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Review Article



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Chronotherapeutics: Clinical Science Based on the Circadian Rhythms

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Abstract

Most physiological, biochemical, and molecular processes in healthy organisms display robust, considerable changes on a 24-hour schedule. The prima facia being that various hormones, neurotransmitters and other intra body components, are secreted in different amounts at different events of the day. Like our body that has an inbuilt 24 hour cycle similarly some diseases also follow the circadian patterns like, hypertension, asthma, arthritis, depression, ulcer, allergic rhinitis, myocardial infarction, sleep disorders etc. These variations affect both the disease states and the plasma drug concentrations. Therefore, we must look forward for developing rational drug-delivery systems that can affect a target cell or organ system at that circadian rhythm and at the same time makes it possible to optimize desired therapeutic outcomes and minimize or avert adverse effects. Present review mentions details of various diseases that can be treated with the help of chronotherapy, potential drugs used for the chronotherapeutic formulations and the market formulations available.

Key words: Chronotherapeutics, circadian rhythm, chronotherapy

Introduction

To introduce the concept of chronotherapeutics, it is important to define the concepts of circadian rhythm, chronobiology and chronotherapy, chronopharmacology.

Circadian rhythms

The phrase "circadian rhythm" was first described by Halberg and Stephens in 1959. Human circadian rhythm is based on sleep activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hourr period). The impact of circadian rhythms in the mechanisms of disease and the pharmacokinetics

and pharmacodynamics of medications constitutes a major challenge in drug scheduling on the basis of circadian rhythms.

Chronotherapy

Coordination of biological rhythms with medical treatment is called *Chronotherapy*. Chronotherapy considers a person's biological rhythms in determining the timing and amount of medication to optimize a drug's desired effects and minimize the undesired ones. The main aim of this drug chronotherapy is to reformulate or revise the existing drug distinctly which gains more results.

Chronobiology

The science dealing with the phenomenon of biological rhythm [2] i.e. differences in physiology according to the time of day, time of month or even the period in living organisms is called chronobiology. It can be said that it is concerned with the biological mechanism of the diseases according to a time structure.

Chronopharmacology

Study of influence of biological rhythm on the kinetics and dynamics of medications is known as chronopharmacology. It also deals with the study of how the dosing time of medications affect biological timekeeping and the features of biological rhythms.

Chronotherapeutics

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time and chronotherapeutic refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. Many researchers have concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body [3].

In 1960s first chronotherapeutic formulation was introduced for the treatment of the various diseases. The corticosteroid was formulated as a first conventional tablet [4]. US, Asia, Europe are the countries where the first chronotherapeutic formulation theophylline was used for the treatment of chronic obstructive pulmonary disease, conventional evening H₂-receptor antagonist for the treatment of the peptic ulcer. Chronotherapeutics deals with the medical treatment according to the human daily working cycle that corresponds to a person's daily, monthly, seasonal or yearly biological clock or in order to maximize the health benefits and minimize the adverse effects. The goal of chronotherapeutics is to align the timing of treatment with the intrinsic timing of illness.

Many drugs display normal, reproducible daily variations in pharmacokinetics and pharmacodynamics. Lemmer [3] identified more than 100 drugs that display significant variation in concentrations or effects, or both, over 24 hour cycle. The best example is heparin. Even when it is administered at a constant infusion rate, the activated partial thromboplastin time and the risk of bleeding vary significantly according to the hour of the day and are higher at night [5]. Optimum therapy is more likely to result when the adequate amount of drug is delivered to the correct target organ at the most appropriate time. And in the treatment of many diseases chronotherapeutic drug delivery offers a new approach in the pharmacologic device design for the effective treatment of different types of diseases. Thus, insight into the chronobiology and chronopathology gave birth to chronotherapeutics.

Advantages of chronotherapy [6-8]

- Chronotherapy is drug-free.
- Predictable, reproducible, and short gastric residence time.
- Less inter- and intra-subject variability.
- Improves bioavailability.
- More effective when a person sleeps for several hours.
- It is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.
- Ease of combining pellets with different compositions or release patterns
- Improves stability
- Improves patient comfort and compliance
- Achieves a unique release pattern
- Extends patent protection, globalizes the product, and overcomes competition

Disadvantages [9]

- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not known.
- Person become less productive during chronotherapy and staying awake till the other schedule will be bit uncomfortable.
- Person will have to take some time off from his busy normal schedule as its timetaking therapy.
- Medical supervision is mandatory for this therapy. And regular consulting of sleep specialists is recommended.
- One has to keep himself awake till the next sleep schedule. so he have to get himself busy so that he stay awake till the other schedule.
- Person going through the therapy may feel unusually hot or cold sometimes.
- Have to consult the doctor regularly to avoid side effects.
- Adjustment until the patient's next schedule can be uncomfortable.

Circadian time framework

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours. The biological rhythm studies help in delineating the sequential organization of human beings. The suprachiasmatic nucleus, hypothalamic pacemaker controls circadian rhythms in response to hormonal variation in the body [10,11] and the dysfunction of circadian rhythms can affect the brain functioning and it can be improved by the chronotherapeutic approach. The circadian rhythm not only affects most physiological functions such as metabolism, physiology, behavior, sleep patterns, hormone production, etc. but also influences the absorption, distribution, metabolism, and elimination (ADME) of drugs, leading to changes in drug availability and target cell responsiveness [12-16]. Manifestations or severity of many diseases over a 24-hour period is well known diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcers, diabetes, and attention deficit syndrome, hypercholesterolemia and hypertension show symptomatic changes due to circadian rhythm city [17-18]. For example in the sleep cycle, growth and thyroid-stimulating hormone, blood lymphocyte and eosinophil number, and plasma concentrations of melatonin and prolactin jumps to peak, alike adrenocorticotrophic hormone, follicle-stimulating hormone, and luteinizing hormone. Large database analyses and epidemiologic studies illustrate that acute myocardial infarction, sudden cardiac death, thrombotic stroke, and angina occur several-fold more frequently in the initial early morning hours (i.e., 6 AM-12 PM), compared with any other time of the day or night [19-21]. Cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am [22].

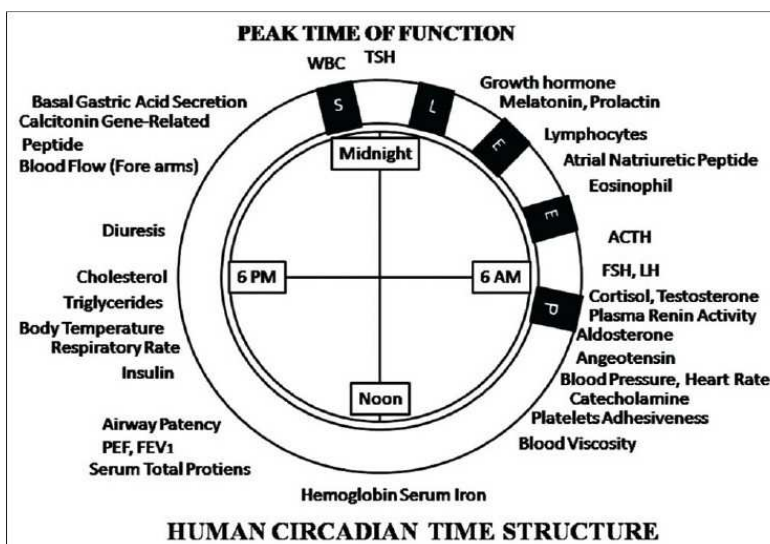


Fig.1. Human circadian time structure [23]

Circadian pattern of diseases

Many of our normal body functions follow daily patterns of speeding up and slowing down, intensifying and diminishing, in orientation with circadian rhythm. In essence, they're the "rhythms of life". Just as physiological functions vary over time, pathological states of disease have circadian rhythms. Therefore, this condition can be taken as advantage to control and modify the administration of drugs. Here is the list of some of the diseases that can be treated using chronotherapeutics.

1. Hypertension
2. Myocardial infarction
3. GERD , Heartburn
4. Asthma
5. Sleep disorder
6. Cancer
7. Arthritis

Table1. Circadian rhythms and manifestations of clinical diseases [24]

Disease/Syndrome	Circadian Rhythmicity
Asthma	Exacerbation more common during few hours prior to awakening.
Rheumatoid arthritis	Symptoms are most intense upon awakening
Stable angina	Chest pain and ECG changes are most common during the first 4 to 6 hours after awakening.
Prinzmetal's angina	ECG abnormalities are most common during sleep.
Allergic rhinitis	Worse in morning upon rising than during the day.
Hypertension	Highest blood pressure readings occur from late morning to middle afternoon
Strokes	Most commonly occur in the early waking hours
Myocardial infarction	Incidents higher in the early morning
Sudden cardiac death	Events worse in early morning after awakening
Peptic ulcer	Pain typically occurs after stomach emptying, following daytime meals, and in the very early morning, disrupting sleep
Hormonal deficiency, diabetes	Glucose level highest at night time
Epilepsy	Seizures often occur only at particular times of the day or night; individual patterns differ among patients

Hypertension

The peak blood pressure is between 6 am and noon, with activation of the sympathetic nervous system prior to awakening, blood pressure begins to increase with the heart rate. These changes in blood pressure corresponds the morning activation in catecholamines, renin, and angiotensin. The blood pressure declines from mid-afternoon and is minimum at midnight [25,26]. Currently, there are four antihypertensive medications that are chronotherapeutic medications using verapamil (Covera HS, Verelan PM), diltiazem (Cardizem LA), and propranolol (InnoPran XL), and there are likely to be more products available as understanding of chronotherapeutics inflates.

Myocardial infarction

Careful analysis of trials illustrate that myocardial infarction (MI), stroke, ventricular ectopy, and sudden cardiac death occur between 6 am and noon. The risk of myocardial infarction is 40% higher, the risk of cardiac death is 29% higher, and the risk of stroke is 49% higher than that expected to occur by chance. The explanation for the higher rate of cardiovascular events is explained by multiple factors like release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone [27].

GERD, Heart burn

Many common digestive diseases including gastro-esophageal-reflex disease (GERD), heartburn and ulcer display strong rhythms in their symptoms and response to medications. Acid reflux and heartburn occurs after daytime meals and nighttime sleep. There are several reasons why heartburn is worse after meals and at night. First, stomach acid production is highly circadian rhythmic. Second, eating and drinking immediately stimulates stomach acid production [28]. Research studies on fasted volunteers show stomach acid secretion is 2-3 times greater between 10:00 p.m. and 02:00 a.m. than in the day [29]. Chronic heartburn problems require medications such as cimetidine, famotidine, nizatidine, ranitidine, lansoprazole and omeprazole that suppress stomach acid secretion. Many studies on these drugs have been performed the results show that the evening once-a-day and the twice-a-day treatment schedules can be used in controlling the acid secretion. As regards patient compliance the evening once-a-day schedule is regarded as the best.

Asthma

Asthma is a disease of the lung airways (bronchi). Causes of asthma attacks include -allergies, cold air, air pollutants, drugs, cigarette smoke, molds, exercise, and infections. Aggravation of asthmatic attacks was more than 100 times greater during nighttime sleep, especially around 4 a.m., than it was during the middle of the day due to limited lung function promoted by circadian changes at that time. Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms [30, 31].

In one study, use of a timed-release formulation of theophylline (Theo- 24) achieved therapeutic drug concentrations during the night and avoided toxic levels during the day. Asthma is well suited for chronotherapy, with beta 2-agonists and oral corticosteroids [32]. The other studies show that a single dose of inhaled corticosteroids are administered at 5:30 p.m. rather than 8 a.m. was nearly as effective as four times doses taken a day. Uniphyll which is a long-acting theophylline preparation manufactured by Purdue Frederick Co. of Norwalk, Conn. and approved by FDA in 1989 causes blood levels to increase and reach their peak levels and this improves the lung function during the difficult early morning hours [33].

Sleep disorders

When working properly, our circadian rhythms create circadian balance. When out of balance, quantity, quality and timing of hormone and neurotransmitter secretion suffer and our bodies suffer disorders like non 24 h sleep-wake syndrome and delayed sleep phase syndrome which are grouped together as circadian rhythm disorder (CRD). Bright light therapy is used for Circadian Rhythm Sleep Disorder. In Delayed Circadian Rhythm Disorder (DCR) a progressive delay of bedtime by 3 hours per day is prescribed, accompanied by strict maintenance of a regular bedtime hour. In Advanced Circadian Rhythm Disorder (ACR) chronotherapy focuses on advancing bedtime by 2-3 hours per night over 1 week until a desired schedule is achieved. For Bimodal Circadian Rhythm Disorder (BCR) and Non 24-hour Sleep/Wake Cycle the therapy is introduced based on the sleep pattern. Short-acting benzodiazepines, such as (Xanax), are often chosen in the early treatment of a circadian rhythm disorder and on the other hand Non-benzodiazepine Hypnotics **such as** (Ambien, Sonata and Lunesta), are also gaining popularity.

Cancer

It has been shown that the biological rhythms for antineoplastic drugs differ in physiology, diet, morphology and its surroundings between the healthy tissue and cancerous tissues. The studies so far suggest that there may be different chronobiological cycles for normal cells and tumor cells. Therefore the target would be to administer the cancer drugs with the time of chronobiological cycles of tumor cells. Chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue [34]. In some studies [35] it is found that the risk of relapse was 2.56 times higher in the children who are treated with the chemotherapy in the morning than in properties and circadian rhythm because maximal acid receiving the same treatment within the evening. The optimal timing of breast cancer has also come under study. Some researchers believe that in premenopausal women, surgical cure of breast cancer is more likely if surgery is performed in the middle of a woman's menstrual cycle in the week or so following ovulation.

Arthritis

RA is a disease in which body's own immune system starts to attack body's tissue. Studies show that pathological symptoms in RA follow circadian rhythm. These inflammatory cells secrete lysosomal enzymes which damage cartilage and bones, while prostaglandins produced in the process cause vasodilatation and pain. Common symptoms includes varied level of pain, swelling, joint stiffness and sometimes a constant ache around the joints

[36]. Newly developed modified release (MR) Prednisolone releases drug four hours after ingestion thus by taking it in evening and adapting it's release to the circadian increase in pro- inflammatory cytokine concentration, the symptoms of RA were found to lessen in early morning [37, 38].Methotrexate can be administered either in the morning (10 A.M.) or evening (6 P.M.) in the treatment of RA [39].Huskisson in 1976 reported that an evening once-a-day treatment with indomethacin was much more effective in controlling the prominent morning symptoms of rheumatoid arthritis than a morning one.

Table 2.List of drugs used in chronotherapy of various diseases [1,40-43]

Drugs	Disease
Celecoxib	Colorectal cancer
Salbutamol sulphate	Nocturnal asthma
Indomethacin, ibuprofen, meloxicam, aceclofenac, diclofenac, oxymorphone, flurbiprofen, Lornoxicam, naproxen sodium, prednisone	Rheumatoid arthritis
Chlorpheniramine	Cough
Furosemide	Hypertension
Nifedipine	Angina
Theophylline, budesonide, albuterol, terbutalinesulphate, montekulast sodium	Asthma
5-aminosalicylic acid	Irritant bowel syndrome
Verapamil, diltiazem, propranolol, simvastatin	Hypertension
Nitroglycerine	Heart attack
Cisplatin, doxorubicin, methotrexate	Cancer
Omeprazole, famotidine, ranitidine, cimetidine	ulcers
Haloperidol, vitamin D3	Others
Glipizide, gliclize	Type 2 diabetes
Sulphonyl urea, insulin	Diabetes mellitus
Methyl phenidate	Attention deficit syndrome
Irinotecan, Oxaliplatin, and Leucovorin-Modulated 5-Fluorouracil	Metastatic Colorectal Cancer
Folinic acid, Methotrexate, Mercaptopurine	cancer

Table 3.List of chronotherapeutic drugs in market and indication of chronotherapy

Brand Name	API	Company	Disease	References
Aftach®	triamcinolone acetate	Nagai	Aphthous ulcers	44
Covera HS	verapamil	Searle until Pfizer	Cardiovascular disease	45
Coreg CR®	carvedilol	Glaxosmithkline pharmaceuticals	hypertension	45
Dilacor XR	diltiazem hydrochloride	Watson Labs	Hypertension and angina	45
Cardizem LA	diltiazem	Biovail	hypertension	46
Innopran XL®	propranolol hydrochloride	Reliant Pharmaceuticals	hypertension	46
Uniphyll®	anhydrous theophylline	Purdue Pharma L.P	asthma	47
Lodotra™	prednisone	SkyePharma	rheumatoid arthritis	47

Zocor®	simvastatin	Merck & Co.	Cardiovascular disease	48
Pepcid® Tablets	famotidine	Marathon Pharmaceuticals, LLC	ulcer	48
Gaster® tablets	Famotidine	AstellasPharamaInc	Ulcer	48
Lipovas® tablets	Simvastatin	ranbaxy	Hyperlipidemia	48
Hokunalin® tape	Tulobuterol	Abbott Japan and Nitto Denko Corporation,	Asthma	48
Veralan PM	Verapamil HCL	Schwarz Pharma	hypertension	48
Invega™	Paliperidone	ALZA Corporation	Schizophrenia	49
Plenadren®	hydrocortisone	DuoCort Pharma AB	Addisons disease	50
Procardia XL	Nifedipine	Biovail	Hypertension and angina	51
Metadate CD ®	Methyl phenidate	Celltech Pharmaceuticals Inc.	attention deficit hyperactivity disorder	51
Coer 24	Verapamil HCL	ALZA Corporation	Hypertension	51
Procardia XL	Nifedipine	Biovail	Hypertension and angina	51
Naprelan®	Naproxen sodium	BlansettPharmacal, Inc	Chronic pain	52
Tiazac	Diltiazem HCL	Forest Laboratories	hypertension	53
Requip® XL™	L-dopa/benserazide	GlaxoSmithKline	parkinsonism	54
Caelyx/Doxil	doxorubicin	Gedeon Richter Plc.	Breast cancer	55
Abraxane	paclitaxel	Abraxis bioscience Inc.	Breast cancer	55

Table 4. Various Patents in the field of Chronotherapy [56, 57, 58]

Implantable electromechanically driven device	U.S. Pat. No.4,003,379
Flexible system for timed controlled or position controlled drug delivery system	U.S. Pat. No. 7048945
Three Dimensional Printing® (3DP) technology	U.S. Pat. No.5,490,962
Self-powered medication systems	U.S. Pat. No.3,692,027
Implantable infusion device	U.S. Pat. No.4,003,379
Pulsatile delivery	U.S. Pat. No. 6635277
Pulsatile technology	U.S. Pat. No. 5914134
Self-powered medication systems	U.S. Pat. No.4,146,029
Microchip drug delivery devices	U.S. Pat. No.5,797,898
Beads	U.S. Pat. No. 5439689
unit dosage forms of diltiazem hydrochloride	CA2215378
pulsatile delivery of diltiazem	US6635277
pulsatile delivery of d-threo-methylphenidate	US6217904
oral pulse dose drug delivery system	US6605300
oral pulse dose drug delivery system	US6322819
once-a-day controlled release diltiazem formulation	US5834023
drug delivery composition for colonic delivery	US6200602
hydrocolloid gums for colonic delivery	US6555136
an injection molded starch capsule for colonic delivery	US6228396
targeted drug delivery system	CA2305762
Pulsed drug delivery of doxylamine	US4842867
Pulsatile drug delivery system	US5229131
Pulsatile particles drug delivery system	US5260069
Pulsatile drug delivery system	US5840329
Pulsatile release histamine H2 antagonist dosage form	US6663888

Conclusion

With the growing awareness about the impact of circadian rhythm city in the treatment of various diseases it gives the most compelling reason to study the novel, potential therapeutic approach like chronotherapeutics. Rapid progress has been made in this area since chronotherapeutics is gaining a lot of consideration by the numerous researchers. Various diseases like, ulcer, myocardial infarction, strokes, asthma, cancer etc. can be treated more effectively if the drugs are given in right amount, in right place and at right time owing to the human body's 24 hour cycle. The timing of drug administration in disease therapy has significant impact upon remedial success, and this is also evidenced with the development of different time controlled technologies in recent years. Therefore, chronotherapeutics remains an eminent area for continuing research for the advancement of quality of life.

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