REVIEW

CHRONOTHERAPEUTIC AGENTS: AN OVERVIEW

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ABSTRACT:

Circadian and other biological rhythms affect diseases, there symptoms and severity of symptoms and drug therapy can be modified keeping these variations under consideration. Chronopharmacology refers to the manner & extent to which the kinetics and dynamics of medication is directly affected by endogenous biological rhythm and also how the dosing time of medications affects biological timekeeping & features. It has a number of advantages as it reduces drug dosage, increases therapeutic efficacy of drug, limits the time of therapy, reduces side effects, slows down speed of progression of disease and especially helpful in preventing drug toxicity in case of compromised body systems. There is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, ankylosing Spondylitis, renal disorders, antimicrobial therapy, diabetes mellitus, ant-inflammatory therapy, peptic ulcer disease etc. Various drug delivery systems have been developed like pulsatile drug delivery systems, Enteric-coated systems, Layered systems, time-controlled explosion systems (TES), sigmoidal release systems (SRS), electric based drug delivery systems system, controlled-release microchip, etc for effective chronotherapy. There is great deal of hope for effective drug therapy using chronopharmacology in near future.

KEYWORDS: Circadian, Chronopharmacology, Drug delivery systems, Chronotherapy, Therapeutic efficacy

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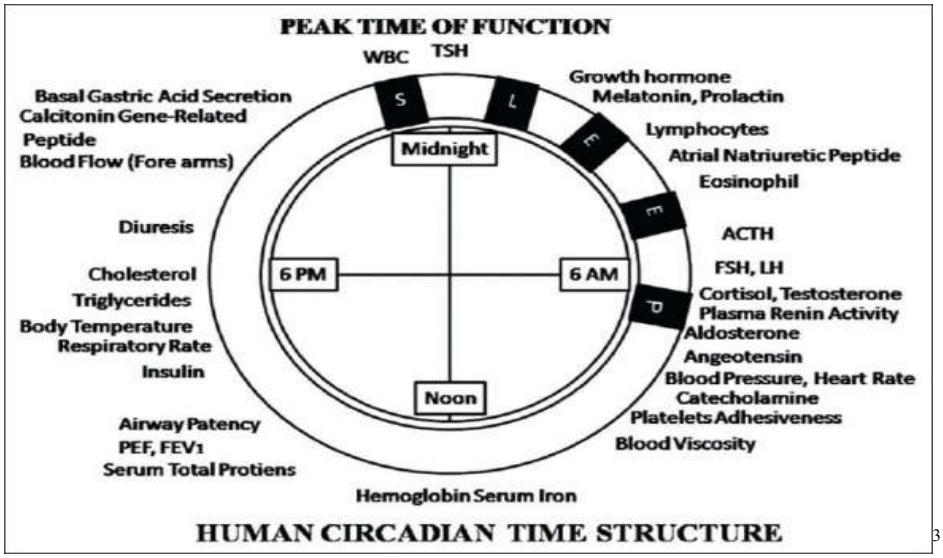
INTRODUCTION:

The treatment of the disease not only depends on the medicine but it also depends on the time, month of administration and biological rhythms like circadian rhythm, Infradian and Ultradian. Our body defence system depends on the various factors like age, gender, genetics etc.Chronopharmacology refers to the manner & extent to which the kinetics and dynamics of medication is directly affected by endogenous biological rhythm and also how the dosing time of medications affects biological timekeeping & features (period, level, amplitude & phase) of biological rhythms. It includes chronopharmacotherapy, Chronopharmacokinetics&Chronotoxity. It includes Chronopharmacokinetics that entails the study of temporal changes in drug absorption, distribution, metabolism and excretion [1]and chronodynamics which includes the effect of biological events and rhythms on body's response to drug action. Chronotherapeutics deals with application of chronopharmacology with a view to treat the patient with optimized drug effect and decreasing the side effects.[2]

It has a number of advantages as it reduces drug dosage, increases therapeutic efficacy of drug, it limits the drug therapy time, it prevents toxicity due to over dosage in patients with compromised organ functioning, it decreases the progression of diseases and it is very useful especially in case of chronic diseases (heart, liver and kidney). The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.



[3]

Fig. 1: Human Circadian time structure

MECHANISM:

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hrs. Normally, circadian rhythms are synchronized according to the body's pacemaker clock, located in the suprachiasmatic nucleus of the hypothalamus. The physiology and biochemistry of human being, not constant during the 24 hrs, but vary in a predictable manner as defined by the timing of the peak and through of each of the body's circadian processes and functions. The peak in the rhythms of basal gastric and secretion, white blood cells (WBC), lymphocytes prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and leuteinizing hormone (LH), is manifested at specific times during the nocturnal sleep span. The peak in serum cortisol,

aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity. Hematocrit is the greatest and airway caliber the best around the middle and afternoon hours,platelet numbers and uric acid peak.[45]Blood pressure peaks upon awakening, especially in patients suffering from hypertension. Cerebrovascular accidents are more susceptible to occur during 10 a.m. to 12 noon. Gastrointestinal acid secretion is increased during 10 p.m. to 2 a.m. Bronchial asthma symptoms are severe in the duration 4 a.m. to 8 a.m. Ankylosing Spondylitis pain is severe during time 6 a.m. to 9 a.m. and arthritic pain shows cardinal symptoms during the first half of the day. Cholesterol synthesis and intake is higher in the evening. Receptor binding affinity, especially for the heart and brain receptors varies throughout the day. Protein binding is increased in the night hours and metabolism is more active in the active phase of the day. If all these changes in variables are taken into account effective drug therapy can be timely and most effectively initiated and can timely limited. [6]

METHODOLOGIES:

PULSATILE DRUG DELIVERY SYSTEMS

In this delivery system, the delivery device is capable of releasing drug after predetermined time delay (i.e. lag time) known as pulsatile drug delivery system. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time" i.e., a period of "no drug release." Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable.

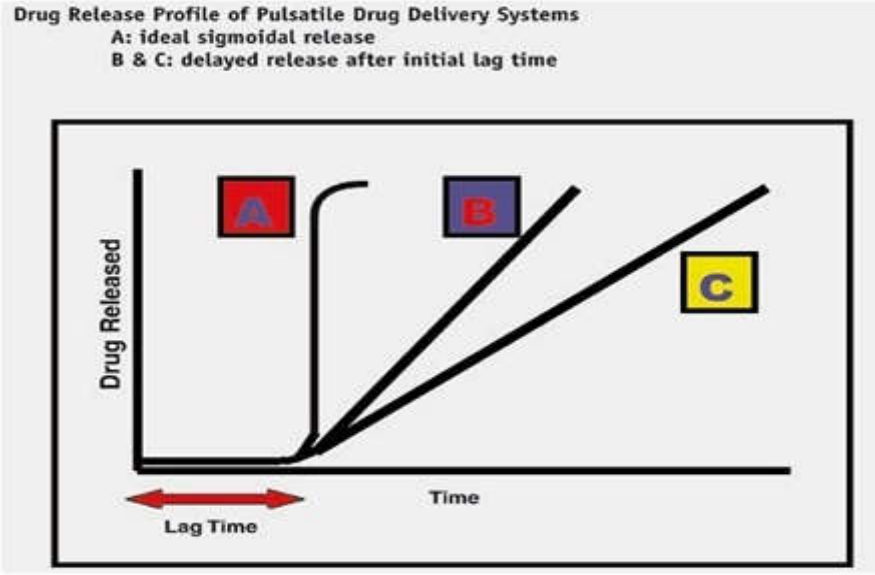


Fig. 2: Pattern of Drug release from pulsatile drug delivery system

A = Release of drug as a "pulse" after a lag time, B = Delivering the drug rapidly and completely after a "lag time" and C = Constant drug release over a prolonged period of time after a "lag time".

Pulsatile drug delivery system can be broadly classified into three classes;

I. Time controlled pulsatile drug delivery

II. Stimuli induced pulsatile drug delivery

III. Externally regulated pulsatile drug delivery[89]

CHRONOTHERAPEAUTIC DRUG DELIVERY SYSTEMS:

1. **Enteric-coated systems**: Enteric coatings have traditionally been used to prevent the release of a drug in the stomach. Enteric coatings are pH sensitive and drug is

released when pH is raised above 5 in the, intestinal fluid. These formulations can be utilized in time-controlled drug administration when a lag time is needed.[10]

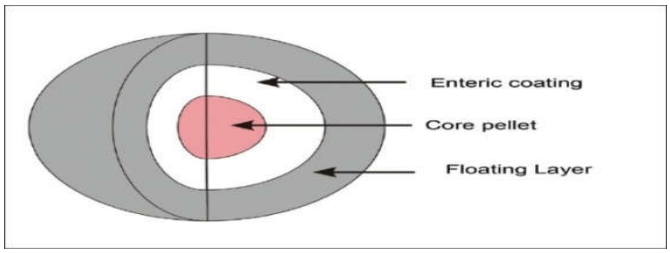


Fig. 3: Enteric coated systems

2. **Layered systems:**
   These are one or two impermeable or semi permeable polymeric coatings (films or compressed) applied on both sides of the core. To allow biphasic drug release, a three-layer tablet system was developed.[11]The two layers both contain a drug dose. The outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable polymers, separates the drug layers.[12,13]
3. **Time-controlled explosion systems (TES)**:
   These have been developed for both single and multiple unit dosage forms. In both cases, the core contains the drug, an inert osmotic agent and suitable disintegrants. Individual units can be coated with a protective layer and then with a semi permeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. As water reaches the core, osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of the formulation can also be achieved through the use of swelling agents. Lag time is controllable by varying the thickness of the outer polymer coating.[14,15]
4. **Sigmoidal release systems (SRS)**:
   For the pellet-type multiple unit preparations, SRS containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times. By applying different coating thicknesses, lag times in vivo of up to 5 hours can be achieved. Release rates from SRS, beyond the lag time, has been found to be independent of coating thickness.[16,17]
5. **Press-coated systems:**
   Delayed-release and intermittent-release formulations can be achieved by press--coating. Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process.[18]
6. **Pulsincap systems:**
   Pulsincaps are composed of a water insoluble body and a water soluble cap, and a drug which is sealed with a hydrogel plug. At a predetermined time after administration, the swollen plug is ejected from the capsule and the drug is then released into the small intestine or colon.[19]
7. **Electric Based drug delivery systems system:**
   This technique generates an electrical potential gradient that facilitates the movement of solute ions across the membrane. Because of charged nature and relatively large molecular size of proteins and peptides, iontophoresis may provide means for their effective delivery.[20]
8. **Controlled-release microchip:**
   In this a microchip device is used which can store one or more compounds inside the microchip in any form (solid, liquid, or gel),

and can release these compounds when there is a demand.[21]

CHRONOTHERAPY IN VARIOUS DISEASES:

1. **Hypertension:**
   Heart rate and blood pressure is high at the time of wakening in the morning i.e. A.M and it begins to decrease in the afternoon and it reaches minimum at midnight[22232425]The blood pressure is comparatively high in case of hypertension patients upon awakening. This physiological condition is described as morning surge or A.M. surge[26]. The systolic blood pressure rises up to 3mmHg/hour for 4-6 hours after getting up called post-awakening and the diastolic myocardial ischemia takes the lead as well in the morning[2728]. The therapy includes giving high dosage of drugs for treatment in the morning and lower dose of drugs in the noon and evening can do the purpose.

2. **Cerebrovascular accidents:**
   Cerebrovascular accidents are more common in the morning hours between 10A.M to 12 noon and it will decrease considerably from noon to midnight. The main aim of chronotherapy in these conditions is to deliver the drug in the higher doses in morning and little lower dose at noon and in midnight times[29].

3. **Bronchial asthma:**
   Bronchial asthma symptoms are severe in the duration 4 a.m. to 8 a.m. Therapy is started by giving long acting formulation of methyl Prednisolone. [30]

4. **Arthritis:**
   Cardinal symptoms of arthritis are more severe during 8 a.m. to 11 a.m. and symptoms can be treated efficiently by giving long acting NSAIDs like Indomethacin.[31].

5. **Myocardial Infarction:**
   The release of the catecholamine's, cortisol, increase in platelet aggregation and the vascular tone will be high in the morning. These are the main reasons for the outburst of the myocardial infarction in the morning with 34% events taking place from 6 A.M till noon. Acute cardiac arrest and transient Cyclooxygenase inhibitor-2 will relieve the pain effectively when taken in the morning.[32]

6. **Peptic Ulcer Disease:**
   Gastrointestinal acid secretion is increased during 10 p.m. to 2 a.m. A histamine-2 receptor antagonist when given at night shows the better result unlike when given at regular intervals around the clock. This is because more acid secretion leads to more pain and perforation of gastric and duodenal ulcers are more subjective at night rather than in day time[33].

7. **Hypercholesterolemia:**
   Cholesterol synthesis and intake is higher in the evening. The morning doses were recommended at first for HMG COA inhibitors but after the discovery of circadian rhythms the profile was re-evaluated and the evening doses were recommended.[34]

8. **Diabetes mellitus:**
   The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion. Providing basal insulin exogenously to patients with diabetes inhibits hepatic glucose production. Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release[35]

9. **Ankylosing Spondylitis:**
   AnkylosingSpondylitis is characterized by

swelling and discomfort of the joints of the back. Overall, back stiffness and pain were a problem throughout the 24 hours, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 am to 09:00 am. Therapy with drugs like diclofenac, naproxen in long acting formulations can be effective[36]

10. **Renal diseases:**
Renal osteodystrophycan be managed with calcium supplements, vitamin-D metabolites orCalcitrio. It has been found that a higher dose of oral D3 is more effective and safe after dosing at evening in patients with renal osteodystrophy.[37]

11. **Local anaesthetics:**
The duration of local anaesthesia was longest when amide-type local anaesthetic agents (Lidocaine, Ropivacaine, Mepivacaine and Betoxycaine) were applied around 3 p.m. The plasma levels of Lidocaine were significantly higher in the evening than at any other time of day.[38]

12. **Antibiotics:**
Food intake and low urinary pH has been found to be protective of the toxicity of aminoglycosides in the afternoon.Knowledge of the administration-time dependenceof aminoglycosides and the underlying mechanisms can be used to develop once-a-day formulations that are significantly less toxic, in particular to the kidney, in patients who require around-the-clock antimicrobial therapy.[39]

13. **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.[40]

14. **Anticancer drugs:**
Anticancer drugs like cyclosporine given in the resting phase show decreased plasma clearance and can be a part of effective dosage regimen.[41]

RECENT ADVANCES:

- It has been found that depression and circadian disturbances are consequences of decreased cellular resilience and lower resistance to stress. The second possibility includes the opposite: decreased cellular/stress resilience and depression are consequences of circadian disturbances. The third possibility is that decreased cellular/stress resilience and circadian disturbances produce reciprocal causal effects leading to depression. Agomelatine opens an innovative chronobiological approach to understanding and treating depression related to cell resilience and stress resistence model.[42]
- The time of administration of spinal local anesthetics influences the duration of anesthesia. To maximize the effectiveness of intrathecal local anesthetics awareness of the biologic rhythms in local anesthetics and pain intensity is a necessity.[43]
- The administration of a higher maximum tolerated dose at the least toxic circadian time, as compared to other dosing times, may result in an improvement in efficacy outcomes,i.e. tumor response and/or survival[44]
- Significant and noteworthy associations between several polymorphisms in circadian genes, night work and breast cancer risk were found among nurses who had worked at least three consecutive night shifts[45].
- The clinical applications of chronopharmacology may lead to improved seizure control in some patients.[46]
- Circadian regulation is important to maintain normal cellular functions, and a disruption of core clock genes can be damaging to the organism's overall well-being[47]
- Chronopharmaceutics based technology has eliminated the drawbacks associated with the conventional colon specific delivery systems.[48]

- It has been found that pathophysiological events such as coronary infarction, angina pectoris, asthma attacks and gastro-intestinal ulcers do not occur at random but exhibit a clear-cut daily rhythmic pattern.[49]
- Variability associated with the time when psychotropic drugs such as the anti-psychotics, stimulates antidepressants and benzodiazepines for example are given has been recently demonstrated. These chronopharmacological effects can be explained by temporal variations in the mechanism of action of the drug on receptors, or of its fate in the body.[50]
- It is has been found that the dosing time of an antimicrobial agent might be clinically relevant in some treatments, thus, clinicians should be aware that the dosing time might affect the clinical response of a drug.[51]

LIMITATIONS:

1. Person may become less productive during chronotherapy.
2. Staying awake till the other schedule is a bit uncomfortable.
3. Medical supervision is mandatory for chronotherapy.
4. Regular consulting of sleep specialists is recommended with therapy.
5. Persons may sometimes feel unusually hot or cold sometimes.

CONCLUSION:

Most appropriate time based drug therapy has a number of advantages as it reduces drug dosage, increases therapeutic efficacy of drug, limits the time of therapy, reduces side effects, slows down speed of progression of disease and especially helpful in preventing drug toxicity in case of compromised body systems. there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, Ankylosing Spondylitis, renal disorders, antimicrobial therapy, diabetes mellitus, ant-inflammatory therapy, peptic ulcer disease etc.

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