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Diseases and conditions requiring chronotherapy: An overview

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ABSTRACT

Chronopharmacology is useful to solve problems of drug optimization, i.e. to enhance the desired efficiency or to reduce its undesired effects. Some of the conditions, which may be significantly benefited are cardiovascular system, cancer, asthma, peptic ulcer, hypercholesterolemia, allergic rhinitis, mood disorders, sleep disorders, epilepsy, alzheimer's disease, parkinson's disease, arthritis, Ankylosing syndrome, diabetes, pain, cerebrovascular accidents, renal disease, gastrointestinal system, GERD, heart burn, Coagulation Disorder, Thrombosis and Infectious disease. Biological rhythms not only impact the pathophysiology of diseases, but the pharmacokinetics and pharmacodynamics of medications. Chronopharmacotherapy is the investigative science that elucidates the biological rhythm dependencies of medications. This review represents the basic concept of circadian rhythm, mechanism and its synchronization with severity and occurrence of various diseases fro m viewpoint of chronopharmacology and chronotherapy. The recent interest is occurring in the field of chronotherapeutics is to match the circadian rhythms of the disease for the successful treatment of disease.

Key words: *Chronopharmacology, Circadian rhythm, Diseases, Chronotherapeutics.*

INTRODUCTION

The term "chrono" basically refers to the study that every metabolic happening undergoes rhythmic changes in time. Chronotherapeutics refers to a therapy in which in vivo availability of drug is timed to match rhythms of disease or disorders in order to optimize therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time (during the 24 h) [1].

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. Cardiovascular system
2. Cancer
3. Asthma
4. Peptic ulcer
5. Hypercholesterolemia
6. Allergic rhinitis
7. Mood disorders
8. Sleep disorders
9. Epilepsy
10. Alzheimer's disease
11. Parkinson's disease
12. Arthritis
13. Ankylosing syndrome
14. Diabetes
15. Pain
16. Cerebrovascular accidents
17. Renal disease
18. Gastrointestinal system
19. GERD, heart burn.
20. Coagulation Disorder and Thrombosis
21. Infectious disease

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1. Cardio vascular system:

From the various studies, it is noted that the many cardiovascular events including myocardial infarction, stroke and sudden death occur during the initial hours of morning activity between 6 AM and 12 noon. And this is much higher during this period that other timing during the day [2].

Blood Pressure is well known to exhibit 24 h variation with a peak in the morning. A number of factors influence diurnal variation of blood pressure which is internal factors such as the autonomic nervous system, vasoactive intestinal peptide, plasma cortisol, plasma renin activity, aldosterone, plasma atrial natriuretic peptide [2].

Heart rate and blood pressure are increased in the early morning hours (morning or A.M. surge). These changes in blood pressure corresponds the morning activation in catechol amines, renin, and angiotensin [3]. The blood pressure declines form mid afternoon and is minimum at midnight. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or "a.m." surge. Systolic blood pressure rises approximately 3 mm Hg/hour for the first 4-6 hours post-awakening, while the rate of rise of diastolic blood pressure is approximately 2 mm Hg/hours [4].The most easily noted and significant blood pressure variations are the diurnal changes related to the sleep-wake cycle [2].

Capillary resistance and vascular reactivity are higher in the morning and decline later in the day [1].

Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. Hence there is an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia [5]. Modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events.

Myocardial infarction Careful analysis of trials illustrate that myocardial infarction (MI), stroke, ventricular ectopy, and sudden cardiac death occur between 6 am and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone [4]. 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 [3]. Myocardial infarction (MI) occurs more frequently in the morning as a result of the concomitant unfavourable timing of several physiological parameters and/or biochemical conditions [6].

2. Cancer:

Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered carefully at selected times that take advantage of tumour cell cycles while less toxic to normal tissue. The rhythmic circadian changes in tumour blood flow and cancer growth are relevant both when tumours are small and growing most rapidly and when they are larger and growing more slowly. Circadian chemotherapy timing meaningfully affects drug toxicity patterns and severity, maximum tolerated dose, average dose intensity, tumour response quality and frequency and the survival of patients with cancer [7].

In normal human bone marrow, DNA synthesis peaks around midday and DNA synthesis in malignant lymphoma cells peaks near midnight. Therefore by treatment at mid night, more tumor cell could be killed with same dose of S-phase active cytotoxic therapy and with relatively little bone marrow damage [1].

The pharmacologic and pharmacokinetic properties of the drug, rhythmic changes in DNA and RNA synthesis, RNA translational activity and mitotic activity may influence tumour cell susceptibility. The cancer chronogenetic therapy found to be effective in tumour suppression in vivo. For example, it has been shown that CLOCK genes dictate sensitivity to the anticancer drug cyclophosphamide [7].

In some studies [8] 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 [3].

3. Asthma:

Asthma may be the most common disease with the largest circadian variation. Because asthma has such a striking circadian variation, several types of chronotherapy have been tried [9]. Aggravation of asthmatic attacks was more than 100 times greater during night time 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. [3].

The exacerbation of asthma during the night represents the changing status of biological functioning due to circadian rhythms in bronchial patency; airways hyper reactivity to acetylcholine, histamine, and house dust; and plasma cortisol, epinephrine, histamine, and cyclic AMP [7]. Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms [3].

One of the study shows that the intake of the time released theophylline i.e. theo24 at 3 P.M achieved a therapeutic dose at night and the toxic levels during the day was avoided (Prevesh kumara et al, 2013). Another study [11] showed that a single daily dose of inhaled corticosteroids, when administered at 5:30 pm rather than 8 am, was nearly as effective as four doses a day. Numerous investigations have demonstrated the usefulness of chronotherapy for asthma, especially for patients with nocturnal asthma [6].

4. Peptic ulcer:

Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night. While gastric, small bowel motility and gastric emptying are all slower at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for H_2 antagonists. Bedtime H_2 - receptor blockade using Chronotherapy overcome problems of sustained or profound decrease of 24-h intragastric acidity including the threat of enteric infection and infestation, potential bacterial overgrowth with possible N-nitrosamine formation [7].

In peptic ulcer patients, there is a high acid secretion, more pain and perforation of gastric and duodenal ulcers are more seen at night rather than in day time gastric acid secretion is highest during the night [12]. A histamine antagonist when given at night shows the better result unlike when given at regular intervals around the clock [10].

Thus suppression of nocturnal acid is an important factor in duodenal ulcer healing. One group of authors studied incidence of ulcer perforation for daily (circadian), weekly (circaseptan) and yearly (circannual) time effect [13]. A circadian rhythm has been found overall that was reproducible and fairly stable across seasons, decades, and days of the week. Duodenal perforations showed highest incidence in the afternoon, while gastric perforations showed a major peak around noon and a secondary peak near midnight. For duodenal ulcer perforation, the circannual pattern was characterized by a 6-month rhythm, with significantly higher incidence in May–June–July and in November– December in most subgroups. A circaseptan rhythm was not found, but there was a significantly higher incidence on Thursday–Friday as compared to Sunday–Monday [14].

5. Hypercholesterolemia:

Hepatic cholesterol synthesis follows circadian rhythm. It is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%– 40% of daily cholesterol synthesis [1].

The morning doses were recommended at first for HMG CO-A inhibitors but after the discovery of circadian rhythms the profile was re-evaluated and the evening doses were recommended as the cholesterol intake and cholesterol biosynthesis is more in the evening hours even in fasting state [10].

One clinical study [15] showed that evening administration of an HMG-CoA reductase inhibitor was more effective at lowering serum cholesterol levels than the same dose given in the morning. Initially, studies involving morning dosing of HMGCoA reductase inhibitors failed to show a reduction in cardiovascular morbidity and mortality. However, the first primary prevention trial that studied evening dosing [16] revealed a significant reduction in serum cholesterol levels as well as rates of such cardiovascular end-points as myocardial infarction, unstable angina, and stroke. On the basis of these findings, it now is recommended that five of the six currently approved HMG-CoA reductase inhibitors be administered between the evening meal and bedtime; atorvastatin calcium may be an exception because of its long elimination half-life.

6. Allergic Rhinitis:

Common symptoms of allergic rhinitis are sneezing, nasal rhinorrhea, red itchy eyes, nasal pruritus and nasal congestion.

The allergic reactions both local and systemic are mediated through interactions of immune and inflammatory responses. Such responses during the day are usually coordinated by adrenocortical function and steroid release with high amplitude daily rhythms. Scientists now believe that the symptoms of allergic rhinitis, and even the skin testing results, can vary according to the time of day [13]. Circadian rhythms may also influence the results of diagnostic skin tests for allergic rhinitis. Skin test results are more likely to be false negative in the morning than in the late afternoon or early evening.

There are two phases of occurrence of allergic rhinitis i.e. early phase (developing within minutes) and late phase (manifesting after 12–16 h). The early phase happens due to release of Histamine, Prostaglandins, cytokines, TNF-α, chemotactic factors etc resulting in sneezing, nasal itch, rhinorrhea. On the other hand late phase is shown due to elaboration, adhesion and infiltration of circulating leukocytes, T cells and eosinophils evoking nasal congestion, obstruction due to the exacerbation of inflammation of the nasal, sinus and other tissue of the upper airway [14].

For sufferers of allergic rhinitis, are typically worsened in the evenings. Immunological reactions: In vivo immune responses vary with circadian rhythms including hypersensitivity reactions in the skin and lungs, acute graft rejection and humoral and cell antibody responsiveness. Circulating levels of immunoglobulin in normal animals and immune complexes in inflammatory states also vary with a predictable circadian pattern. Studies in the rat and in man have shown that the time of day at which an antigen is encountered has an influence on the expression of any subsequent cell-mediated immunity, when the responses measured after a fixed interval. This suggests that immune processes are modulated by intrinsic biological rhythms. The study in rats demonstrated a circadian rhythm in delayed hypersensitivity to oxazolone. The response is T cell-mediated although there are B cells and possible serum components [6].

7. Mood Disorders:

The deprivation of sleep in the half of the night and the timed exposure to day light-intensity and artificial light still experimental therapies, may ease the depression pre menstrual or during menopause and benefit both women and men with seasonal and other mood disorders. Such a variation was not detected in the

mood disorders when sustained release dosage forms of nifedipine and isosorbide mononitrate were used [17].

In human populations, it is known that disruptions in circadian rhythms including the sleep/ wake cycle through environmental means can produce mood-related problems in vulnerable individuals. The impact of acute alterations in rhythms is evident to anyone who has experienced "jet lag" after a long flight across multiple time zones. A more chronic example is seasonal affective disorder (SAD) or "winter depression", which is the most common of all mood disorders, affecting upwards of 10% of the population at temperate latitudes [18]. Individuals with SAD are negatively affected by the shorter days and later sunrise of the winter months and develop a syndrome characterized by carbohydrate craving, lethargy, fatigue, and sadness. There is a high incidence of major depressive disorder observed during and after shift work experience with increased risk associated with duration of exposure [19]. Interestingly, rats kept in constant darkness for 6 weeks also have behavioral features that are similar to depression, and these may be the result of neuronal damage to monoamine systems [20].

8. 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). Many biological signalling e.g. sleep disorder occurring in the central and autonomous nervous systems show complex time structure with rhythm and of sleep required by each person is usually constant, although there is a wide variation among individuals [9]. Sleep consists of a rhythmic (circadian) combination of the changes in physiological, biochemical and psychological processes. When the circadian rhythm is disturbed, or when the individual processes are abnormal during sleep, it may result in a variety of disorders. One such example is delayed sleep-phase syndrome which is characterized by severe sleep-onset insomnia. Normally, sleep is impossible until 3 a.m. or later until there is great difficulty in awakening in the mornings at the normal time. The ability to cope up with circadian rhythm disturbances also differs from person to person. Identification of the individual variation would be of importance in dealing with certain sleep disorders [14].

9. Epilepsy:

The circadian rhythm also plays a significant role in seizures of epilepsy. The influence of the biological clock on seizure of some partial seizures has been found in animals or humans. The behavioural chronobiology provides the detection of new regulation processes that concerns central mechanisms of epilepsy because the circadian psycho physiological patterns of epilepsy show dynamic biological systems which show some inter modulating endogenous processes between observation and seizure susceptibility. Such chronobiologic studies applied to epileptic behaviour and this suggests the development of new heuristic aspects in the field of comparative psychophysiology [7].

The circadian rhythm may also take a significant role in seizures of some types of epilepsy. The influence of the biological clock on seizure of some partial seizures has been found in some experimental animal models. The methodology for measurement of the circadian rhythm in humans is also investigated. Behavioural Chronobiology provides the detection of probable new regulation processes concerning the central mechanisms of epilepsy [21]. Because of this fact, the circadian psychophysiological patterns of epilepsy show dynamic biological systems which recommend some intermodulating endogenous processes between observation and seizure susceptibility. Furthermore, such chronobiological studies applied to epileptic behaviour suggest the development of new heuristic aspects in the field of comparative psychophysiology [14].

Significantly more seizures were observed from 1100 to 1700h and from 2300 to 0500h fewer seizures were seen. Daytime peak incidences were observed for all types of seizures and more differentiated for complex partial seizures, seizures of extratemporal origin (in children) and seizures of temporal origin (in adults). The total number of seizures, complex partial seizures and tonic seizures (in children) were low in the period 2300 to 0500h. Also, significantly fewer seizures of temporal and extratemporal origin (in children) were observed in this period. An important finding in one rodent model of limbic epilepsy was that a true endogenous mediated circadian rhythm in seizure occurrence was shown when the animals were placed in constant darkness.

10. Alzheimer's disease:

Change of circadian rhythm is also seen in patients with Alzheimer's disease. Individuals with Alzheimer's show less diurnal motor activity, a higher percentage of nocturnal activity, lower inter daily stability of motor activity, and a later activity acrophase (time of peak) than normal healthy individuals. Alzheimer's disease leads to pathological changes in the suprachiasmatic nucleus and thus it disrupts circadian rhythms of the brain's function. The core body temperature is also higher in patients with this disease. The circadian abnormalities are seen together with cognitive and functional deterioration in this disease. No other change has been evaluated [14].

The temperature mesor was also higher in individuals with Alzheimer's disease. Neuro fibrillary tangles are present in the hypothalamus of people with Alzheimer's disease [22], and neurochemical abnormalities include lower choline acetyl transferase activity and serotonin concentration [23]. The higher amplitude of the circadian cycle of body temperature observed in this study may be also related to this hypothalamic dysfunction. Alternatively, the higher mesor of body temperature could be due to low melatonin secretion, which has been described in patients with Alzheimer's disease [24].

11. Parkinson's disease:

Autonomic dysfunction seen in Parkinson's disease discloses many alterations in circadian rhythm of blood pressure, amplified diurnal blood pressure variability and postprandial hypotension [25]. But existence of circadian rhythm in this disease has not been evaluated. Clinical data shows daily fluctuations of motor activity pattern but the effect of the phase of the disease and the subsequent roles of drugs are difficult to estimate [14].

Possible dysfunction in the circadian system in PD has received less attention, yet problems in circadian timing are common in neurodegenerative diseases The reduction in magnitude of circadian output would be expected to have functional consequences throughout the body [26].

PD patients are prone to misalignment of the circadian rhythm due to dopamine deficiency as well as various other factors that disrupt input to the SCN (suprachiasmatic nucleus). Indeed, many patients with PD display a phase advance of their circadian rhythm which may contribute to the increased prevalence of sleep disturbances and depression The actigraphic measurements (measuring rest activity) indicated that statistically PD patients have lower activity levels when out of bed and higher activity levels when in bed, and that, the circadian rest-activity rhythm in PD decreases with disease severity. The circadian rhythm disturbances are important to consider the mechanism of non-motor symptoms that occur from early stage of PD [20].

12. Arthritis:

The plasma concentration of C - reactive protein and interleukin-6 of patients with rheumatoid arthritis follow circardian rhythm. Rheumatoid arthritis can be distinguished from osteoarthritis by the time of day when the patient's joints are most painful and morning stiffness is characteristic feature of rheumatoid arthritis whereas symptoms are often worse in the afternoon and worse in evening in osteoarthritis. Non-steroidal anti-inflammatory drugs are taken for relieving the morning pain and stiffness of rheumatoid arthritis so the medicines are taken late at night and it is better for the treatment. Chronotherapy for all forms of arthritis uses standard treatment that includes the non-steroidal anti-inflammatory drugs and corticosteroids but in the treatment the dosages time are match with the rhythms of disease which are timed to ensuring that the highest blood levels of the drug coincide with peak pain. [7].

The new cyclooxygenase-2 inhibitors are effectively relieve the osteoarthritis symptoms when taken in the morning and better results are obtained in rheumatoid arthritis when small part of the dose is taken in the evening [4]. 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. Methotrexate can be administered either in the morning (10 A.M.) or evening (6 P.M.) in the treatment of RA. One research study [3] showed 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.

13. Ankylosing Spondylitis:

It is characterized by swelling and discomfort of the joints of the back. The 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 and 09:00 than between noon and 15:00 [6].

14. Diabetes:

In case of type I diabetes circadian rhythms of necessity of Insulin and its action are frequently asked question from point of physiological interest and clinical importance. Generally insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show cyclic rhythmicity of 8–30 min which can conclude optimal action. The basal mode of Insulin release acts on B cell in both stimulatory and inhibitory fashions. Target cell sensitivity to insulin action and hyperglycaemia may be impaired by stress hormones, cortisol, epinephrine and growth hormone. Partly intrinsic rhythmicity, dehydration and prolonged insulin withdrawal may induce a secondary feed-back signal on Insulin release which can help to raise blood glucose levels. The modulators of Insulin release and action are secreted in a circadian fashion and secondarily impress the mode of Insulin release. So, any difference between a daily maximum and minimum in plasma Insulin concentration besides its short-term rhythmicity has to be considered as a complex secondary circadian rhythm. It is in particular due to variable secondary early-morning and lateafternoon Insulin resistance [14].

15. Pain:

Pain threshold follow the different pattern in different tissues. The sensitivity threshold of the gingiva to a cold stimulus was maximal at 6:00 pm and reached a peak at 03:00 am. Tooth sensitivity was lowest between 03:00 pm and 6:00 pm, with a peak in pain intensity at 08:00 am [1].

In arthritis there is circadian rhythm in the plasma concentration of C-reactive protein and Interleukin-6 of patient with rheumatoid arthritis. Besides, different opioid peptides like 5-hydroxytryptamine, Bradykinin, Glutamate, NO, substance P, Cytokines and Prostanoids are involved in the activation of nociceptors.

Brain concentration of substance P in rat model is highest in night with compared to daytime. It was reported that levels of endogenous Opioid peptides are higher at the starting point of the day and lower in the evening both in neonate and adult human volunteers. Patients with osteoarthritis tend to have less pain in the morning and more at night. While patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day. The symptoms are swelling of finger and pain at joint. Patients with gastrooesophageal reflux disease feel night time pain. But renal colic shows morning peak independent of gender and presence or absence of visible kidney stones. The choice of analgesics and the route of their administration depend on the nature and duration of the pain. Aspirin, Paracetamol, NSAIDs and Morphinomimetics are indicated against nociceptive pain, while anticonvulsants, tricyclic antidepressants and local anaesthetics are used against neurogenic pain [14].

16. 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. Various ACE inhibitors like Atenolol, Nifedipine and amolodipine are more effective when administered during night [10].

17. Renal diseases:

Renal osteodystrophy is a condition due to chronic kidney disease and renal failure, with elevated serum phosphorus levels, low or normal serum calcium levels, and stimulation of parathyroid function, resulting in a variable admixture of bone disease. This condition can be managed with calcium supplements, vitamin-D metabolites or Calcitrio. It has been reported that a higher dose of oral D3 is more effective and safe after dosing at evening in patients with renal osteodystrophy [1].

The urinary system which plays a pivotal role in the elimination of a drug has many instances of circadian rhythms altering either the clearance or the urinary flow causing nephrotoxicity. Amino glycosides can produce renal toxicity with chronic administration. Because these antibiotics are primarily eliminated by renal excretion, diminishing renal function with time may cause greater drug accumulation and more toxicity. There is clearly a need to monitor therapy to limit the duration of therapy, especially in patients who already have compromised renal function. Theophylline causes increase in the renal flow by increasing the clearance levels and thereby increase in the urine flow and renal excretion. Carbamazepine shows time dependence in its disposition [27].

18. Gastrointestinal system:

The gastrointestinal motility, the intraluminal pH, blood flow to stomach and enzymatic action are not the only factors that influence the gastro intestinal absorption of the drug. It even depends on the circadian rhythms and all the above mentioned factors are also influenced by the time of the day. Most of the drugs we generally take are lipophilic and they are found to have more rate of absorption in early mornings rather than any hour of the day [6].

19. 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 night time 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. 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. Chronic heartburn problems require medications such as cimetidine, famotidine, nizatidine, ranitidine, lansoprazole and omperazole 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 [3].

20. Coagulation Disorder and Thrombosis:

The fluidity and retention of the blood within the circulatory system are essential for life and these dual roles are obtained through the actions and interactions of multiple variables in blood which together form the haemostatic system. Circadian rhythm has been found in many components of circulatory and haemostatic systems such as muscle cells, aorta, peripheral vascular muscle and endothelium and these alterations in the time structure of circadian rhythms may lead to hypercoagulability and thrombosis or hemorrhage. Homeostasis is affected by various factors such as peripheral resistance, blood flow, blood viscosity, blood pressure and heart rate. The peripheral vascular resistance decreases during afternoon hours resulting in rise of blood flow at that time is diurnally active. The vasomotor tone of the coronary and peripheral arteries of the vasoconstrictor response to adrenaline is increasing in the morning than in the afternoon. Beta thromboglobulin also shows the peak concentration around 6 a.m. and low values between noon and midnight. Factor VII are prominent in circadian variation with highest values between 8 a.m. and noon but its antigen concentration. The peak time of Factor IX is also around 9 a.m. and the peak concentration of natural coagulation inhibitors like protein C, protein S and anti thrombin occurs at 6 a.m. and lowest values occur between noon and midnight. The rhythmic variations are seen in the fibrinolytic systems but these may be different all local tissue level [28].

21. Infectious diseases:

Periodic time-dependent changes in the incidence of infectious diseases are well known. The elevation of body temperature, fever due to bacterial infections is higher in the evening while that due to viral infections is more likely in the morning. Influenza is epidemic in the winter season. It was reported that the morbidity and the mortality were greatest during the winter and least during the summer both in the Northern and Southern Hemispheres. The weight of the nasal secretions is highest in the morning in patients with cold and decreased over the day and increased again somewhat in late evening. Recently the Centers of Disease Control of the US publishes prominent patterns in meningococcal meningitis(January Peak), mumps (April Peak),

pertusis (August Peak), varicella (April Peak), and typhoid (August Peak). Though the reason of the seasonal patterns of individual infectious disease is complex and multiple factors are involved, seasonal cycles in infectious diseases are generally attributed to seasonal differences in weather/atmospheric conditions, virulence or prevalence of casual pathogens, and/or variations in the behaviour of the host [14].

CONCLUSION

Circadian rhythms have an important impact on drug effectiveness and toxicity. Chronopharmacology aims to improve the understanding of circadian changes in both desired effects (chronoeffectiveness) and tolerance (chronotolerance) of medications. Chronopharmacology involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. The main aim of this article is to inform biologists, clinicians, pharmaceutical scientists and other medical professionals the importance of biological clocks and chronopharmacology to human health and disease. Another objective is to speed the further experimental and clinical research in the field of chronopharmacotherapy.

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