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Review Article

Chronopharmacokinetics of drugs in toxicological aspects: A short review for pharmacy practitioners

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ABSTRACT

A rough 24-hour cycle driven endogenously in biochemical, physiological or behavioral processes is called circadian rhythm. Chronobiology is the study of biological temporal rhythms. For decades, we know that the biological rhythm and the drug metabolism are also affected from daylight and chronopharmacology became recognized by scientists in the early 1970s. Its lateral branch chronocopharmacokinetics is the study of rhythmic, predictable-in-time differences in the pharmacokinetics of drugs. Chronopharmacokinetic studies are performed at every step of the biotransformation i.e., absorption, distribution, metabolism and excretion. Feeding schedules, sex and phenotype must be taken into consideration while applying pharmacotherapy to increase the efficiency and to decrease side effects. The impact of drugs on circadian rhythm should be not neglected. On the other hand, new special drug delivery systems can be used to synchronize drug concentrations according to circadian rhythms. "Chronopharmaceuticals" can identify the proper dosing time and this amelioration will lead to improved progress and diffusion of pharmacotherapy. Chronopharmaceuticals coupled with nanotechnology could be the future of drug delivery systems, and lead to safer and more efficient disease therapy in the future. In this review, we will discuss the pharmacokinetic effects of circadian rhythm and its toxicological outcomes. Besides, we will try to give some practical points for clinical pharmacist/pharmacy practitioners, concerning chronopharmacokinetics.

Keywords: Absorption; circadian rhythm; chronopharmacology; chronocokinetics; distribution; excretion; metabolism

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INTRODUCTION

Circadian rhythm is an endogenously driven rough 24-hour cycle in biochemical, physiological or behavioral processes. Circadian rhythms have been widely observed, in plants, animals, fungi and cyanobacteria. It is evident that daily synchrony between external light/dark cycles and internal circadian rhythms is essential for optimal health.[1-3] Although circadian rhythms are endogenous, they are adjusted to the environment by external cues called "zeitgebers".[4-6]

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The formal study of biological temporal rhythms such as daily, tidal, weekly, seasonal and annual rhythms is called chronobiology.[7]

The main task of the circadian clock is the optimization of metabolism and energy utilization for sustaining life processes in the organism.[8] On the other hand, rest and activity cycles, heart rate, blood pressure, bile and urine production, and transport in liver and intestine as well as endocrine functions are all subjected to daily fluctuations.[9] For example, heart rate and locomotor activity begins to slow down after 6 pm. After midnight, vigilance and core body temperature decrease. However, melatonin concentrations begin to increase after midnight.[10] It was demonstrated that the circadian cytological reorganization in the liver of the rat was associated with functional readjustment. At the end of the activity span (onset of light), the liver cells contain the largest amount of glycogen and the smallest amount of proteins.[11]

Chronopharmacology is the study of rhythmic, predictable-in-time differences in the effects and/or pharmacokinetics/dynamics of drugs both in animals and in humans.[12] Chronopharmacology became recognized by scientists in the early 1970s and nearly for four decades, we have been knowing the impact of biological rhythm on the drug metabolism.[12,13]

The mammalian timing system works in a hierarchical manner with a central pacemaker located in the suprachiasmatic nucleus (SCN).[14] At a molecular level, there is no difference in the circadian clock of SCN neurons and peripheral cells.[7,15] However, there is a major distinction in their synchronization: SCN neurons phase is engendered by light-dark cycles perceived by the retina,[16] whereas peripheral oscillators phase is adjusted by chemical zeitgebers, like for example signals generated by feeding-fasting rhythms.[17,18] In the last decade, microarray studies in several model species have suggested that several xenobiotic-metabolizing genes are expressed in daily rhythms. [19,20] As a consequence, the circadian pharmacokinetics as well as pharmacodynamics that modulate both drug effectiveness and toxicity are manifestations of the circadian regulation of xenobiotic detoxification process. These could be important in clinical practice as they enable treatment modification in order to increase efficacy and safety of a certain drug or decrease side effects.[21] Besides, they may also have consequences on several diseases and their symptoms.[22]

In this review, we will discuss the pharmacokinetic effects of circadian rhythm and its toxicological outcomes. Besides, we will try to give some practical points for clinical pharmacist/pharmacy practitioners.

PHARMACOKINETIC OUTCOMES OF CIRCADIAN RHYTHM: CHRONOPHARMACOKINETICS

Chronopharmacokinetics is defined as dosing time-dependent and predictable rhythmic variations in parameters used to characterize the pharmacokinetics (or the bioavailability) of a drug.[22] Chronokinetics of certain drugs may involve changes from a mono- to a multicompartmental model as a function of drug dosing time.[23]

Chronopharmacokinetic studies have been demonstrated that the time of administration is a possible factor of variation in the pharmacokinetics of a drug. On the other hand, such kinetic changes can be either sex-, age- or phenotype-related. A statistically significant sex-related difference in the chronokinetics of several drugs, including antibiotics, has been shown in humans.[24] Dosing time-dependent changes of sustained-release indomethacin have been demonstrated in young adults but not in elderly subjects.[25] The polymorphism in the human potency in the acetylation of some drugs (e.g., isoniazid, procainamide, and hydralazine) was shown to be genetically determined. Comparison of slow and rapid acetylor types of healthy young subjects has shown statistically significant differences in the chronokinetic pattern of such drugs.[26]

Chronopharmacokinetics of drugs have been validated for many species including humans, with both acute and chronic administration even for sustained release preparations having a half life ($t_{½}$) as long as 84 h.[22] Several physiological factors such as gastrointestinal, cardiovascular, hepatic and renal changes vary according to time of day. Therefore, both the subject synchronization and dosing time of a drug must be known for the correct interpretation of pharmacological data.[27-29] Absorption (e.g., for oral: Gastric pH, gastric motility, gastric emptying time, gastrointestinal blood flow, transporters, time for gastric emptying; for parenteral: Transdermal permeability, ocular permeability, pulmonary permeability), distribution (e.g., blood flow through an organ and binding capacity of plasma proteins), metabolism (e.g., hepatic flow, xenobiotic-metabolizing enzymes) and excretion (e.g., renal blood flow, glomerular filtration, tubular reabsorption, transporters, electrolytes and urinary pH) of drugs may change according to the circadian clock with regard to physical properties of drugs (e.g., lipid solubility).[30-34] Therefore, we can discuss the chronokinetic changes under four subtitles:

Circadian rhythms in absorption

In humans, for orally administered drugs, absorption was shown to be affected by circadian rhythm as gastric acid secretion and gastric pH, gastric motility, gastric emptying time, and gastrointestinal blood flow vary according to the time of day.[35,36] These changes may have an impact on the time-dependent difference of drug absorption. For instance, circadian changes in pH may affect drug ionization according to its physicochemical properties. On the other hand, gastric emptying time is another important factor in the absorption of drugs. Gastric emptying rates were compared between morning (8 am) and evening (8 pm) in male subjects and it was found that gastric emptying $t_{½}$ for the evening meal was significantly longer for solids but not for liquids compared with those of the morning meal.[37] The increase in evening meal gastric emptying time may also cause a delay in reaching peak plasma concentrations for several drugs. Such variations may be related to the physicochemical properties of a drug, since most lipophilic drugs seem to be absorbed faster in the morning as compared

to evening.[23,38] The mechanisms underlying the chronokinetics of lipophilic drugs involve a faster gastric emptying time and a higher gastrointestinal perfusion in the morning.[36] However, such changes have not been shown for hydrophilic drugs.[39]

Circadian rhythms in distribution

In biological fluids and tissues, circadian changes related to drug distribution are shown to change according to time of day.[39] Blood flow depends on several regulatory factors, including the sympathetic and parasympathetic systems whose activities are known to be circadian time-dependent with a predominant diurnal effect of the sympathetic system.[40] Thus, daytime increases and night time decreases the blood flow and local tissue blood flows may explain a possible difference in drug distribution depending on dosing time.[41,42]

The liver activity varies due to circadian rhythm. As a consequence, the levels of plasma proteins (albumin, globulins) changes from day time to night time. Most human plasma protein concentrations including albumin, and α_1-glycoprotein fall down to their lowest during the night time, increase by day and reach to highest around noon. As a result, daily variations have been reported for drug protein binding. Touitou *et al.* (1986) have shown that in young healthy adult subjects the circadian amplitude of plasma protein was rather small (8-15%) compared with that of healthy elderly subjects (average age ~ 75 yr). An impressive nocturnal fall was observed for the latter (circadian amplitude of 20%), a result which suggests that the free fraction of drugs usually bound to plasma proteins increases during the nocturnal rest as a function of aging.[43] The effects of circadian rhythm on the plasma protein binding of drugs were first demonstrated for cortisol, which reaches to its highest level around noon. Furthermore, the synthetic analogs for cortisol were also shown to be affected by circadian rhythm.[41,42]

Circadian rhythms in plasma protein binding have been demonstrated for several mood stabilizers, valproic acid, 5-fluorouracil (5-FU), ketoprofen, carbamazepine, diazepam, lidocaine, prednisone, and cisplatin.[44-50] In rats, the peak time of protein binding occurs during the nocturnal activity spans, which also correspond to the peak time of plasma protein binding for disopyramide, lidocaine, and carbamazepine.[44,45] On the other hand, circadian rhythm was shown to affect the protein binding of cis-diamindichloroplatinum and it was shown that around 4 pm it reached to a plateau.[47] However, some drugs [i.e., ketoprofen, as a nonsteroidal anti-inflammatory drug (NSAID), and two anticancer agents, 5-FU and adriamycin] are not delivered at a constant rate over the 24-h span.[45,49-52]

As a particular concern in drug binding to erythrocytes, circadian time-dependent changes in the passage of drug into erythrocytes have been demonstrated for drugs such as local anesthetics, indomethacine, and theophylline.[53] Furthermore, P-glycoprotein, the product of the multidrug resistance (MDR) gene which contributes to renal, biliary, and intestinal elimination of drugs, and the intestinal H(+)/peptide co-transporter 1 (PEPT1) play important roles as a nutrient and drug transporter function as a xenobiotic transporter and exhibit 24-h variation.[54,55]

From toxicological point of view, drugs with a small volume of distribution and/or high protein-binding capacity and drugs which have a narrow therapeutic index may be affected by the changes in circadian rhythm and wrong dosing of such drugs in night time may cause mild to moderate toxicity.

Circadian rhythms in metabolism

Hepatic drug metabolism seems to depend on liver xenobiotic-metabolizing enzyme activity and/or hepatic blood flow.[56,57] Both factors show circadian time-dependent differences. Circadian rhythm can affect blood flow in liver and thus, can affect the clearance of several drugs, including propranolol.[58]

In mammals, most of the xenobiotics are metabolized in mainly in liver. However, there is also extrahepatic metabolism in brain, kidney, lung and other tissues. Xenobiotic metabolism is composed of three groups of proteins with distinct functions. The phase I group contains the microsomal cytochrome P_{450} (CYP450) enzymes. Phase II, or conjugating enzymes, comprises sulfotransferases (SULT), UDP-glucuronotransferases (UGT), NAD(P)H:quinine oxidoreductases (NQO), epoxide hydrolases (EPH), glutathione-S-transferases (GST), and N-acetyltransferases (NAT). Conjugation provides the lipophilic compounds to be hydrophilic enough to subsequently control and facilitate their excretion into bile, faces and/or urine. After phase II reactions, the xenobiotic conjugates may be further metabolized in phase III reactions.[59-61] Interestingly, genome-wide analysis of liver transcriptome revealed that proteins involved in the phase I–III reactions are expressed in a circadian fashion.[62-65] Moreover, phase I-III enzyme activities show circadian time-dependent differences in extrahepatic tissues such as brain.[66,67] It is thus conceivable that the circadian expression of proteins involved in xenobiotic detoxification is responsible for the daytime-dependent drug metabolism that modulates drug effectiveness and toxicity.

Variations of several oxidative reactions catalyzed by the CYP450 enzymes been reported for substrates such as aminopyrine, paranitroanisole, hexobarbital and 4-dimethyaminobenzene, aniline, benzphetamine,

benzpyrene and imipramine.[68,69] It seems that drug metabolism resulting from oxidative microsomal reactions reaches its peak during the activity span and its lowest during the rest span. Conversely, sulfate conjugations are much faster during rest than during activity.[70]

Here we should also mention peroxisome proliferator-activated receptors (PPAR), particularly alpha. The major function of PPARα is to regulate lipid and glucose homeostasis[71] and the requirement of the PPARα detoxification pathway has been shown recently in the case of toxic compounds contained in vegetal food such as sesame grains.[72] PPARα is activated by compounds referred to as peroxisome proliferators (PP), such as lipid lowering fibrates, phthalate-ester plasticizers, as well as endogenous fatty acids. In response to these xenobiotic toxic compounds, activated PPARα stimulates the expression of phase I and II proteins such as CYP4A and uridine 5′-diphospho-glucuronosyltransferase (UGT).[73-75] PPARα expression is affected by circadian rhythm at the mRNA and protein level.[76] The change in the expression of PPARα can affect the metabolism of fatty acids, cholesterol, steroids and other lipids, which are substrates for CYP4A enzymes. Besides, the metabolism of UGT substrates like endogenous compounds (bilirubin, testosterone, andosterone, retinoids, mineralocorticoids, bile acids, fatty acids) and drugs (morphine, codeine, oxazepam, lorazepam, acetaminophen, zidovudine) can also be affected by the changes in PPARα expression.[77] On the other hand, other PPARs were shown to regulate the circadian clock. It can be suggested that the central circadian clock components and PPARs exhibit a reciprocal regulation.[78] As PPARs serve as sensors which integrate energy and metabolic homeostasis to circadian clock, the aberration of clock genes by external or internal factors could result in altered expression of metabolic genes, leading to disturbance of energy status in affected organisms. This imbalance is known to attribute to metabolic syndrome, a complex disease with distinct hallmarks including obesity, dyslipidemia, hypertension, and elevated plasma glucose level.[79] Novel research investigating this relationship could deepen the understanding of pathogenesis, which may pave ways for new strategies to fight against metabolic syndrome.

Circadian rhythms in excretion

The circadian timing system plays a key role in the changes of toxicity of drugs by influencing their metabolisms in the liver and intestine in addition to their excretion via bile flow and urine. Rats with chronic biliary drainage under a rigid lighting schedule (light on at 6 am and off at 6 pm) exhibited a remarkable circadian rhythm of bile flow, biliary concentrations and excretory rates of bile salts, cholesterol and phospholipids.[80] On the other hand, the excretion rates of these polyamines were found to highest in the morning in healthy volunteer subjects.[81] A significant decrease in the rate and extent of ciprofloxacin excretion following 10 pm administration was observed.[82] Excretion of 17-oxosteroids was also shown to be affected from circadian clock.[83]

SOME PRACTICAL POINTS FOR CLINICAL PHARMACISTS AND PHARMACY PRACTITIONERS

Several variables influencing pharmacokinetics (i.e., meal content, meal times, fasting, galenic formulation, posture, activity-rest) have to be controlled before the admistration of drugs. Particularly, the time of administration should be controlled in order to prevent variations in drug pharmacokinetics. Clinical pharmacists and pharmacy practitioners should take into account that the application time may be as important as the dose and route for certain drugs, particularly for those that has a narrow therapeutic range.[84,85] Moreover, variables like sex, race and phenotype should be considered by pharmacists before drug administration and dosing regimens should be modified considering all the factors mentioned.

If the symptoms of a disease are distinctly circadian phase-dependent (like symptoms of myocardial infarction, angina pectoris, nocturnal asthma, peptic ulcer), pharmacists should also warn the patients for the correct time of administration of the drug used for the treatment of such disease. For example, in asthma patients, as lung function undergoes circadian changes and reaches to a low point in the morning hours, chronotherapy for asthma should be aimed at getting maximal effect from bronchodilators during early morning hours. As gastric secretion reaches to its highest at night, chronotherapy for peptic ulsers should be at evening, with once daily H_2-receptor antagonists (like ranitidine, famotidine). Rheumatoid arthritis symptoms are usually intense on awakening and NSAIDs should be administered in morning and noon times due to the symptom timing of this disease. Cardiovascular diseases like hypertension, heart attack and stroke mostly occurs in morning time as blood pressure is at its lowest at night time and makes a steep rise in the awakening period. Therefore, medications curing such diseases should be preferably administered at morning time. It is known that chronobiological cycles for normal cells and cancer cells are different. Blood flow to tumors and tumor growth rate are greater during activity phase than rest phase and usually midnight therapy

was shown to be more effective. A right choice for the time of administration of cancer drugs should be made after observing the cell cycle changes of the cancer cells in the patients.[84,85]

CONCLUSION

Circadian rhythms have an important impact on drug effectiveness and toxicity. Chronopharmacology aims to improve the understanding of circadian changes in both desired effects (chronoeffectiveness) and tolerance (chronotolerance) of medications.[84,85] Therefore, pharmacotherapy may be applied by the appropriate timing of conventional tablets and capsules, which can be applied according to the rhythmic markers. This occasion can increase their therapeutic effects and/or reduce their side effects. Besides, the efficiency of pharmacotherapy can be enhanced by administering drugs at times during which they are best tolerated.[22] Furthermore, feeding schedules, sex and phenotype must be taken into consideration while applying pharmacotherapy to increase the efficiency and to decrease side effects. The impact of drugs on circadian rhythm should be not neglected. On the other hand, new special drug delivery systems can be used to synchronize drug concentrations according to circadian rhythms. These drugs are called as "chronopharmaceuticals" which are featured as future pharmaceuticals. These medications can identify the proper dosing time and this amelioration will lead to improved progress and diffusion of pharmacotherapy. Chronopharmaceuticals coupled with nanotechnology could be the future of drug delivery systems, and lead to safer and more efficient disease therapy in the future.[86,87]

AUTHORS' CONTRIBUTION

Both authors contributed the idea of paper and the manuscript preparation.

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