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Review Article

Chronopharmacodynamics of drugs in toxicological aspects: A short review for clinical pharmacists and pharmacy practitioners

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ABSTRACT

For many decades, researchers are aware of the importance of circadian rhythm in physiological/biochemical properties and drug metabolism. Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. It has been attaching substantial attention in the last years. Chronopharmacodynamics mainly deals with the biochemical and physiological effects of drugs on the body, the mechanisms of drug action, the relationship between drug concentration and effect in relation to circadian clock. In this review, we will focus on mammalian circadian pharmacodynamics and discuss new chronotherapy approaches. Moreover, we will try to highlight the chronopharmacodynamics of cardiovascular drugs, anti-cancer drugs, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) and give some practical concerns for clinical pharmacists and pharmacy practitioners, concerning this issue.

Keywords: Analgesics; anti-cancer drugs; cardiovascular drugs; chronodynamics; chronopharmacology; circadian rhythm; non-steroidal anti-inflammatory drugs

INTRODUCTION

Circadian rhythms are discernible in physiological and biochemical properties of the human body, such as core body temperature and corticosteroid and melatonin levels.[1-3] This time keeping system, termed the endogenous clock, has evolved into a free-running entity that produces circadian rhythms even when time zeitgebers are absent.[4]

An average human suprachiasmatic nuclei (SCN), a pacemaker which controls the mammalian timing system, runs with a period slightly exceeding 24 hours and the SCN consists of neuron clusters whose electrical potential frequency fluctuates spontaneously with an approximate 24-hour periodicity.[5,6] Circadian clock provides the optimization of metabolism and energy utilization for sustaining life processes in the organism.[7,8] It is clear that daily food intake, metabolism and detoxification as well as several physiological processes are regulated by the circadian rhythm.[7,9,10]

Chronopharmacologic phenomena can be viewed as resulting from an adaptation of the organism to cyclic environmental changes in 24 hours and the toxicity of xenobiotics is modified by the chronicity of cellular activity of organs.[11,12] In toxicology, animal housing of rodents are performed according to 12 hours dark and light cycles to control the secretions of several hormones; however, applications in clinic according to the circadian rhythm have only gained attention in the last decades. We know that the circadian pharmacokinetics and particularly pharmacodynamics that modulate drug effectiveness and toxicity are manifestations of the circadian regulation of xenobiotic detoxification and could have important clinical applications since they allow treatment modification in order to increase efficacy and safety of a certain drug or decrease side effects. However, studies omitting the timing of dosing may be the partial cause of the reports that found so many substances carcinogenic.[12]

Different cells of different functional organs have different periodicities and their functions are influenced by circadian changes at varying levels.

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Moreover, the gender, age, physical activity, disease states and phenotypic properties of the individual have a big impact on these functions.[13] Concerning the effects of circadian clock, successful applications of drug therapy in asthma, allergic diseases, psychotic states, hypertension, coronary heart disease and diabetes were achieved.[14]

In this review, we will focus on mammalian circadian pharmacodynamics and discuss new chronotherapy approaches. Moreover, we will try to highlight the chronopharmacodynamics of cardiovascular drugs, anti-cancer drugs, analgesics and non-steroidal anti-inflammatory drugs and will give some practical concerns for clinical pharmacists and pharmacy practitioners.

Chronesthesy and chronopharmacodynamics

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body as well as the mechanisms of drug action and the relationship between drug concentration and its effect. One particular example may be drug-receptor interactions.[15] Biological rhythms at the cellular and subcellular levels can provoke significant dosing-time differences in the pharmacodynamics of medications that are unrelated to their pharmacokinetics. This phenomenon is called "chronesthesy".[16-24] Firstly, this term was used to describe rhythmic and temporally predictable alterations in the susceptibility or the sensitivity of a target biological system to a drug, which cannot be expounded by chronokinetic changes. Afterwards, considering many experimental findings chronesthesy was considered as the chronopharmacologic counterpart of the pharmacodynamic concept.[25-27] Chronopharmacodynamics basically endeavors with mechanisms of time-related variation in effects and metabolism of drugs in healthy organisms. However, the term "chronesthesy" can be used instead of chronopharmacodynamics which is a long and difficult word. Rhythms in receptor number or conformation, secondary messengers, metabolic pathways, and/or free-to-bound fraction of medications help explain this phenomenon. Here we can discuss the impact of timing on the pharmacodynamic properties of several drugs.

Cardiovascular drugs

There is evidence in literature that circadian clock has impact on the pharmacodynamics of several cardiovascular drugs. These drugs are summarized in Table 1.[28-33]

Table 1: The cardiovascular drugs that have evidence for the impact of circadian rhythm on their pharmacodynamics

Cardiovascular active drugs	
Beta blockers	Calcium channel blockers
Acebutolol	Amlodipine
Atenolol	Nifedipine
Bevantolol	Nisoldipine
Bopindolol	Nitrendipine
Labetalol	Verapamil
Mepindolol	ACE inhibitors
Metoprolol	Captopril
Nadolol	Enalapril
Oxprenolol	Nitrates
Pindolol	Glyceryl-trinitrate
Propranolol	Isosorbite-dinitrate
Sotalol	Isosorbide-5-mononitrate
Diuretics	Others
Hydrochlorothiazide	Clonidin
Indapamide	Prazosin
Piretanide	Potassium chloride
Xipamide	

ACE inhibitor: Angiotensin Converting Enzyme inhibitor

Beta-receptor blocking drugs (β-blockers) consist of an important group of cardio-active drugs. These medications still have great therapeutic value in the treatment of cardiovascular disorders like coronary heart disease, hypertension and arrhythmias. Different β-blockers vary not only in their specific effects like receptor affinity, receptor selectivity, intrinsic sympathomimetic activity, and in their nonspecific effects related to the lipophilicity of the drug, but also in their biotransformation. Lipophilic β-blockers are usually subject to hepatic biotransformation whereas hydrophilic ones are mainly eliminated by renal excretion. Various β-blockers have been studied in several animal experiments and in volunteers for their chronopharmacodynamic properties. The peak concentration of propanolol was achieved in the application between 8 A.M. and 2 P.M.. However, when applied on 2 A.M., the heart rate can be slightly changed in the following 6 hours. Therefore, it can be stated that sympathetic tonus, which is demonstrated by the rhythm in plasma noradrenaline and cAMP levels, affects the pharmacodynamics of the particular drug and it can be concluded that propanolol should be applied in hours when sympathetic tonus is high.[28]

Anti-anginal drugs such as nitrates favorably shift the ratio of myocardial oxygen demand and supply, by relieving chest pain and reducing the duration and frequency of acute ischemic events.[29] Isosorbidedinitrate, an important nitrate derivative, shows its highest therapeutic effect around 2 A.M. when it highly induces decrease in blood pressure and increase in heart rate. In contrast, at 8 A.M. isosorbitedinitrate did not significantly increase reflexly induced tachycardia during orthostatis.[28] These findings are also in concert

with the data that a maximum orthostatic liability is observed around 3 A.M.[30]

Calcium channel blockers are used in the treatment of coronary heart disease, myocardial infarct, cerebrovascular diseases and hypertension for several years.[31] Verapamil and diltiazem have a more prominent cardiac effect, whereas dihydropyridine type blockers such as nifedipine have a more dominant vasodilator effect. Several chronopharmacologic studies were performed on various calcium channel blockers and in general their blood pressure lowering effect was found to be higher in daytime than night time and the circadian clock dependent effects of these drugs show similar pattern as β-blockers.[32,33]

Anticancer drugs

In clinical practice, doctors and other health care personnel do not pay adequate importance for the time of administration of anti-cancer therapy. Besides, the timing for anti-cancer drug administration is rarely indicated in study protocols or seldom reported in the reports from clinical trials.[34] As a consequence inter-individual and intra-individual variations can be observed.

For the convenience of hospital staff, most intravenous chemotherapy is being applied during daytime and oral drugs are usually administered once daily, preferentially administered in morning, without putting forward a rationale for this time of dosing.[35-40] This conventional approach cannot be used for some of the drugs as this lack of attention to the timing of therapy supposes that biological parameters are either constant throughout the 24 hours, or that their variations are unpredictable and/or stochastic. However, the timing of therapy must be based on data on appropriate circadian rhythms obtained from rodent and human chronotherapy studies in order to rationalize the administration time for each drug and optimize its therapeutic index.[41]

For anti-cancer drugs used in infusion form, in order to define the drug regimen, dose administered per unit (usually body surface area or body weight), duration of infusion and frequency of administration are the parameters commonly used.[41] If the cancer drug will be infused for a short time, chronotherapy studies can be performed with a timed bolus or a short infusion where the timing of administration (start, peak and stop times) are stipulated.[35,42] On the other hand, a constant-rate infusion over 24 hours, or integral multiples of this span, does not consider chronopharmacodynamic properties. Therefore, this procedure should be used as a control administration schedule for studies of cancer chronotherapy for drugs whose pharmacologic properties enable long term infusion.[35]

The dissimilarities between the conventional and the chrono-modulated applications are not limited to the time of administration, but include differences in delivery profile, infusion duration and drug sequence.[43] A new anti-cancer delivery system named as "chrono-modulated delivery" introduces another infusion parameter, "the time of peak-flow rate". In this form of application, the administration pattern does not remain constant. It is rather semi-sinusoidal, with an increasing flow rate, a peak administration rate at a time specification and a gradual symmetric decrease in flow rate. The chrono-modulated application profile is particularly convenient for drugs with a short half-life where a relatively long duration of administration is choosen.[41]

Here we can give the examples for the change in the pharmacodynamics of some anti-cancer drugs: DNA synthesis in the main target tissues of 5-fluorouracil (5-FU)-induced toxicity (e.g., bone marrow, skin, and oral and rectal mucosa) is lowest during the night and highest during daytime.[35,44-51] Therefore, at night when the whole-body clearance of 5-FU is increased, the proportion of healthy cells potentially damaged by 5-FU is decreased. Whole-body pharmacodynamics of 5-FU, therefore displays variation along the circadian time scale, with a synchronous phase between different target tissues. The anabolic enzymes (orotatephosphoribosyltransferase, uridinephosphorylase, and deoxythymidine kinase) that produce cytotoxic forms of 5-FU have their highest activity during the dark span of rats or mice, when 5-FU is most toxic to healthy tissues.[8] The activity of the "thymidylatesynthetase", which is the target enzyme of 5-FU has also been studied at the cellular level in the oral mucosa cells of 6 healthy volunteers. The activity of this particular enzyme showed a circadian rhythm with a trough between midnight and 4 A.M.[45] Therefore, the molecular target of 5-FU is less active at night. This results in a cellular chronopharmacodynamic pattern of this drug consistent with its lower cytotoxicity to the oral mucosa during the night. The circadian profiles of whole-body and cellular chronopharmacokinetics and chronopharmacodynamics in humans would therefore predict a better tolerability of healthy tissues for a nightly administration of 5-FU. This hypothesis has been approved by several clinical studies. On the other hand, the anti-tumor effects of interferon-β (IFN-β) in mice are more efficient during the early rest phase than during the early active phase. The dosing schedule-dependent effect of IFN-β is also closely related to that of IFN receptors and "interferon-stimulated gene factor (ISGF)" expression in tumor cells or lymphocytes.[21,52]

Tyrosine kinase is an enzyme that transfers a

phosphate group from ATP to a protein in the cell. Imatinib mesylate is a molecule that inhibits the function of various receptors with tyrosine kinase activity. In mice, the influence of dosing time on the ability of imatinib to inhibit tumor growth has been investigated. It was observed that the growth of tumor cells implanted in mice was more severely inhibited by the administration of imatinib during the early rest phase than during the early active phase. The dosing time-dependency of anti-tumor effects is parallel to that of the imatinib-induced antiangiogenic effect. Therefore, the potent therapeutic efficacy of the drug could be expected by optimizing the dosing schedule.[53]

Analgesics and non-steroidal anti-inflammatory drugs

Both in rodents and in humans, biological rhythms in pain sensitivity have been studied extensively.[54-56] Morphine shows a broad range of other pharmacological effects in addition to its potent analgesic properties. In humans, reduction in gastrointestinal motility, sedation, inhibition of the micturition reflex, and miosis were observed. In rodents, though some of the pharmacologic effects were similar; different reactions were also found, like mydriasis as an opposite reaction.[57] Pharmacological tolerance to the analgesic effect of morphine was observed in several studies after chronic administration of morphine in both experimental and in humans. However, the clinical tolerance in humans develops more slowly. However, chronopharmacological studies on the development of tolerance to the analgesic effect induced by morphine are very rare. This should be an important research field for scientists as such opioids are important pain killers, especially for the end-stage of cancer. Among few studies performed on morphine chronopharmacodynamics, Yoshida *et al*., (2003) used hot-plate method induce pain in mice and the researchers detected the chronopharmacodynamic response towards morphine by using this model.[58] The researchers found that there was a significant 24 hours rhythm in the latency of thermal response after morphine injection with a trough at the light phase and a peak at the dark phase. Especially, at the dark phase, the time spent on the hot-plate after morphine injection was significantly longer compared with non-drugged state. The rhythmic pattern of analgesic effect induced by morphine was similar to that of the sensitivity of mice to painful stimuli in non-drugged state.[58] The results of that study were consistent with the previous findings performed by naloxane and morphine.[54,59] Chronopharmacological studies were also performed on the heat-pain reducing effects of fentanyl in humans. A peak in pain relief occurred late in the afternoon (5.30 P.M.) and a trough in the early morning hours (5.30 A.M.).[60] On the other hand, the analgesic effects of two other opioids [dihydrocodeine (DHC) and tramadol] were investigated in humans. The results indicated that the painful intensity of the chemical stimuli strongly increased during evening sessions. In addition, both DHC and tramadol exerted stronger analgesic effects when administered in the evening.[61]

The kaolin-induced pain mouse model seems to be useful for the chronopharmacodynamic evaluation of analgesic agents. In a study using this model, chronopharmacodynamic effect of indomethacin, a NSAID drug, was evaluated. Indomethacin was adminstered orally to mice at 2 A.M., 8 A.M., 2 P.M., or 8 P.M., and the suppressive effect on kaolin-induced writhing was determined after each timed dosing. After dosing at 8 A.M., indomethacin remarkably decreased the number of writhes during the critical span of 2-6 P.M., the time when writhing reaction was greatest during the 24 hours, while the suppressive effect of the medicine after dosing at the other clock times was relatively small. These findings suggest the analgesic effect of indomethacin in mice with the kaolin-induced writhing is greater after dosing in the early resting period, which is similar to that reported in patients with nocturnal pain.[62]

Some practical points for clinical pharmacists and pharmacy practitioners

Desired effects or side effects of medications are dependent not only on the physico-chemical properties of the compound, but also on its dosage, its pharmacokinetics, and particularly on its pharmacodynamics.[63,64] As pharmacodynamics is affected by circadian variability, circadian rhythm should be taken into account before the administration of a drug in order to prevent the temporal variations in the mode of action. Therefore, clinical pharmacists and pharmacy practitioners should take into account that the time of administration might be very important in eliminating the risk of toxicity of certain medications, particularly cardio-active, anti-cancer and NSAID drugs.[63,64]

For β-blockers, particularly for propanolol, the time of administration should be between 8 A.M. and 2 P.M. as peak concentration is achieved when the sympathetic tonus is high. Similarly, the blood pressure lowering effect of calcium channel blockers was found to be higher in daytime than night time. Besides, as hypertension, heart attack and stroke mostly occurs in morning time, daytime administration of these drugs gives opportunity to prevent diseases of cardio-vascular origin.

For anti-cancer drugs, rather than choosing daytime administration for the convenience of the health

care personnel, a valid application procedure should be administered. As the chronopharmacodynamic properties of each drug as well as each pharmaceutical form (infusion, oral) might differ from each other, the right administration time should be chosen according to studies performed on each particular medication. Besides, the manufacturers should be forced to include the time of administration to the package inserts of these drugs.

NSAIDs comprise a very important group of medications, used in a variety of diseases. These drugs should be administered at morning time when the pain is at its highest, especially in rheumatoid arthritis. Morning time administration usually provides a day-long reduction in pain and an increase in life quality.

CONCLUSION

Circadian rhythms are endogenous in nature and have been well-documented for eukaryotic organisms. The important feature of endogenous biological rhythms is their anticipatory character. Rhythmicity inherent to all living systems provides an easier adaptation and better survival under different environmental conditions during the 24 hours cycle as well as during changing seasons. Considering this knowledge, it is conceivable that not only the right amount of the right substance must be at the right place, but also this must occur at the right time. In man nearly all functions of the body including those influencing pharmacokinetic and pharmacodynamic parameters show marked daily variations. Chronesthesyis the administration time of a drug based on the circadian or other bioperiodic rhythm, related to the rhythm in receptor number or conformation and rate-limiting steps in metabolic pathways. We can conclude that concerning the available data, there is clear evidence that the dose/concentration-response relationship of drugs can be significantly dependent on the time of day. Thus, circadian time has to be taken into account as an important variable influencing a drug's pharmacodynamics and/or its effects or side effects.

AUTHORS' CONTRIBUTION

Authors contributed equally to this work and Terken Baydar is the corresponding author of this paper.

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