TIME DEPENDENT PHARMACOKINETICS: A REVIEW

Mohd Abdul Hadi*

Assistant Professor, Department of Pharmaceutics, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

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. 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.

INTRODUCTION
When the actual time of administration of a drug substance particularly influences the pharmacokinetic parameters of the drug, the overall phenomenon is known as the time dependent pharmacokinetic.

However it is pertinent to state at that point in time that the aforesaid non-linear pharmacokinetics may be the result of a typical pathologic alteration with regards to the respective drug absorption-distribution-elimination.
Time dependent pharmacokinetic generally refers to non-cyclic changes in the rate processes of absorption, distribution, metabolism and excretion over a period of time.

Time dependent pharmacokinetic leads to nonlinear pharmacokinetics and thus needs separate study. Dose dependent kinetics involves a change in rate process when dose is change time dependent pharmacokinetics are as a results of alteration in the physiology or biochemistry of and organ or a region in the body that influences drug disposition. Time dependent kinetics may also occur due to chemical induced (auto-induction or autoinhibition) and physiology related factor. Drug undergoing time dependent pharmacokinetic have variable clearance, variable plasma, elimination half-life. A few examples on toxicity are given below:

- 5 fluorouracil (anti-cancer drug) when lease toxic given in the morning in rodents.
- Aminoglycoside: significant nephrotoxicity occur more frequently when drug are given during rest period (24:00 to 9:00).

The type of dosage form does not have any influence, but time of administration is important. GI motility is greater during morning when compare to night. Lipophilic drug are absorbed better in the early morning than in the late afternoon.

CLASSIFICATION
TIME DEPENDENT PHENOMENA ARE CLASSIFIED INTO TWO CATEGORIES.
1. PHYSIOLOGICALLY INDUCED TIME DEPENDENT. EX: Chronopharmacokinetic.
2. CHEMICALLY INDUCED TIME DEPENDENT. EX: Auto-Induction, Autoinhibition.

1. PHYSIOLOGICALLY INDUCED TIME DEPENDENT
   - Absorption-elimination parameters.
   - Distribution.
   - Enzymatic metabolic activity.
   - Systemic clearance.
   - Renal clearance.
2. CHEMICALLY INDUCED TIME DEPENDENT

- Auto-induction: Induction of the enzymes by the drug is responsible for elimination thereby increasing the clearance of the drug. Ex: Carbamazepine, Rifampicin etc.
- Auto-inhibition: The metabolites formed increase in concentration and further inhibit metabolism of the parent drug (Product inhibition). Ex: verapamil, allopurinol.

**Chronopharmacokinetics**

It deals with the study of the temporal changes in absorption, distribution, metabolism and elimination and thus takes into account the influence of time of administration on these different steps. Therefore the word temporal is related to time. The temporal change may me cyclical or non-cyclical Time dependent pharmacokinetics: generally refers to a non-cyclical change in rate process Time dependent pharmacokinetics lead to nonlinear pharmacokinetics Time dependent pharmacokinetics is due to auto-induction or auto inhibition.

E.g. repeated doses of carbamazepine induce the enzymes responsible for its elimination (ie, auto-induction) Auto- inhibition may occur during the course of metabolism of certain drugs.

Drug ADME are influenced by many different physiological functions of the body which may vary with time of day. The time of day has to be regarded as an additional variable factor influencing the kinetics of a drug since many drugs are affected by time of administration and the activity or rest period of the human or animal.

Dose dependent pharmacokinetics involves a change in the rate process when the dose is changed, where as time dependent pharmacokinetics is a result of alteration in physiology or biochemistry in an organ in the body that influences drug disposition.

Circadian rhythms in gastrointestinal pH can affect drug dissolution, and circadian rhythms in gastric emptying, motility, and blood flow can affect the rate, and in certain cases the amount, of drug absorption.

Rhythms in hepatic bile function and flow as well as renal blood flow, glomerular filtration, and tubular function can affect drug elimination.
RELATED TERMS

- Chronesthesia: Changes in the sensitivity or susceptibility of a target system over a period of time.
- Chronobiology: Science that studies biological rhythms.
- Chronotherapeutics: Application of chrono biological principles to the treatment of diseases.
- Chronopathology: It is the study of biological rhythms in disease processes and morbid and mortal events.

AIM OF CHRONOPHARMACOKINETICS

The main aim of Chrono pharmacokinetic studies is to control the time of administration. It can be responsible for variations of drug kinetics and also to explain Chrono pharmacological effects observed with certain drugs.

BODY RHYTHMS

BODY RHYTHMS: Body rhythms are biological processes that show cyclical variations over time. There are 3 rhythms:-

1) Circadian Rhythms: “Circa” means about and “dies” means day.

2) Ultradian Rhythms: Oscillation of shorter duration is termed as Ultradian. (More than one cycle/day).

3) Infradian Rhythms: Oscillations that is longer than 24 hr. (less than one cycle/day).

Circadian rhythms: Humans demonstrate a series of changes which lasts about a day including temperature, respiration and metabolism, sleep-wake cycle.

Infradian rhythm: (meaning more than 1 day). An example of an infradian rhythm would be a woman's menstrual cycle which lasts for 28 days.

Ultradian rhythms: Heart beat is a good example of an ultradian rhythm.

The best-known circadian rhythms Temperature, hormone secretion, metabolism, sleep/wake cycle.

The circadian system is biphasic Increased sleep tendency and decreased performance capacity during two periods throughout the 24-hour day— from 2 AM to 6 AM and from 2 PM to 6 PM.
These periods are sometimes referred to as circadian lulls.

Disruption of the normal circadian rhythm or incomplete circadian adaptation leads to: acute and chronic sleep deprivation, decreased alertness, increased subjective fatigue and decreased physical and mental performance.

The term circadian coined by Franz Halberg comes from Latin Circa “around” and dieem “day”.

1) CIRCADIAN RHYTHMS: EX: Sleep walk cycle, Blood pressure, Pulse rate, Metabolic, Gastro intestinal rhythm.
2) ENDOGENOUS RHYTHM: EX: ACTH output, Corticosteroid output, Circulating neutrophil, circulating eosinophils, rapid eye movement.

**NEED OF CHRONOPHARMACOKINETICS**

When possible daily variation in pharmacokinetics may be responsible for variations in drug effects. When drugs have a narrow therapeutic range. When symptoms of a disease are clearly circadian phase – dependent (e.g. Nocturnal asthma, angina pectoris, myocardial ischemia). When the adverse effects can be avoided or minimized because of the time of administration.

**CIRCADIAN DEPENDENCE OF DRUG PHARMACOKINETICS**

Time-dependent changes in kinetics may result from circadian variations at each step, e.g. absorption, distribution, metabolism and elimination.

**ABSORPTION:** It is altered by circadian changes in gastric emptying time gastrointestinal blood flow gastric acid secretion and pH Most lipophilic drugs seems to be absorbed faster when the drug is taken in the morning compared with the evening.
Ex:
1) Absorption of valproic acid larger in the morning than in the evening.
2) lipophilic drug (phenytoin) - faster absorption in morning.
3) Paracetamol - extent of absorption is less in night.
4) NSAIDs: indomethacin and ketoprofen better absorption in the morning and greater bioavailability.

**DISTRIBUTION:** It is altered by circadian changes in body size and composition blood flow to various organs drug protein binding Peak plasma concentrate ion of plasma proteins like albumin occurs early in the afternoon, while troughs are found during the night. Ex: maximum binding of antineoplastic like cisplatin to plasma proteins is in afternoon and minimum in the morning.

**METABOLISM:** it is altered by circadian changes in liver enzyme activity hepatic blood flow for drugs with low extraction ratio depends on liver enzyme activity. For drugs with high extraction ratio depends on hepatic blood flow.

**EXCRETION:** It is altered by circadian changes in glomerular filtration renal blood flow urinary PH tubular reabsorption All lower during the resting period than in activity period. Ex: acidic drugs like sodium salicylate excreted quickly after evening than morning administration.

At each of these steps, biological rhythms may influence the kinetics of a drug, as indicated in Table.

**Possible physiological factors influencing circadian stage-dependent pharmacokinetics of drugs**

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Elimination</th>
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CIRCADIAN RHYTHM AND SEVERITY OF CLINICAL DISEASES

Circadian rhythms and severity of clinical diseases: Disease Circadian rhythmicity osteoarthritis symptoms worse in middle or later of the day Rheumatoid arthritis Most intense on awakening Peptic ulcer Symptoms worse in the early (sleep) am Bronchial asthma Exacerbations more common during sleep.

APPLICATIONS

1) Treatment of Asthma: A normal lung function undergoes circadian changes and reaches a low point in the early morning hours. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during early morning hours.
   a. Ex: Theophylline preparation taken once a day in the evening→blood level reaches peak.
2) Peptic ulcer-Morning: proton pump inhibitor(Omeprazole), Evening- H2 receptor antagonist( Ranitidine).
3) Hypertension-highly concentration-early morning.

DRUGS THAT UNDERGO CHRONOPHARMOCOKINETICS

1) Antibiotics- Aminoglycosides,Amikacin
2) Anticancer drugs- Cyclosporin,methotrexate,5-floururacil
3) Anti-Hypertensive Drug-propranolol, nifedipine
4) Anti-epileptic drug- Valporic acid
5) NSAIDs-Ketoprofen, indomethacin

- Antibiotics Administration-time-dependent differences in the pharmacokinetics and toxicity of antimicrobial agents have been documented in Table

<table>
<thead>
<tr>
<th>Results</th>
<th>Antibiotics</th>
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<tbody>
<tr>
<td>Higher mean serum levels at 5 a.m. Higher trough serum levels at 9 a.m.</td>
<td>Netilmicin</td>
</tr>
<tr>
<td>Higher serum levels at 9 p.m.</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Longer serum half-life between 8 pm. and midnight Lower renal clearance between 8 p.m. and midnight Higher AUC (serum) between 8 p.m. and midnight</td>
<td>Gentamicin and isepamicin</td>
</tr>
<tr>
<td>Lower renal clearance at 8 p.m. Higher renal cortex accumulation at 1:30 a.m. Lower renal clearance at 1:30 a.m.</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Higher AUC (serum) at midnight</td>
<td>Cefodizime</td>
</tr>
<tr>
<td>Longer serum half-life at midnight</td>
<td>Sulfamethoxazole</td>
</tr>
<tr>
<td>Lower urine excretion at 10 p.m.</td>
<td>Ciprofloxine</td>
</tr>
<tr>
<td>No significant circadian difference in serum half-life and renal clearance</td>
<td>Netilmicin</td>
</tr>
<tr>
<td>No significant circadian difference in renal clearance</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>
This is particularly true for the aminoglycosides, as their nephrotoxicity is greatest when administered during the resting period. Food intake and low urinary pH has been found to be protective of the toxicity of aminoglycosides at this time of the day\textsuperscript{16}. Knowledge of the administration-time-dependence of aminoglycosides and the underlying mechanisms can be used to develop once-a-day formulations that are significantly less toxic, in particular to the kidney, Anti-Hypertensive Drug Cardiovascular drugs such as nifedipine, oral nitrates and propranolol, plasma peak concentration is twice as high and time to reach peak concentration is shorter after morning dosing compared with evening dosing\textsuperscript{18}. Such a variation was not detected when sustained release dosage forms of nifedipine and isosorbide mononitrate were used. The underlying mechanisms of their Chrono pharmacokinetic pattern involve a faster gastric emptying time and a greater gastrointestinal perfusion in the morning. Shiga et al documented that atenolol, in contrast to propranolol, is not absorbed more rapidly after morning administration compared with post-evening administration.\textsuperscript{32} This confirms that the absorption rate of a lipophilic, but not hydrophilic, drugs is faster after morning dosing.

Anti-inflammatory drugs Studies on NSAIDs, e.g., indomethacin and ketoprofen, have also shown that these drugs have a greater rate and/or extent of bioavailability when they are given in the morning than when they are given in the evening due to better morning absorption. Earlier and higher peak concentrations were obtained when ketoprofen and indomethacin was given at 07:00 and 07:00 or 11:00 respectively than at other times of the day or night\textsuperscript{19}. Greater blood flow of the gastrointestinal tract in the morning than in the evening may explain this phenomenon. Circadian changes in renal function, plasma protein binding or hepatic blood flow could also explain temporal variation in drug plasma levels. Many variables are known to influence pharmacokinetics.

Treatment of Gastrointestinal Disease Gastric acid secretion is highest at night. Chrono therapy of peptic ulcers with evening once daily dosing of H2 receptor antagonist. Ex: Ranitidine. Treatment of Arthritis For osteo arthritis, ibuprofen given in the noon. The same drug will be effective when taken after the evening meal for rheumatoid arthritis.

Treatment of Cardiovascular Disease Diseases such as hypertension, heart attack and stroke mostly occurs early in the morning. BP at its lowest during sleep cycle and rises steeply during early morning awakening period. Treatment of Cancer Chrono biological cycles for normal cells and tumors cells may be different. Cancer drugs administer should be timed to cycles of tumor cells making them more effective against cancer and less toxic to normal
tissues. Blood flow to tumors and tumors growth rate are greater during activity phase than rest phase.

LIMITATIONS

1. Difference between species- Rodents and humans.
2. Harmful to Rodents/experimental animals.
3. Large number of animals.
4. Very complex-Anti cancer drug development

CONCLUSION

The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 h rhythms of biochemical, physiological and behavioral processes under the control of circadian clock. The knowledge of 24 h rhythm in the risk of disease plus evidence of 24 h rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for pharmacotherapy.

The concept of drug treatment was earlier “right dose of drug for the right person” is now changed to “right time of dose for a right person”. Drug release pattern if designed in time controlled manner maximum therapeutic effect can be achieved with minimum side effects.

Hence time of a day should be considered as an additional variable that influences the kinetics of the drug.

REFERENCES

8. C.V.S. Subrahmanyan, Biopharmaceutics and Pharmacokinetics, 499-503.