The Role of Circadian Timing System on Drug Pharmacokinetics and Detoxification: A Short Review for Clinicians and Pharmacy Practitioners

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Abstract: Drug efficiency and toxicity has been known for long time to depend on the time of administration, however the mechanisms involved have only started to emerge recently. There is clear evidence that the molecular circadian clock is involved in this process. The molecular clock acts either directly or through the rhythmic expression of clock-controlled transcription factors that regulate the expression of detoxification enzymes or indirect pathways. The circadian clock-coordinated drug detoxification has a strong impact in the pharmacokinetics of drugs and with the known chronodynamic mechanisms influencing drug efficiency, constitutes the basis of chronopharmacology. Feeding schedules, sex and phenotype alongside with time of the day, must be taken into consideration while applying pharmacotherapy, so as to increase efficiency and decrease side effects. 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 modification; will lead to improved progress and dispersal 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.
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Introduction

The efficiency and toxicity of drugs have been known for long to change during a 24-hour period; however the molecular mechanisms involved in these regulations have started to emerge only recently. Biological rhythms influence a broad range of biological processes including neuronal, endocrine, metabolic and behavioral functions. These rhythms are generated by clocks that are endogenous in nature and oscillate even in the absence of environmental cues (Johnston *et al*., 2016). It is evident that daily synchrony between external light/dark cycles and internal circadian rhythms are essential for optimal health (Hooven *et al*., 2009; Hatori *et al*, 2017).

The formal study of biological temporal rhythms such as daily, tidal, weekly, seasonal and annual rhythms is known as chronobiology (Partch and Sancar, 2005). Chronopharmacology on the other hand, is the study of rhythmic, predictable-in-time differences in the effects and/or pharmacokinetics/dynamics of drugs both in animals and humans (Nainwal *et al*., 2011), while chronotherapeutics is the science of preventing or treating illnesses according to biologic rhythms. It involves the timing of pharmacological and non-pharmacological interventions, such as surgery, physical agents, and psychotherapy. The goal is to minimize toxicity or adverse effects, and/or to enhance treatment efficacy through adequate treatment timing and shaping (Selfridge *et al*., 2016).

The mammalian timing system works in a hierarchical manner with a central pacemaker located in the suprachiasmatic nucleus (SCN) (Schibler and Sassone-Corsi, 2002). 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 certain drugs or decrease side effects (Ballesta *et al*., 2017). The goal of this review is to describe the molecular mechanisms involved in rhythmic drug metabolism and excretion, pharmacokinetic effects of circadian rhythm and its toxicological aftermaths, as well as some practical/clinical applications for clinicians, clinical pharmacist/pharmacy practitioners.

Molecular Basis of Circadian Rhythms

Work in multiple species has led to the development of a transcriptional-translational feedback loop (TTFL) molecular model of circadian rhythms. The mammalian TTFL model consists of multiple interlocking loops (Partch *et al*., 2014). At the center of this model is a primary loop in which transcription factor CLOCK and BMAL1 stimulate the transcription of 3 Period (Per) genes and 2 Cryptochrome (Cry) genes. The translated PER and CRY proteins then form protein complexes that translocate into the nucleus and repress the transcriptional activation of their own genes by CLOCK and BMAL1. The precise temporal dynamics of this loop are regulated by post-transcriptional and pos-ttranslational modifications (Lim and Allada, 2013; Partch *et al*., 2014).

Interlinked with the primary loop are multiple secondary loops, many of which involve important biochemical components of cellular metabolism. The best of these secondary loops involves the circadian transcription of the nuclear receptor REVERBA (NR1D1) by CLOCK-BMAL1 dimers acting through E-box regulatory elements; the resulting REVERBA/NR1D1 protein then inhibits BMAL1 transcription through retinoic acid-related orphan receptor response elements, resulting in circadian rhythms of BMAL1 mRNA expression (Preitner *et al*., 2002).

Additional loops involving nuclear receptors have been reported, for example, the interaction between clock genes and PPARA in mouse liver (Canaple *et al*., 2006). More recently, redox-sensing molecules have been linked to the circadian clock machinery. For example, CLOCK-BMAL1 heterodimers drive rhythmic expression of nicotinamide phosphoribosyltransferase, which is a rate-limiting enzyme involved in the NAD^+ salvage pathway; NAD^+ acts as a cofactor for Sirtuin (SIRT1), which regulates the activity of CLOCK-BMAL1 among its other metabolic functions (Peek *et al*., 2015).

In addition, cellular redox state and core signaling pathways are also closely interlinked with the TTFL model (Milev and Reddy, 2015). Soon after the discovery of mammalian clock genes, came the identification of rhythmic clock output genes, called clock-controlled genes. Early works focused on individual output genes that are transcriptionally regulated by core clock proteins (Ripperger *et al*., 2000). Soon afterward, multiple groups used microarray technology to identify the extent of circadian rhythmicity within the transcriptome (Duffield, 2003).

Although there are some variability between studies and methods, it is generally accepted that ~10% of the transcriptome in any given mouse tissue is under circadian control. Many of these genes are rhythmic in a tissue-specific context, and recent analysis of mouse transcriptome in 12 organs revealed that 43% of all protein coding genes exhibit circadian rhythmicity in one or more tissues (Zhang *et al*., 2014).

Analysis of multiple human and mouse transcriptomic data sets, highlights the close linkage between circadian rhythms and metabolic gene expression (Laing *et al*., 2015). It has been estimated that 6–20% of the murine proteome exhibits circadian rhythms in tissues such as the SCN (Chiang *et al*., 2014) and liver (Mauvoisin *et al*., 2014). Some of these studies have reported inconsistent rhythmicity in transcripts and proteins derived from the same gene, a feature that is likely to be explained by rhythms in post-transcriptional mechanisms such as degradation rate (Lück *et al*., 2014). Daily rhythms in the metabolome have been described in mouse blood (Minami *et al*., 2009) and tissue samples (Eckel-Mahan *et al*., 2012). Genetic disruption of the molecular clock also has profound effects on metabolite profiles (Castro *et al*., 2015), thus strengthening the functional links between clocks and the metabolome. In addition to these mouse studies, human metabolome analyses also revealed that up to 20% of detectable metabolites in matrices such as plasma and saliva exhibit daily rhythms (Davies *et al*., 2014). It is therefore clear that molecular rhythmicity occurs at multiple levels of organization, from genes to protein and metabolites, in both rodents and humans.

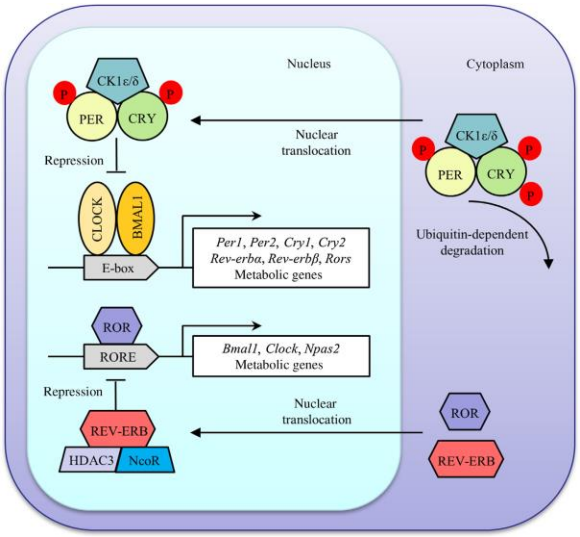

Fig.1. Simplified Model of the Molecular Circadian Clock.

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 bioavailability) of a drug (Ohdo *et al*., 2011). Chronokinetics of certain drugs may involve changes from a mono to a multi-compartmental model as a function of drug dosing time (Baraldo, 2008). Chronopharmacokinetic studies have 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 (Anthony and Berg, 2002).

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 (t½) as long as 84 hours (Ohdo *et al*., 2011). Several physiological factors such as gastrointestinal, cardiovascular, hepatic and renal changes vary according to time of day. Therefore, both subject synchronization and dosing time of a drug must be known for the correct interpretation of pharmacological data (Lemmer, 2009).

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) (Paschos *et al*., 2010). Chronokinetic changes can therefore be discussed under four subtitles:

1. Circadian Rhythms in Absorption

Absorption of drugs administered via the oral route have been 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 the day (Konturek *et al*., 2011). These changes may have 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. In a particular study, gastric emptying rates were compared between morning (8 am) and evening (8 pm) in male subjects, and it was found that gastric emptying (t½) for the evening meal was significantly longer for solids but not for liquids compared with those of the morning meal (Hershcovici *et al*., 2011). 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 (Baraldo, 2008).

The mechanisms underlying the chronokinetics of lipophilic drugs involve a faster gastric emptying time and a higher gastrointestinal perfusion in the morning (Konturek *et al*., 2011). However, such variations have not been demonstrated for hydrophilic drugs (Labrecque and Bélanger, 1991).

2. Circadian Rhythms in Distribution

Circadian changes related to drug distribution are known to change according to time of the day (Kervezee *et al*., 2017). 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 (Anderson *et al*., 1999). Thus, circadian variability in blood flow may explain a possible difference in drug distribution depending on dosing time (Stow and Gumz, 2011).

The liver activity varies due to circadian rhythm, and as a consequence, the levels of plasma proteins (albumin, globulins) changes over s 24-hour period. Most human plasma protein concentrations including albumin, and a1-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 (Jones *et al*, 2017).

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 have also been shown to be affected by circadian rhythm (Stow and Gumz, 2011).

Circadian rhythms in plasma protein binding have also been demonstrated for several mood stabilizers; valproic acid, 5-fluorouracil (5-FU), ketoprofen, carbamazepine, diazepam, lidocaine, prednisone, and cisplatin (Nachkebia *et al*., 2009). 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 (Ritschel and Forusz, 1994). 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 (Hecquet *et al*., 1985). 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 (Saif *et al*., 2009).

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 anestheics, indomethacine, and theophylline (Bruguerolle and Lemmer, 1993). Furthermore, P-glycoprotein; the product of the multidrug resistance (MDR) gene which contributes to renal, biliary, and intestinal elimination of drugs, intestinal peptide co-transporter-1 (PEPT1) which plays important role in nutrient and drug transport, all exhibit a 24-hour variation (Murakami *et al*., 2008).

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. As a consequence, wrong dosing of such drugs at night hours may cause mild to moderate toxicity.

3. Circadian Rhythms in Metabolism

Hepatic drug metabolism seems to depend on liver xenobiotic-metabolizing enzyme activity and/or hepatic blood flow (Smolensky, 2001). Both factors show circadian time-dependent alterations. Circadian rhythm can affect blood flow in liver and thus, can affect the clearance of several drugs (Alvarez *et al*., 1997; Dyar KA and Eckel-Mahan, 2017).

In mammals, most of the xenobiotics are metabolized mainly in the 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 P450 (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 facilitate their excretion into bile, feaces and/or urine. After phase II reactions, the xenobiotic conjugates may be further metabolized in phase III reactions (Xu *et al*., 2005).

Interestingly, genome-wide analysis of liver transcriptome revealed that proteins involved in the phase I–III reactions are expressed in a circadian fashion (Akhtar *et al*., 2002). Moreover, phase I-III enzyme activities show circadian time-dependent differences in extrahepatic tissues such as brain (Asher and Schibler, 2011). 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 have been reported for substrates such as aminopyrine, paranitroanisole, hexobarbital and 4-dimethyaminobenzene, aniline, benzphetamine, benzpyrene and imipramine (Bass and Takahashi, 2010). It appears that drug metabolism resulting from oxidative microsomal reactions reaches its peak during the activity span and lowest during the rest span. Conversely, sulfate conjugations are much faster during rest than during activity (Hoffman *et al*., 1990). Novel research investigating these relationships could deepen the understanding of pathogenesis, which may pave ways for new strategies to fight against metabolic syndrome.

4. Circadian Rhythms in Excretion

The circadian timing system plays a key role in the toxicity profile 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) were shown to exhibit a remarkable circadian rhythm of bile flow, biliary concentrations and excretory rates of bile salts, cholesterol and phospholipids (Lo Sasso *et al*., 2008).

On the other hand, the excretion rates of these polyamines were found to be highest in the morning in healthy volunteer subjects (Pöyhönen *et al*., 1990). A significant decrease in the rate and extent of ciprofloxacin excretion following 10 pm administration was observed in another similar research (Rao *et al*., 1997). Excretion of 17-oxosteroids was also shown to be affected by circadian clock (Ghiciuc *et al*., 2011).

Clinical Relevance of Chronopharmacokenetics for Clinicians, Clinical Pharmacist and Pharmacy Practitioners

Several variables influencing pharmacokinetics (i.e., meal content, meal times, fasting, galenic formulation, posture and rest) have to be controlled before the administration of drugs. Particularly, the time of administration should be controlled in order to prevent disparities in drug pharmacokinetics. Clinicians, 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 have a narrow therapeutic range (Baydar and Erkekoglu, 2009a).

Furthermore, variables like sex, race and phenotype should be considered before drug administration, and dosing regimens should be modified considering all the factors mentioned. If the signs/symptoms of a disease are distinctly circadian phase-dependent (like symptoms of myocardial infarction, angina pectoris, nocturnal asthma, peptic ulcer), patients/clients should be warned on the correct time of administration of the drug used for the treatment of such diseases (Baydar and Erkekoglu, 2009b). In asthma patients for instance, lung function undergoes circadian changes and reaches to a low point in the morning hours, chronotherapy for asthma should therefore be aimed at getting maximal effect from bronchodilators during early morning hours.

As gastric secretion reaches to its highest at night, chronotherapy for peptic ulcers 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 and as such, blood flow to tumors and tumor growth rate are greater during activity phase than rest phase and usually midnight therapy has been 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 (Baydar and Erkekoglu, 2009a; Baydar and Erkekoglu, 2009b).

Concluding Remarks

Circadian rhythmicity has an important impact on drug effectiveness and toxicity. Chronopharmacology aims to improve the understanding of circadian changes in both desired effects (chrono-effectiveness) and tolerance (chrono-tolerance) of medications and evaluates the metabolism of drugs in mammals according to time of the day. The circadian timing system plays a key role in the toxicity of drugs by influencing their metabolisms in the liver and intestine in addition to their excretion via bile flow and urine. Therefore, pharmacotherapy may be applied by the appropriate timing of conventional tablets and capsules, which can be applied according to 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.

On the other hand, new special drug delivery systems known as “chronopharmaceuticals” can be used to synchronize drug concentrations according to circadian rhythms. These medications can identify the proper dosing time and this amelioration will lead to improved progress and diffusion of pharmacotherapy. It is conceivable that chronopharmaceuticals coupled with nanotechnology could be the future of drug delivery systems, and lead to safer and more efficient disease therapy in the future.

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