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Review Article

CHRONOPHARMACOKINETICS: AN OVERVIEW

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ABSTRACT

Vital signs and several constituents of the serum and urine show a circadian rhythm. Such a rhythm is also seen in the onset of various diseases. Time dependent changes in the blood volume, functions of liver and kidney etc. have implications for drug availability and circadian changes should be taken in account in pharmacokinetic studies. These changes are the subject of chronopharmacokinetics.

INTRODUCTION

Circadian rhythms have been documented throughout plant and animal kingdom at every level of eukaryotic organization. These rhythms are endogenous in nature, driven by oscillation or clocks and persist under free running (e.g. constant darkness) conditions. The genes expressing the biological clock have been identified in various species. The important feature of endogenous biological rhythms is their anticipatory behaviour. Rhythmicity inherent to all living systems allows them to adopt more easily and to better survive under changing environmental conditions during the 24 hours of a day as well as during changing seasons. The science dealing with the phenomenon of rhythmicity in living organisms is called chronobiology. The branch dealing with the pharmacologic aspects of chronobiology is termed chronopharmacology, which may be further subdivided in to chronotherapy, chronopharmacokinetics and chronotoxicity.[1]

No wonder in man all functions of the body including those influencing pharmacokinetic parameters such as drug distribution, metabolism and excretion display significant daily variations and hence the need for "chronopharmacokinetics".

DEFINITION

Chronopharmacokinetics investigates the variation in drug plasma levels as a function of time of day and the mechanisms responsible for time dependent variations.

Reasons

These time dependent changes are probably due to circadian variation in GIT (e.g. Gastric emptying time, mucosal motility) or diurnal variation of protein binding[3]. Rhythms in the onset and symptoms of several diseases are well established e.g. Coronary infarction, angina pectoris, stroke, ventricular tachycardia. MI and angina pectoris have an early morning peak between 8-12 hrs. Migraine is another disorder that exhibits periodicity in its symptoms and so chronotherapy may be beneficial in treating the problem[1,4]. In case of Sumatriptan, which is the drug of choice in migraine, the variations may be due to time dependent changes in the extent of absorption or circadian variations in hepatic blood flow[4].

Chronopharmacokinetics may also be due to variations in levels of various metabolic enzymes such as Cyt. P450 (Cyp 3A). In a study carried out by Ohno M. et al, the ratio of 6 beta hydrocortisol to cortisol, (which is a measure of Cyp 3A activity) exhibited diurnal variation (2.8 fold on average).

Gastrointestinal perfusion, liver and kidney functions are also organized across the 24 hours of a day. Several studies have indicated that pharmacokinetics of mainly lipophilic drugs can be circadian phase dependent. These studies show that after oral dosing, peak drug conc. Cmax is in general higher or time to peak (tmax) shorter after morning compared with evening administration[6].

To summarize, circadian variations in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow glomerular filtration, renal blood flow, urinary pH and tubular reabsorption may play a role in such kinetic variations.

APPLICATIONS

There is now convincing evidence that the time of day has to be taken in consideration both in clinical pharmacokinetic and pharmacodynamic studies[6]. 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 chronokinetic studies[7]. Such a programming can be of immense help in diseases such as angina where attacks are likely to occur during 8-12 hrs. The drug release can be accordingly planned to be at maximum during this period.

Similarly, patients of essential hypertension can be given a programmed delivery system to check early morning rise in blood pressure.

The phenomenon of chronopharmacokinetics can not only be exploited to prevent rhythmic attacks as in angina but also can be used to prevent toxicity as in case of gentamicin induced nephrotoxicity. Perez de la Cruz M.J. et al proved that the presence of calcium diminishes gentamicin plasma levels and amount accumulated in kidney. Calcium probably generated a diminution in renal damage and consequently gentamicin renal excretion increases. They further substantiated their claim by co-administering one calcium channel blocker (Verapamil) which reduced the calcium protective effect on the nephrotoxicity of gentamicin[8].

Another application of chronopharmacokinetics is its importance in the design and evaluation of transdermal drug delivery systems[9]. Gries J. M. et al have shown that nicotine patches need to be designed assuming a non constant clearance of nicotine over 24 hrs periods and that the effect of circadian variations in clearance could be compensated for in patch design.

Chronopharmacokinetics is often exploited to treat angina where higher and more consistent plasma levels of calcium channel blockers are required during day time to counteract higher blood pressures in hypertensive patients due to circadian variations. Such an attempt was successfully made by Eradidi and Midha[10] where in they found that between 5 to 12 hrs of administration of a new extended release Diltiazem HCL Capsule formulation, mean plasma levels of Diltiazem were significantly higher than other formulation.

Role of chronopharmacokinetics in various drugs has been studied. DA 8159, a new erectogenic was administered to rats at 10:00 hrs and 22:00 hrs but no significant differences foundl[11]. Recently chronopharmacokinetics of Tacrolimus in kidney patients[12] and metronidazole[13] in healthy volunteers has been studied.

Propanolol is absorbed more rapidly after morning dosing than after night time dosing in younger hypertensive subjects[14].

Malamary et al[15] investigated the chronopharmacokinetics of Cyclosporine A in male wistar rats following oral administration. The rats were trained to a 12: 12 light-dark cycle. A comparison of the pharmacokinetic profiles across time of administration revealed that absorption first pass metabolism and tissue distribution of Cyclosporine A in rats are circadian dosing dependent. Similar findings were earlier reported by Cipolle et al who studied circadian influences on cyclosporine pharmacokinetics in five recipients of pancreatic allografts.

Ohdo, S. et al[16] carried out experiments to investigate the circadian rhythm in the pharmacokinetics of Valproic Acid using ICR male mice trained to 12:12 light-dark cycle and reported that plasma valproic acid concentrations were higher in the light phase. They also reported lower clearance of the drug in the light phase.

Canal et al[17] studied the chronopharmacokinetics of Doxorubicin in patients with breast cancer and reported that the total body clearance of Doxorubicin was significantly decreased when the drug was administered at 21:00 hr (as compared to 09:00 hr admn.), resulting in longer elimination half life and an increase in AUC. However, Eksborg S. et al[4] had entirely different reports of the same drug when they administered it to ten patients with gynecological malignancies and concluded that in seven of the ten patients, morning dose (07:00 am) gave higher *AUC* as compared to evening dose (7 pm) in a randomized cross - over design.

Nifedipine[18,19,21] is another drug where it has been established that evening dose gives lower bioavailability as compared to morning dose. A circadian time dependency was also found in nifedipine-induced effects on blood pressure and heart rate as monitored by 24 hr. ambulatory blood pressure measurements[l9].

Lemmer and Holle[20] investigated the chronopharmacokinetics of imipramine and desipramine in rat forebrain and plasma after single and chronic treatment with imipramine. They concluded that the pharmacokinetics of imipramine and desipramine are circadian phase dependent. It was assumed that circadian variations in drug distribution are more likely to contribute to drug's chronopharmacokinetics than variations in drug's metabolism.

Studies of theophylline pharmacokinetics in humans have shown that a higher peak concentration and area under the curve (AUC), with a shorter time to peak (tp) occur after a morning dose than after an evening dose. Dye, J.A. et al[22] established that similar to human studies, the tp was shorter following the morning dose when they studied the chronopharmacokinetics of theophylline in six cats maintained on a 12: 12 light-dark cycle. These findings were successfully exploited by Fuchs et al[9] who designed a new liquid sustained release formulation of theophylline and reported that maximum serum levels of drug coincided perfectly with the critical morning dip at 2-4 am with a nocturnal excess of 15.5% to 11.9%. This circadian-tailored asymmetric dosage regimen proved to take in to account the chronopathology of asthma.

Treffel et al[23] studied chronopharmacokinetics of 5-methoxylpsoralen in eight healthy subjects and reported that the evening intake of the drug induced a higher 5-methoxypsoralen concentration and a higher AUC than morning or afternoon ingestion.

Taggart A.J. et al[26] studied the pharmacokinetics of a single 100mg indomethacin suppository in twelve healthy volunteers on two occasions at least 7 days apart. The study failed to show a significant change in single dose kinetics with the time of suppository administration.

Malan J. et al[27] failed to detect any statistically significant differences in pharmacokinetic parameters when they administered single 1g dose of paracetamol to six male volunteers on three different times of the day with each dosing spaced at least 1 week apart.

Brugerolle B.[28] studied pharmacokinetics of disopyramide in mice and reported that the protein binding of the drug exhibited circadian phase dependence.

Minora and Waterhouse[38] studied aspects of chronopharmacokinetics of ethanol in eight healthy subjects (three male subjects and five female subjects). The subjects aged 20-25 years were asked to ingest 0.8 gram of ethanol/kg of body weight within two minutes. An analysis of urinary samples revealed significant circadian rhythms of ethanol removal rates in both male and female subjects. Sturtevant E M[29] also hinted at the rhythmicity in elimination curves of ethanol. Bienert et al studied the influence of time of day on propanolol pharmacokinetics and pharmacodynamics in rabbits.

Different models have been used for chronopharmacokinetic studies although more often than not it has been healthy male volunteers.

A list of various models is summarized in Table I.

Table 1: Various animal models used by chronokinetic studies

S. No.	Name of Drug	Model	Ref no.
1	Cyclosporin A	Rats	15
2	Diltiazem	Human	10
3	Doxorubicin	Breast cancer patients	17
4	Ethanol	Rats	31
5	Gentamicin	Rabbits	08
6	Lithium	Mice	35
7	Methotrexate	Mice	33
8	Pentazocine	Dog	37
9	Phenylbutazone	Horse	36
10	Phenytoin	Epileptic patients	34
11	Propanolol	Rabbits	30
12	Sertraline	Human	32
13	Sumatriptan	Human	04
14	Theophylline	Cat	36
15	Valproic Acid	Mice	16

DESIGN OF A CHRONOPHARMACOKINETIC STUDY

In a chronopharmacokinetic study many factors of variation must be controlled:

1- Factors related to drug itself: Influence of food, Galenic formulation, Drug Interactions,

2- Subject related factors: Age, Gender, Pathology, Posture, Exercise Synchronization.

3- Factors related to conditions of administration: Single or repeated dosing, constant rate delivery, route of administration.

There are some instances in which a chronopharmacokinetic study is needed.

1- When possible daily variations in pharmacokinetics may be responsible for time dependent variations in drug effects.

2- When drugs have a narrow therapeutic index.

3- When symptoms of a disease are clearly circadian phase dependent (e.g. nocturnal asthma, angina pectoris, myocardial infarction, ulcer)

4- When drug plasma concentrations are well correlated to the therapeutic effect in case the latter is circadian phase dependent.

Variables influencing pharmacokinetics such as fasting, meals and meal times, galenic formulation, posture, activity-rest have to be controlled according to the aim of investigation.

The main aim of chronokinetic studies is to control the time of administration, which among others can be responsible for variations of drug kinetics but also may explain chronopharmacologic effect observed with certain drugs.

CONCLUSION

Chronopharmacokinetics is a successful tool in the hands of clinical pharmacist, which if judiciously exploited can help in better therapeutic drug monitoring, thus reducing side effects and providing better patient care.

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