (T $\frac{1}{2}$). Below are key findings from several studies on the chronopharmacokinetic profile of digoxin:

- 1. Morning vs. Afternoon Administration:
- A clinical study involving 10 patients with congestive heart failure showed that digoxin administered in the morning (7:00 a.m.) resulted in the highest concentration 1 hour after administration. However, when the same dose was administered in the afternoon (4:00 p.m.), the time to reach peak concentration was extended to 2 hours. Interestingly, the average drug concentration and AUC values were higher after the afternoon dose, indicating that the time of day affects both the pharmacokinetic profile and drug bioavailability.
- 2. Healthy Volunteers Study:
- Another clinical study assessed healthy volunteers who received 0.250 mg of digoxin per os at 8:00 a.m. or 8:00 p.m. Blood samples were taken over 48 hours to determine C max, T max, AUC, and elimination half-life. The study found that morning administration of digoxin led to a reduction in T max and an increase in C max, suggesting faster absorption and peak concentration in the morning. However, other pharmacokinetic parameters such as AUC and T ¹/₂ did not show a significant difference between the morning and evening doses.
- 3. Morning Administration and Fluctuations:
- In a study by Kopecka et al., morning administration of 0.125 mg of digoxin resulted in higher C max values and higher fluctuations in digoxin concentration compared to evening administration. The study also found that C min (minimum concentration) just before the next morning dose was significantly higher in the morning administration

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group. This finding suggests that morning administration may lead to greater fluctuations in digoxin concentrations compared to evening dosing, which could affect the drug's effectiveness and safety profile.

Chronopharmacokinetics of Other Drugs

- 1. Procainamide:
- Procainamide, an antiarrhythmic drug, was also studied for chronopharmacokinetic variability. A clinical study involving patients with premature ventricular beats who were administered 500 mg of procainamide at either 10:00 a.m. or 8:00 p.m. found no significant differences in the drug's blood concentration or its active metabolite (N-acetylprocainamide) in relation to the time of administration. Additionally, parameters like AUC, elimination half-life, and clearance did not differ significantly between morning and evening dosing.
- However, experimental studies in rats showed that procainamide metabolism was influenced by the time of day. When rats were administered 50 mg of procainamide at 4:00 a.m., 10:00 a.m., 4:00 p.m., or 10:00 p.m. under a 12-hour light-dark cycle, there was a significant difference in the rate of metabolism at different times of the day. This suggests that while human studies may not show large chronoPK effects for procainamide, animal models reveal the potential for circadian variation in drug metabolism.

Summary and Clinical Implications

The chronopharmacokinetic variability of digoxin and other drugs highlights the importance of considering administration timing when interpreting TDM results. For digoxin, morning administration seems to result in higher peak concentrations and greater fluctuations in drug levels, while afternoon doses tend to result in more stable drug concentrations. This could impact the efficacy and toxicity of digoxin, especially in patients with heart failure or arrhythmias who require precise dosing to avoid toxicity while maintaining therapeutic effects. TDM protocols for digoxin and similar drugs must account for the timing of administration to ensure accurate dosing and avoid under- or overdosing. For instance, higher fluctuations in drug concentrations after morning administration may increase the risk of digoxin toxicity, particularly in patients with impaired renal function. Thus, understanding and integrating chronoPK principles into the clinical management of such drugs is essential to optimize therapy and improve patient safety. In conclusion, chronoPK can significantly influence the pharmacokinetics of many drugs, including digoxin and procainamide, which necessitates time-appropriate sampling and administration schedules for effective therapeutic monitoring.

The importance of chronopharmacokinetics (chronoPK) in the context of Therapeutic Drug Monitoring (TDM) is underscored by the variability in drug concentrations due to the timing of administration. As demonstrated in several clinical studies, the time of day when drugs are administered can significantly influence their pharmacokinetic profiles (absorption, distribution, metabolism, and elimination), which, in turn, can affect the drug's efficacy, toxicity, and overall therapeutic outcome.

Chronopharmacokinetics of Various Drugs

1. Theophylline

- Theophylline, a drug used in the treatment of respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), has been studied for its chronopharmacokinetic properties. In one study, healthy volunteers were given 5 mg/kg of theophylline per os at 9:00 a.m. or 9:00 p.m.. The study found that theophylline concentration measured 0.5 hours after morning administration was significantly higher than after the evening dose. However, no significant differences were found in the pharmacokinetic parameters during the elimination phase (e.g., total clearance, half-life). This suggests that the circadian variability in theophylline concentrations is largely influenced by absorption rather than elimination .
- Other studies showed that morning "trough" concentrations of theophylline were higher than evening troughs, with a 10-16% difference. This variation emphasizes the importance of consistent blood sampling times for theophylline TDM. If blood samples are taken at different times of the day, the variability in concentration could lead to inaccurate dosing and potential therapeutic failure or toxicity.
- A study on modified-release theophylline preparations in healthy volunteers also confirmed this trend, with mean blood concentrations assessed 4-8 hours after morning dosing being 40% higher than after evening administration This suggests that the time of day can influence both absorption and distribution phases of the drug's pharmacokinetics.
- 2. Immunosuppressants: Mycophenolate Mofetil, Tacrolimus, and Cyclosporine
- The immunosuppressive drugs like mycophenolate mofetil, tacrolimus, and cyclosporine also exhibit circadian variations in their pharmacokinetics, which can significantly impact their effectiveness in transplant patients.

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- For mycophenolate mofetil, experimental studies in rats revealed that C max (maximum plasma concentration) and plasma clearance varied depending on the time of day the drug was administered. The highest C max was observed at 7 hours after light onset, and the lowest at 19 hours, correlating with lower clearance at the same time. This circadian variation may explain variability in mycophenolate tolerance, especially with respect to hematological and digestive toxicity, which peaks when plasma levels are highest.
- Similarly, for tacrolimus, studies in kidney transplant patients demonstrated that blood concentrations and AUC (area under the curve) after the morning dose were significantly higher than after the night dose, indicating the influence of circadian rhythms on the pharmacokinetics of this drug. These findings highlight the need for consistent monitoring times to ensure appropriate drug levels and immunosuppressive efficacy.
- A study examining cyclosporine in liver transplant recipients found that blood concentrations taken 2 hours after morning doses were significantly higher than those after evening doses, although C trough and AUC values did not differ significantly between morning and evening administrations. These results suggest that, while morning dosing leads to higher peak concentrations, adjustments may be necessary for night-time dosing to maintain optimal therapeutic levels.
- 3. Aminoglycosides
- Aminoglycosides (e.g., gentamicin, tobramycin) are often monitored due to their potential nephrotoxicity. Several experimental studies have shown that nephrotoxicity is maximal when these drugs are administered during the day (rest phase) compared to the night (activity phase) in rats. This is because the renal elimination of aminoglycosides is influenced by circadian rhythms, with lower elimination during the rest phase, leading to higher drug accumulation in the kidneys and increased risk of renal toxicity.
- Similarly, in human patients, renal toxicity has been observed more frequently when aminoglycosides are administered during the night, which corresponds with lower renal function during the resting phase. This underscores the importance of considering the time of day for aminoglycoside administration to minimize toxicity, especially in patients with impaired renal function. TDM of aminoglycosides, therefore, must account for this circadian variation in drug elimination to optimize safety and efficacy.

3. CONCLUSION

To summarize, numerous studies have documented chronopharmacokinetic differences in drugs commonly monitored through Therapeutic Drug Monitoring (TDM). These variations highlight the critical need to collect blood samples at specific times, accounting for potential differences in drug concentrations due to circadian rhythms and other time-dependent factors. Given the impact of chronoPK on the pharmacokinetics of drugs, it is essential that official TDM recommendations and protocols integrate considerations of these fluctuations. By acknowledging chronopharmacokinetic phenomena, healthcare providers can improve the accuracy and reliability of drug concentration assessments, leading to better therapeutic outcomes and minimized risks of toxicity. Thus, the timing of sample collection should be carefully planned to ensure that results accurately reflect the drug's pharmacokinetic profile, ultimately enhancing the efficacy and safety of treatment.

4. REFERENCES

- Andrys-Wawrzyniak, I.; Jabłecka, A. Chronobiology, chronopharmacology on medicine (part I). Farm. Współ. 2008, 1, 94–108.
- [2] Andrys-Wawrzyniak, I.; Jabłecka, A. Chronobiology, chronopharmacology on medicine (part II). Farm. Współ. 2008, 1, 156–168.
- [3] Ballesta, A.; Innominato, P.F.; Dallmann, R.; Rand, D.A.; Levi, F.A. Systems chronotherapeutics. Pharmacol. Rev. 2017, 69, 161–199.
- [4] Reinberg, A.; Ashkenazi, I. Concepts in human biological rhythms. Dialogues Clin. Neurosci. 2003, 5, 327–342.
- [5] Ayyar, V.S.; Sukumaran, S. Circadian rhythms: Influence on physiology, pharmacology and therapeutic interventions. J. Pharmacokinet. Pharmacodyn. 2021, 48, 321–338.
- [6] Bicker, J.; Alves, G.; Falcao, A.; Fortuna, A. Timing in drug absorption and disposition: The past, present and future of chronopharmacokinetics. Br. J. Pharmacol. 2020, 177, 2215–2239.
- Smith, D.H.G. Pharmacology of cardiovascular chronotherapeutic agents. Am. J. Hypertens. 2001, 14, 296S– 301S.
- [8] Lemmer, B. Chronopharmacology of cardiovascular medications. Biol. Rhythm Res. 2007, 38, 247–258.
- [9] Lemmer, B. The importance of biological rhythms in drug treatment of hypertension and sex-dependent modifications. ChronoPhysiol. Ther. 2012, 2, 9–18.



- [10] Latha, K.; Uhumwangho, M.U.; Sunil, S.A.; Srikant, M.V.; Murthy, K.V.R. Chronobiology and chronotherapy of hypertension—A review. Int. J. Health Res. 2010, 3, 121–131
- [11] Dubielski, Z.; Zamojski, M.; Wiechecki, B.; Moze 'nska, O.; Petelczyc, M.; Kosior, D.A. The current state of knowledge about the ' dipping and non-dipping hypertension. Arter. Hypertens. 2016, 20, 33–43
- [12] Bilo, G.; Grillo, A.; Guida, V.; Parati, G. Morning blood pressure surge: Pathophysiology, clinical revelance and therapeutic aspects. Integr. Blood Press. Control 2018, 11, 47–56.
- [13] Kario, K. Morning surge in blood pressure and cardiovascular risk. Evidence and perspectives. Hypertension 2010, 56, 765–773.
- [14] Potucek, P.; Klimas, J. Chronopharmacology of high blood pressure—A critical review of clinical evidence. Eur. Pharm. J. 2019, 66, 1–4.
- [15] Emet, M.; Ozcan, H.; Ozel, L.; Yayla, M.; Halici, Z.; Hacimuftuoglu, A. A review of melatonin, its receptors and drugs. Eurasian J. Med. 2016, 48, 135–141.
- [16] Williams, W.P., 3rd; McLin, D.E., 3rd; Dressman, M.A.; Neubauer, D.N. Comparative review of approved melatonin agonists for the treatment of circadian rhythm sleep-wake disorders. Pharmacotherapy 2016, 36, 1028–1041.
- [17] Wichniak, A.; Wierzbicka, A.; Wal ecka, M.; Jernajczyk, W. Effects of antidepressants on sleep. Curr. Psychiatry Rep. 2017, 19, 63.
- [18] Altınyazar, V.; Kiylioglu, N. Insomnia and dementia: Is agomelatine treatment helpful? Case report and review of the literature. Ther. Adv. Psychopharmacol. 2016, 6, 263–268.
- [19] Ohdo, S. Chrono-drug discovery and development based on circadian rhythm of molecular, cellular and organ level. Biol. Pharm. Bull. 2021, 44, 747–761.
- [20] Voigt, R.M.; Forsyth, C.B.; Keshavarzian, A. Circadian rhythms: A regulator of gastrointestinal health and dysfunction. Expert Rev. Gastroenterol. Hepatol. 2019, 13, 411–424.
- [21] Dallmann, R.; Brown, S.A.; Gachon, F. Chronopharmacology: New insights and therapeutic implications. Annu. Rev. Pharmacol. Toxicol. 2014, 54, 339–361.
- [22] Kapadia, S.; Kanase, V.; Kadam, S.; Gupta, P.; Yadav, V. Chronopharmacology: The biological clock. Int. J. Pharm. Sci. Res. 2020, 11, 2018–2026
- [23] Erkekoglu, P.; Baydar, T. Chronopharmacokinetics of drugs in toxological aspects: A short review for pharmacy practitioners. J. Res. Pharm. Pract. 2012, 1, 3–9.
- [24] Baraldo, M. The influence of circadian rhythms on the kinetics of drugs in humans. Expert Opin. Drug Metab. Toxicol. 2008, 4, 175–192.
- [25] Lemmer, B. Chronopharmacokinetics: Implications for drug therapy. J. Pharm. Pharmacol. 1999, 51, 887–890.
- [26] Gachon, F.; Olela, F.F.; Schaad, O.; Descombes, P.; Schibler, U. The circadian PAR-domain basic leucine zipper transcription factors DBP, TEF and HLF modulate basal and inducible xenobiotic detoxification. Cell Metab. 2006, 4, 25–63.
- [27] Murakami, Y.; Higashi, Y.; Matsunaga, N.; Koyanagi, S.; Ohdo, S. Circadian clock-controlled intestinal expression of the multidrug-resistance gene MDR1A in mice. Gastroenterology 2008, 135, 1636–1644.e3.
- [28] Lo Sasso, G.; Petruzzelli, M.; Moschetta, A. A translational view on the biliary lipid secretory network. Biochim. Biophys. Acta 2008, 1781, 79–96.
- [29] Prins, J.M.; Weverling, G.J.; van Ketel, R.J.; Speelman, P. Circadian variations in serum levels and the renal toxicity of aminoglycosides in patients. Clin. Pharmacol. Ther. 1997, 62, 106–111.
- [30] Ben-Cherif, W.; Dridi, I.; Aouam, K.; Ben-Attia, M.; Reinberg, A.; Boughattas, N.A. Chronotolerance study of the antiepileptic drug valproic acid in mice. J. Circadian Rhythm. 2012, 10, 3.
- [31] Ben-Cherif, W.; Dridi, I.; Aouam, K.; Ben-Attia, M.; Reinberg, A.; Boughattas, N.A. Circadian variation of valproic acid pharmacokinetics in mice. Eur. J. Pharm. Sci. 2013, 49, 468–473.
- [32] Gross, A.S. Best practice in therapeutic drug monitoring. Br. J. Clin. Pharmacol. 2001, 52, 5S–10S. [PubMed]
- [33] Buchthal, F.; Svensmark, O.; Schiller, P.J. Clinical and electroencephalographic correlations with serum levels of diphenylhydantoin. Arch. Neurol. 1960, 2, 624–631.
- [34] Sion, B.; Begou, M. Can chronopharmacology improve the therapeutic management of neurological diseases? Fundam. Clin. Pharmacol. 2021, 35, 564–581.
- [35] Reith, D.M.; Andrews, J.; McLaughlin, D. Valproic acid has temporal variability in urinary clearance of metabolites. Chronobiol. Int. 2001, 18, 123–129.

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- [2] 36.. Johno, I.; Nakamura, T.A.; Horiuchi, T.; Nadai, M.; Kitazawa, S.; Yoshimine, N.; Kuzuya, F. Diurnal variation in pharmacokinetics of valproic acid with unequal dosing intervals. Chem. Pharm. Bull. 1988, 36, 2551–2556
- Nakano, S.; Watanabe, H.; Nagai, K.; Ogawa, N. Circadian stage-dependent changes in diazepam kinetics. Clin. Pharmacol. Ther. 1984, 36, 271–277.
- [2] Labrecque, G.; Belanger, P.M. Biological rhythms in the absorption, distribution, metabolism, and excretion of drugs. Pharmacol. Ther. 1991, 52, 95–107.
- [3] Ohdo, S.; Nakano, S.; Ogawa, N. Circadian changes of valproate kinetics depending on meal condition in humans. J. Clin. Pharmacol. 1992, 32, 822–826.
- [4] Taylor, D.R.; Duffin, D.; Kinney, C.D.; McDevitt, D.G. Investigation of diurnal changes in the disposition of theophylline. Br. J. Clin. Pharmacol. 1983, 16, 413–416.
- [5] Regazzi, M.B.; Rondanelli, R.; Vida, E.; Farinelli, F.; Upton, R.A. A theophylline dosage regimen which reduces round-the-clock variations in plasma concentrations resulting from diurnal pharmackokinetic variation. Eur. J. Clin. Pharmacol. 1987, 33, 243–247.
- [6] Dridi, I.; Ben-Cherif, W.; Aouam, K.; Ben-Attia, M.; Klouz, A.; Reiberg, A.; Boughattas, N.A. Circadian variation of mycophenolate mofetil pharmacokinetics in rats. Eur. J. Pharm. Sci. 2014, 58, 20–25.
- [7] Fontova, P.; Colom, H.; Rigo-Bonnin, R.; van Merendonk, L.N.; Vidal-Alabro, A.; Montero, N.; Melilli, E.; Meneghini, M.; Manonelles, A.; Cruzado, J.M.; et al. Influence of the circadian timing system on tacrolimus pharmacokinetics and pharmacodynamics after kidney transplantation. Front. Pharmacol. 2021, 12, 636048.
- [8] Baraldo, M.; Risaliti, A.; Bresadola, F.; Chiarandini, P.; Rocca, G.D.; Furlanut, M. Circadian variations in cyclosporine C2 concentrations during the first 2 weeks after liver transplantation. Transplant. Proc. 2003, 35, 1449–1451.
- [9] Rebuelto, M. The molecular clock: A focus on chronopharmacological strategies for a possible control of aminoglycoside renal toxicity. ChronoPhysiol. Ther. 2012, 2, 1–7.
- [10] Rohini Gupta, Brij Mohan Gupta, Vijay Khajuria, Nusart Kreem Bhat, Apeksha Gupta; Chronopharmacology: An Overview.