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A Review on Time Dependent Pharmacokinetics

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ABSTRACT

In order to design proper protocol for drug administration is consideration of circadian rhythm in drug pharmacokinetics. Several studies have concluded that all organisms including humans are highly organized by circadian rhythms. These changes in cycles will influence on physiological function thus, can influence on pharmacokinetics phases. Drug pharmacokinetic parameters can be changed according to the time of administration. The main objective of the chronopharmacokinetic study is to control the time of administration which among others can be responsible for variations of drug kinetics but also chronopharmacological effects observed with certain drugs. This article gives brief information regarding the changes of pharmacokinetics of the drug due to circadian rhythms.

Keywords: Chronopharmacokinetics, circadian rhythms, absorption, distribution, metabolism, elimination, chronopharmacology.

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INTRODUCTION

The study of the movement of a drug from its administration site to the place of its pharmacologic activity and its elimination from the body is called pharmacokinetics. Factors affecting drug movement in the body are (A) drug release from the dosage form (B) absorption from the site of administration into the bloodstream (C) distribution to various body organs (D) rate of elimination from the body by metabolism or excretion of unchanged drug[1]. Time dependent pharmacokinetics generally refers to a noncyclical change in the drug absorption or drug elimination rate process over a period of time[2]. Absorption, distribution, metabolism and elimination are influenced by many different physiological functions of the body which may vary with time of the day. Thus, pharmacokinetic parameters characterizing these different steps, conventionally constant in time, depend on the movement of drug administration. Time dependent changes in kinetics may proceed from circadian variation in each step i.e absorption, distribution, metabolism and elimination. Thus, circadian variations in gastric acid secretion, pH, motility, gastric emptying time, drug protein binding, liver enzyme activity, and hepatic blood flow, glomerular filtration, renal blood flow and urinary pH may play role in such kinetics variations[3]. The main aim is know the moment of administration of drug to achieve desired drug plasma concentration so as to eliminate chances of discomfort feel by the patient due to the higher intensity of symptoms of a disease for which drug therapy is required. These studies also aim to administer drug plasma concentrations are either least toxic or totally safe for body.

Chronopharmacology examines the influence of the momentum of drug administration and body response according to the temporal structure of organism. Chronokinetic studies have been reported in human and animal in order to explain chronopharmacodynamic phenomenon and demonstrate that time of drug administration influences the kinetics of drug. Time dependent changes in kinetics may proceed from circadian, metabolism, and elimination.

Drug chronopharmacokinetics knowledge may be clinically relevant as it may have implications for drug prescription by modulating the distribution of the total daily dose along the 24 hour scale. When conducting a chronokinetic study it is not only necessary to take into account differences in the time of administration but to also have strict control of all other possible variables which are known to influence pharmacokinetic processes. New tools such as new formulation procedures or pumps with or constant or programmable delivery rates, now make a possible to deliver a drug at a definite time or during a span of time and at a controlled rate in chronokinetic studies [4].

Body Rhythms

Biological rhythms control much of the body's normal functions, including performance, behavior, sleep and endocrine rhythms. These functions are primarily regulated by the circadian clock, a cluster of nerves located on the hypothalamus in the brain.

Circadian rhythms are biochemical, physical and behavioral cycles whose period is approximately 24 hours. These cycles are coordinated by molecular oscillators in the neurons of the suprachiasmatic nucleus. These oscillators represent the key component in the human biological clock, which is coordinated with alternation of day and night by specialized light sensitive cells in the retina.Physically the circadian clock located in the suprachiasmatic nucleus (SCN) in the hypothalamus of the brain hemisphere. The SCN is a tiny pin head sized area containing very small neurons[5]. The SCN is connected with the autonomic nervous systems for dispersion its time of day message, either by setting the sensitivity of endocrine glands like thyroid, adrenal or by directly controlling an endocrine output of pineal gland i.e melatonin synthesis[6] and other functions that play a role in making us feel sleepy or awake[6].

In the morning, with exposure to light, the SCN sends signals to raise body temperature and produce hormones like cortisol. The SCN also responds to light by delaying the release of the other hormones like melatonin, which induce sleep and produced when the eyes signal to the SCN that it is dark. Melatonin synthesis increase as light decreases and reaches it maximal level between 2 to 4 am[7]. Other systems also follow a daily rhythm, many of which are controlled by hormones and other compounds that receive signals from the biological clock. For example the hormones responsible for hunger and metabolism are increase and decrease over the course of the day, compounds that embolden the inflammatory response rise at night and those that inhibit it rise during the day[8].

The identification of the circadian clock at the molecular level makes possible the transition from observational studies of drug efficacy and toxicity at different times of day to cause effect studies that provide a link between the circadian clock and drug pharmacokinetic parameters [9].

Sleep – wake and other daily patterns are of circadian rhythms which are governed by the body's biological clock, held deep within the brain. But research has been finding that the body's clock is responsible for more than sleep and wakefulness. Other systems like hunger, mental alertness, stress, heart function and immunity also operate on a daily rhythm. Disturbances in body's daily rhythms can cause problems.

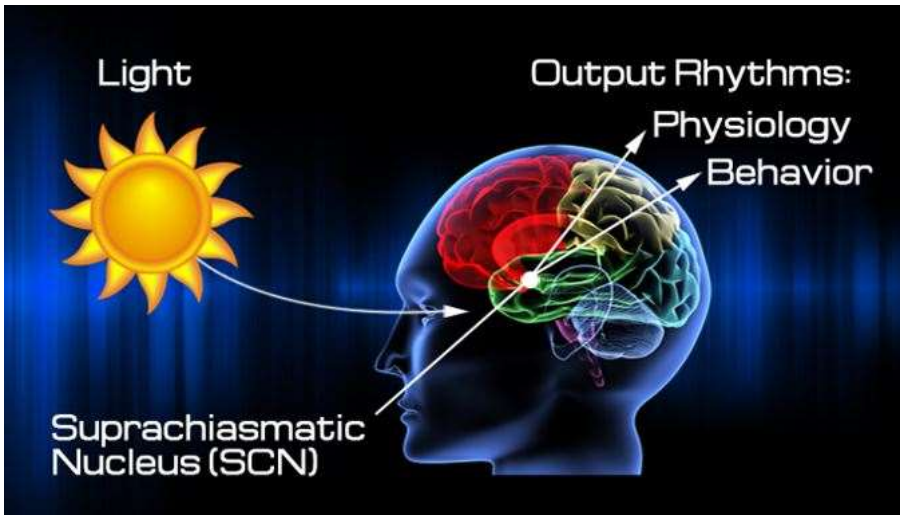

Figure 1: Suprachiasmatic Nucleus located in brain

There are two major categories of biological rhythms, endogenous and exogenous. Endogenous rhythms come from within and are regulated by the organism itself, day to night. These are four categories of biological for examples the body temperature cycle. Exogenous rhythms are the results of external factors, such as a change in the seasons, or the transition from rhythms that extend beyond just classifying them based on internal and external sources. This systems maintains that criteria, but extends to include the duration of the cycle as a defining factor. The resulting categories are circadian rhythms ultradian rhythms and infradian rhythms.

Circadian Rhythms

Circadian rhythms are rhythmic or cyclical changes in plasma drug concentrations that may occur daily, due to normal changes in body functions. Some rhythms changes that influenced body functions and drug response are controlled by genes and subject to modification by environmental factors. The mammalian circadian clock is a sustaining oscillator, usually with in a period of 24 hours that cyclically controls many physiological and behavioral systems. It is evident that daily synchrony between external light or dark cycles and internal circadian rhythms is essential for optimal health. Although circadian rhythms are endogenous, they are adjusted to the environment by external cues called zeitgebers[10]. Circadian rhythms are regulated through periodic activation of transcription by a set of clock genes. Some well-known circadian physiologic parameters are core body temperature (CBT), heart rate (HR) and other cardiovascular parameters. These fundamental physiologic factors can affect disease states, as well as toxicity and therapeutic response to drug therapy.

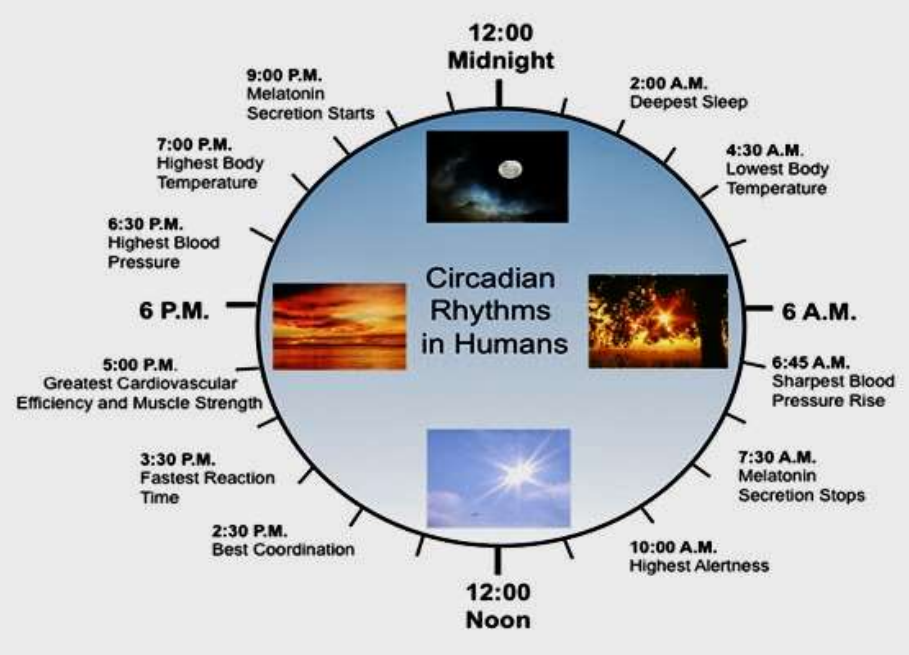

Figure 2: circadian rhythm cycle

Ultradian rhythms

Ultradianrhythms are defined as an endogenous rhythm pattern that occurs on a shorter time scale than circadian rhythms. An Ultradian rhythm is a recurrent period or cycle repeated throughout a 24- hour period[11]. As of the brief cycle time the frequency of occurrence is higher. There are many ultradian rhythms like respiration, heart beat etc…

Infradian rhythms

Infradian rhythms are rhythms that are longer than 24 hours. These can be rhythms that exceed 24 hours by a few hours they may be cycles of a few days, a few weeks, a few months, a year or even of many years[12]. Examples include menstrual cycle and seasonal affective disorder.

Classification of time dependent pharmacokinetics

A major distinguishing feature between dose and time dependency is that the latter involves an actual physiological or biochemical change in the organs of the body associated with the drug disposition. A typical Michaelis-Menten constant is a dose dependency, drug clearance changes with concentration and such a system should not be considered time- dependent simplybecause the values of pharmacokinetic parameters also change with time. If that system was truly time dependent, drug Clarence should change with time while drug concentration is at steady state[13].

They are divided into two classes.

1. Physiologically induced time dependence

- Chronopharmacokinetics

2. Chemically induced pharmacokinetics

- Auto induction
- Auto inhibition

Physiologically induced time dependence

Chronopharmacokinetics

Chronopharmacokinetics investigates the variation in drug plasma levels as a function of time of day and the mechanisms responsible for time dependent variations[14]. Most of the pharmacy research that the death of patients are due to heart attack is more at 2 to 4 am, and when remaining to the arthritis patients suffers a lot at 6 am in the morning. Even arthritis comes occurs in the early morning. So, as then where time specific we needed whom the knowledge of chronopharmacokinetics. Which help to design us to design the dosage form that release the drug at specified time that reduce patient compliance.

Reasons for chronopharmacokinetics

In some cases we have to study the chronopharmacokinetics these are when drugs have narrow therapeutic index, when symptoms of diseases are based on circadian phase dependent like asthma, hypertension, ulcer diseases etc), when possible daily variations in pharmacokinetics may be responsible of time dependent variation in drug effects and if drugs have some serious adverse effect can be minimized by change in the time of administration[15].

Circadian rhythms in absorption

The absorption of an orally administered drug is depends on the many factors like Physico-chemical properties of drug, pH, gastric emptying time, area and structure of the membrane. For example circadian changes in pH may affect the drug ionization. Most lipophilic drugs appear to be absorbed faster when the drug is taken the morning compared with the evening. No circadian variation in absorption of drugs has been observed in case of highly water soluble drugs[16]. It is because of chronopharmacokinetics of lipophilic drugs involves a faster gastric emptying time and a higher gastrointestinal perfusion in the morning. Feeding conditions also contribute to dosing time dependent difference in drug absorption[17]. Shiga et al documented difference in chronopharmacokinetics profiles of propranolol a lipophylic β-blocker and atenolol, a hydrophilic β- blocker, in patients with hypertension showing that propranolol but not atenolol is absorbed more rapidly in the morning time administration compare with evening time administration. Drug absorption by other routes of administration may also influenced by biological rhythms. For example skin penetration of eutectic mixture of lidocaine and prilocaine was depends on the time

of administration. Lidocaine plasma levels were higher after evening administration as compared with morning administration in children, in rats it was opposite[18].

Circadian rhythms in distribution

Time dependent variation in drug binding to plasma proteins influences the distribution of drugs that are highly protein bound and have a small volume of distribution[19]. Circadian changes in biological fluids and tissues related to drug distribution are documented to vary according to time of day. Blood flow depends on several regulatory factors including sympathetic and parasympathetic systems which activities are known to be circadian time dependent with a predominant diurnal effect of the sympathetic systems. Thus, diurnal increase and nocturnal decrease of blood flow may explain a possible difference in drug distribution depending on dosing time[20]. Circadian rhythms may change the activity of liver. As a result, the plasma proteins like albumin & globulin may changes from daytime to night time. Albumin and α_2-glycoprotein concentrations were decreases to their lower during night time, increase by day and reach to highest around noon. As a result a daily variation occurs in the drug protein binding. For example Cis-diaminedichloro platinum (cis-DDP) is an anti-neoplastic agent which shows maximum binding to plasma proteins is in afternoon and minimum in the morning.

Circadian rhythms in plasma protein binding have been demonstrated for several mood stabilizers, valproic acid, ketoprofen, prednisone, cisplatin, diazepam, lidocaine and 5- fluorouracil. 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 low to moderate toxicity.

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. 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. The effects of circadian rhythms on the plasma protein binding of drugs were first demonstrated for cortisol, the concentration was found to be higher at afternoon. Synthetic cortisol was also affected by circadian rhythms.

Circadian rhythms in drug metabolism

Hepatic drug metabolism seems to depend on liver xenobiotics – metabolizing activity and/or hepatic blood flow and both factors shows circadian time dependent differences. Enzyme activities show circadian time dependent differences in many tissues such as kidney, liver and brain.

Conjugation, hydrolysis and oxidation were shown to be circadian time dependent. For the drugs with high extraction ratio, metabolism depends on hepatic bold flow while for a drugs with low extraction ratio; metabolism depends on liver enzyme activity. These parameters may be influenced by circadian variations. Circadian variation in hepatic blood flow induces change in liver perfusion and temporal variations in the clearance of various high liver extractions of drugs. For example nicotine is metabolized rapidly, so that hepatic extraction indicates that clearance is likely to be dependent on liver blood flow. Nicotine clearance is subjected to an average 17% circadian variation with lower clearance at night time and highest clearance at day time[21].

T.L.Holcslaw et al. (1975) studied the relationship between circadian rhythms in the pharmacological actions and similar rhythms in the hepatic metabolism of these drugs were examined in mice. The rate of metabolism of p-nitroanisole and hexabarbital by hepatic 9000 X g supernatant fractions was found to be higher at 2400 hours (middark phase) compared to 1200 hours (mid light phase). The rhythms in *in vitro* hexobarbital and in vivo merperidine metabolism were inversely related in time with similar rhythms in duration of hexobarbital sleep time and meperidine analgesia. Reversal of the usual lighting cycle inverted the rhythm in hexobarbital metabolism while abolishing the rhythm in pharmacological response to hexobarbital; meperidine was similarly affected. These results show that circadian rhythms in the action of hexobarbitak and meperidine were well correlated with similar rhythms in the disposition of these drugs[22].

A. Jori et al. (1971) done a research on four substrates i.ehexobarbital, imipramine, p-nitroanisol and aminopyrine are metabolized by the rat liver with a rhythm showing a minimum or a maximum between 10 am and 2 pm. The minimum was reached during light and the maximum during darkness when the illumination schedule was respectively from 6.30 am to 6.30 pm or from 6.30 pm to 6.30 am. The change in drug metabolism corresponds also to a change in the level of plasma corticosterine[23].

In recent years, research on molecular mechanisms of circadian oscillation and rhythmic transcription of clock output regulators such as an enzyme of the Cytochrome P450 super family in liver has progressed. Recently, Tada et al. reported in renal transplantation patients that, despite a lack of statistical differences in pharmacokinetics of tacromalimus between 0900h and 2100h, lower nighttime AUC corresponded to the occurrence of clinical acute rejection of transplants.

Circadian rhythms in drug elimination

Drugs are eliminated from the body are either unchanged or metabolites and kidney is the most important organ for their elimination. The process involved in the urinary excretion of drugs and their metabolites are glomerular filtration, active tubular secretion and tubular reabsorption.

Modification of urine pH during day or night can also alter the excretion rate of drugs. Circadian rhythms have been described for glomerular filtration rate (GFR), effective renal plasma flow, tubular secretion, urine output, excretion of electrolytes and many endogenous substances. The clearance of inulin and p-aminohippuric acid were largest in the middle of the activity period and smallest in the rest period in rodents[24]. Thus the urinary excretion of the many drugs depends on these rhythmic variations. The physicochemical properties of drugs are particularly important in elimination process, renal elimination of hydrophilic drugs (mainly excreted unchanged by the kidneys) has been shown to circadian time dependent.

Urine pH in man is usually lower during sleep than during the day. This will affect the elimination kinetics of drugs which are to a significant excreted unchanged, if the renal clearance is pH dependent. Such pH dependence may occur if the drug is pH acidic or basic, subject to renal tubular reabsorption of the ionized moiety and particularly if it also has a pK_a from 4 to 8. For example the average biologic half-life of the sulfonamide sulfasymazine in patients at bed rest has been observed to be 35 hours during the night and only 13.5 hours during the day. It has been suggest that this marked difference may be due not only to diurnal change in urine pH, but also to distributional effects secondary to change in pH of extracellular fluid[25].

Recently, the chronokinetics of norfloxacin and ceftriaxone are two anti-antimicrobial agents, in rats showing a higher elimination during the acidity period (e.g., during the nighttime). As far ciprofloxacin is concerned, these results are in good agreement with data obtained in human. These results are of particularly importance for determination of the in vivo efficacy, daily variation in kinetics of ciproflaxicin.

Chemically induced time dependence

Auto induction

Induction of enzymes by the drug is responsible for the elimination. There by increase the clearance of the drug. It is called auto induction. It is depends on the dose and concentration of the drug. It affects the time to attain steady state and limits one's ability to use information from a single dose to predict kinetics after repeated dose or continuous administration.

A number of therapeutic consequences such as it may affect the time to achieve steady state and limits the use of information from a single dose to predict kinetics after repeated dose or continuous administration. Examples include repeated doses of carbamazepine, rifampicin induces the enzymes responsible for their elimination.

Auto inhibition

It occurs during the metabolism of drugs. The metabolites formed increase in concentration and further inhibit the metabolism of the parent drug[26]. This phenomenon is also called as product inhibition or allosteric inhibition or feedback inhibition. Clarithromycin is an inhibitor of intestinal and hepatic CYP3A4 activity and thus gradually inhibits its own metabolism as well as that of co-administered drug[27].

Example: Allopurinol, verapamil inhibit the xanthine oxidase enzyme.

Chronopharmacology

Inchronopharmacokinetics the chronopharmacology is useful to solve problems of drug optimization i.e to enhance the desired efficiency or to reduce its undesired effects. In the human organism the metabolic chance of a pharmacologic agent is not constant as a function of time[25]. Chronopharmacology surely holds promise for the creation of the most favorable conditions for drug effects, safety and therefore signify an important method of improving the treatment of many diseases. The goal of chronopharmacology is to optimize the therapeutic effect and control the adverse effects without altering the functioning of the drug in the body[28].

Chronopharmacokinetics studies have been reported for many drugs in an attempt to explain chronopharmacodynamic phenomena and demonstrate that the time of administration is a possible factor of variation in the kinetics of a drug. Many drugs are affected by time of administration and the activity or rest period of the human[29]. The effectiveness and toxicity of many drugs vary depending on the time. Such chronopharmacological phenomenon is influenced by not only the pharmacodynamics, but also the pharmacokinetics of medications[30].

The main goal of researchers in drug delivery systems of formulations is to meet the therapeutic needs relating to particular pathological conditions. Research in the chronopharmacology field has established the importance of biological rhythms in drug therapy and it is tool for development of new approach. Optimal clinical outcomes cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation drug release should also vary with time[31].

Chronopharmacokinetics of some classes of drugs

Antibiotics

It depends upon the administration time differences in the pharmacokinetics of antimicrobial agents[32]. Many studies have reported temporal variations in the pharmacokinetics of antimicrobial drugs. Various Animal models study concludes that the antibiotics having the beta-lactum ring that have concentration independent killing effect was observed in vitro study, the time that the antibiotic concentration remains greater than the MIC. It is very important in determination of in

vivo efficacy. Another important feature of chronokinetic study is that not only the efficacy of the drug may increase but also the toxicity of some drugs may decrease at different time of day[33].

Gentamicin: The pharmacokinetics of gentamicin has both the effectiveness and toxicity of both the effectiveness of gentamicin varied over the 24hr period. The clearance of gentamicin was higher in the activity period and longer serum half life and higher serum AUC reached at the beginning of the day. The rate of urinary excretion was very high.

Aminoglycosides: For this drug peak renal toxicity was observed when aminoglycosides were injected in the middle of the rest period, while lower toxicity was found when they were given in middle of the activity period. From these studies it is clear that the renal toxicity of aminoglycosides can be decreased by administration of drug as a single injection to patients during they are active (at day time).

Ceftriaxone: Total clearance of ceftriaxone varies rhythmically during the day, with it reaches maximum during the rest period and its minimum during the activity period.

Anti hypertensive drugs

Hypertension occurs mostly in the morning time as blood pressure is at its lowest a t night time and makes a sharp rise in the awaking period. Clinical chronopharmacological studies with antihypertensive drugs gave confirmation that effects on the rhythms in blood pressure and heart rate are depends on the time of day. Medication for these diseases should be preferable administered at morning time. Drugs like nifedipine, verapamil, oxprenolol and propranolol etc., revealed daily variations in the drugs kinetics. In general Cmax was higher and Tmax shorter after morning than evening dosing of these rather than lipophilic drugs.

The controlled release tablet of calcium channel blocker verapamil delays the release of drug for 4 to 5 hours following its recommended bedtime intake. Medication is released for long time so highest concentration is reached at morning around the time of awakening, with an elevated level sustained throughout diurnal activity. bed time administration is more effective for anti hypertensive drugs.

Anti cancer drugs

In human bone marrow, skin and oral and rectal mucosa, DNA synthesis, a stage of the cell division cycle associated with increased openness to S- phase specific agent's decreases by 50% or more between 1 to 4am when compared with daytime. The activity of dehydropyrimidine dehydrogenase in human mononuclear cells increases y 40% around midnight[34].

5-fluorouracil is an anticancer agent it is delivered at the same rate over the course of the day by continuous IV infusion. The mean plasma concentration levels fluctuate, with the highest levels late at night and lowest at midday. Administration of oxaliplatin during early to midnight led to decrease the toxicity and tumor growth as well as an increase half life.

Non steroidal anti inflammatory drugs (NSAIDS)

Rheumatoid arthritis symptoms are usually intense on awaking and NSAIDS should be administered in the morning and noon times due to the symptom timing of this disease. NSAIDS are having greater rates and contents of bioavailability when administered in the morning than evening.

Indomethacin: Noticeably higher and earlier peak concentrations were obtained when drug was given in the morning than night.

Ibuprofen: The chronopharmaco kinetics behavior of the press coated ibuprofen tablet under fasting conditions has the opposite to that with the capsule formulation. The peak plasma levels were obtained significantly high in every dose due to faster absorption. Bioavailability is more in the evening.

Anti- Asthmatic drugs

Recently many people are suffering with asthma. Asthma is attacked more frequently in night time and/or early in the mornings. Nocturnal asthma is common in asthmatic disease. Asthma is treated by anti asthmatic drugs like theophylline, salbutamol, terbutaline etc.

Theophylline: It is the drug of choice in treatment of acute asthma, which having Cmax has lower and Tmax has longer after evening administration than after morning administration. But sustained release tablets of theophylline shows different pharmacokinetic parameters. sustained release theophylline exhibits a shorter Tmax and greater Cmax when administered in the morning than evening.

Anti ulcer drugs

H_2 blockers are used in the treatment of peptic ulcers. A histamine antagonist when given at night shows the better results unlike when given at regular intervals around the clock. This is because the more acid secretion, more pain and perfusion of gastric juice are more subjective at night rather in day time. They should be taken in once a day in late afternoon or early night when acid secretion is increasing, autonomously whether the compound have a shorter or long half life. Lansoprazole is a proton pump inhibitor similar to H_2 blockers should be administered in the morning and omeprazole in intragastric pH is more prominent after morning than evening administration.

Examples for H_2 blockers are ranitidine, cimetidine, farmotidine. Ranitidine is having less drug infusion in night time than day time.

Opioid analgesics

Strongest analgesic effects were observed when tramadol and dihydrocodeine were applied in the evening to relive painful stimuli. Peak morphine use occurred at 9am and least use at 3 am in postoperative patient undergoing elective cholecystectomies. Finally a recent study of meperidine reveals a circadian variation of meperidine induced analgesia in sickle cell anemia patients with maximal analgesic effect occurring with the morning dose[35].

Future approach

New tools such as new formulation procedures or pumps with constant or programmable delivery rates now make it possible to deliver a drug at a definite time or during a definite span of time and at a controlled rate in chronokinetics.

Now a day's pulsatile drug delivery is gaining popularity in pharmaceutical field. The main advantage in this system is that drug is released when necessity comes. As result chance of development of drugs resistance seen in convetional and sustained release formulations can be reduced[36]. Some anticancer drugs are very toxic. These drugs cause serious problem in conventional and sustained release therapies. Now many FDA approved chronotherapeutic drugs are available in the market.

Main purpose of development of this formulation is to find out the circadian rhythm that is a suitable indicator that will stimulate the release of the drug from the device. Next point is absence of suitable rhythmic biomaterial, which should be biodegradable, biocompatible, and reversibly responsive to specific bio marks in a rhythmic manner[37].

Table 1: **Chronopharmacokinetics of drugs whose kinetics in humans varies according to the time of day of treatment[38].**

Cardiovascular drugs	
Beta blockers	Propranolol
Calcium channel blockers	Diltiazem, Nifedipine, Verapamil
Angiotensin converting enzymes	Enarapril
Organic nitrates	Isosorbidedinitrate, Isosorbide 5- mononitrate
Others	Digoxin, Potassium chloride
Anti-cancers	Cisplatin, Doxorubicin,5-florouracil, Cyclosporine, Methotrexate, Busulphan
Anti-asthmatic	Amiophylline ,Theophylline, Turbutalline, Prednisolone
Psychotropic drugs	
Benzodiazepines	Diazepam, Mesazolam, Lorazapam, Temazapam,

Others	Melatonine, Hexobarbitone, Amitryptyline, Nortryptyline, Lithium, haloperidol, Valporic acid, Carbamazapine
NSAIDS	Acetyl salicylic acid, Indomethacin, Ketoprofen, Phenacetin, Paracetamol
GI agents	Cimetidine , Omeprazole
Antibiotics	Ampicillin, Gentamicin, Griseofulvin, Sulphasymazine, Amikacin
Miscellaneous	Ethanol, Mequitazine, 5-methoxypsoralene.

CONCLUSION

The concept of drug treatment was earlier "right drug for the right person" is now changed to "right dose for the right person at right time. Time dependent pharmacokinetics can sometimes be responsible for daily variation drug effects or adverse effects. The effectiveness and toxicity of many drugs differ depending on administration of dosage form related to circadian rhythms in the body. On this basis, the pharmacokinetic variations linked to circadian rhythms can modify drug plasma concentrations and therefore their efficacy and/or toxicity as well. Drug release pattern if designed in a time controlled manner, maximum drug can be available at peak hours with minimum side effects or toxicity.

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