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Chronotherapeutics: Emerging Role of Biorhythms in Optimizing Drug Therapy

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The presence of circadian rhythms in human health and illness has been alluded to since the time of Hippocrates. However, it was not until the 1960's that a large variety of physiologic functions and biologic rhythms were described. Biologic variations have now been reported for several physiologic processes and play an important role in the manifestation of many illnesses. The past decade has witnessed rapid advances in the field of chronobiology, which are now being incorporated into clinical medicine, pharmacology and pharmacy practice. A number of chronotherapeutic medications, aiming at synchronizing medications and the intrinsic biorhythms of disease have been developed by novel drug delivery technology. In some cases, conventional medications are being administered according to circadian rhythms. This article focuses on biorhythms and the emerging role of chronotherapeutics in optimizing the treatment of several diseases.

Important findings from the new science of chronobiology- the scientific study of biological rhythms- clearly reveal that biological functions and processes are not static over time. Rather, they are variable in a predictable manner as rhythms of defined periods[1]. Some of the rhythms that affect our bodies include (www.fda.gov/fdac/features/1997/397_chrono.html), ultradian, which are cycles shorter than a day (for example, the milliseconds it takes for a neuron to fire, or a 90-minute sleep cycle); circadian, which last about 24 hours (such as sleeping and waking patterns); infradian, referring to cycles longer than 24 hours (for example, monthly menstruation) and seasonal, such as seasonal affective disorder (SAD), which causes depression in susceptible people during the short days of winter.

CIRCADIAN RHYTHMS AND THEIR IMPLICATIONS

Circadian rhythms are self-sustaining, endogenous oscillations, exhibiting periodicities of about one day or 24 hours[2]. Normally, circadian rhythms are synchronized according to the body's pacemaker clock, located in the suprachiasmic nucleus of the hypothalamus[1,3].

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The physiology and biochemistry of a human being is not constant during the 24 hours, but variable in a predictable manner as defined by the timing of the peak and trough of each of the body's circadian processes and functions. The peak in the rhythms of basal gastric acid secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and leutinizing 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, respectively. Finally, insulin, cholesterol, triglycerides, platelet numbers, and uric acid peak later during the day and evening[1]. Hence, several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock, as shown in fig.1.

Through a number of clinical trials and epidemological studies, it has become evident that the levels of disease activity of a number of clinical disorders have a pattern associated with the body's inherent clock set according to

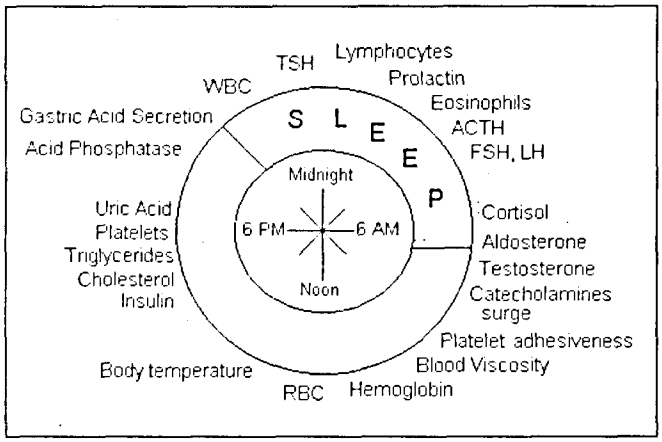

Fig. 1: A 24-hour clock diagram of the peak time of selected human circadian rhythms with reference to the day-night cycle.

circadian rhythms[4]. Infact just as the time of day influences normal biologic processes, so it affects the pathophysiology of disease and its treatment[5,6]. Examples of some of the diseases are shown in table 1.

Predictable circadian variation can be useful in diagnosis of certain diseases. For instance, when evaluating a patient suspected of Addison's disease, it is necessary to obtain only a single blood sample early in the morning. If the 6 am cortisol level is normal or elevated, Addison's disease is extremely unlikely, since nearly all people who sleep during the night have their highest cortisol levels in the early morning. The disease with the greatest intrinsic circadian variation is probably asthma, which has a 300- fold difference in incidence between the peak at 2 am to 4 am, and the trough at 10 am to 12 pm[7,8].

CHRONOTHERAPEUTICS: THERAPY IN SYNCHRONY WITH BIORHYTHMS

Chronotherapeutics, or delivery of medication in concentrations that vary according to physiological need at different times during the dosing period, is a relatively new practice in clinical medicine[4] and thus many physicians are unfamiliar with this intriguing area of medicine. It is important that physicians understand the advantages of chronotherapy so that they can make well-informed decisions on which therapeutic strategies are best for their patients- traditional ones or chronotherapies[9].

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hours, chronotherapeutic formulations may use various release mechanisms e.g., time-delay coatings (Covera-HS™), osmotic pump mechanisms (COER-24™), matrix systems (Geminex™), that provide for varying levels throughout the day[2].

POTENTIAL ROLE OF CHRONOTHERAPY IN TREATMENT OF VARIOUS DISEASES

A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy

TABLE 1: CIRCADIAN RHYTHM AND THE MANIFESTATION OF CLINICAL DISEASES.

Disease or syndrome	Circadian rhythmicity
Allergic Rhinitis	Worse in the morning/upon rising
Asthma	Exacerbation more common during the sleep period
Rheumatoid Arthritis	Symptoms are most intense upon awakening
Osteoarthritis	Symptoms worse in the middle/later portion of the day
Angina Pectoris	Chest pain and ECG changes more common in early morning
Myocardial Infraction	Incidence greatest in the early morning
Stroke	Incidence higher in the morning
Sudden cardiac death	Incidence higher in the morning after awakening
Peptic ulcer disease	Worse in late evening and early morning hours

TABLE 2: DRUGS THAT HAVE BEEN DEVELOPED OR ARE UNDER DEVELOPMENT AS CHRONOTHERAPIES.

CLASS	EXAMPLES
Cardiovascular drugs	Verapamil, propranolol, diltiazem, nifedipine, enalapril
Antiasthmatic drugs	Methylprednisolone, prednisolone, albuterol, terbutaline, theophylline
Anticancer drugs	Cisplatin, oxaliplatin, doxorubicin, 5-fluorouracil, folinic acid, methotrexate, mercaptopurine
Non-steroidal antiinflammatory agents	Ibuprofen, ketoprofen, indomethacin, tenoxicam, acetylsalicylic acid
Anti-ulcer agents	Cimetidine, ranitidine, famotidine, pirenzipine, omeprazole
Anticholesterolemic agents	Simvastatin, lovastatin
Others	Vitamin D_3, diazepam, haloperidol

of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity. Table 2 lists the various drugs that have been studied or are under study as chronotherapies.

CARDIOVASCULAR DISEASES[10-34]:

Chronotherapy for cardiovascular diseases has been studied extensively. It is documented that several functions of the cardiovascular system are subject to circadian rhythms. Researchers have reported an increased onset of sudden cardiac death in the first three hours after awakening. Ischemic events, chest pain, and ST-segment depression are most problematic during the initial 3-5 h of diurnal activity. In patients with effort angina, the highest activity occurs between 6 am and noon. This coincides with peaks in diurnal variation of frequency of acute myocardial infraction, stroke and sudden death.

24-h ambulatory blood pressure monitoring and Holter monitoring reveal the marked circadian rhythms in blood pressure in hypertensive patients. In most hypertensive patients, there is a fairly marked rise in BP upon awakening that is called the morning surge. At this time, the systolic BP rises approximately 3 mm Hg/h for the first 4-6 h post-awakening while the rate of rise of diastolic blood pressure is approximately 2 mm Hg/h. In most patients with essential hypertension, the blood pressure generally declines from mid-afternoon and reaches its lowest between midnight and 3 am.

A number of potential underlying common triggering mechanisms, including catecholamine secretion, sympathetic nervous system activity, blood pressure, heart rate, cortisol secretion, platelet aggregability, exhibit similar surges. As a result of these coinciding morning peaks, myocardial oxygen demand is increased and oxygen supply reduced after a person arises in the morning. A relative imbalance in myocardial oxygen demand and supply due to the interaction of these factors may be more prominent in the early morning hours than at other times of the day, thus resulting in lower morning thresholds for the development of cardiovascular events (fig. 2).

The first chronotherapeutic agent for hypertension and angina pectoris, controlled onset extended release (COER) verapamil (Covera-HS™, Pharmacia, Peapack, USA) was recently developed and marketed to match drug delivery to the circadian BP and myocardial ischemia rhythms. The strategy used was wrapping the entire tablet in a water-

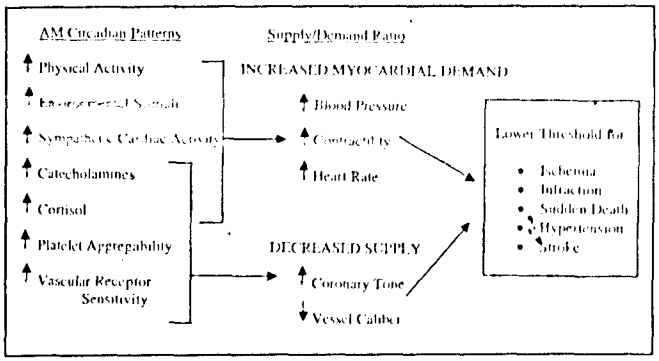

Fig.2: Possible causes of morning increase in the incidence of coronary event

soluble delay coat that disintegrated when exposed to gastrointestinal fluids over a 6-8 h period. By administering the medication at bedtime, very little of the verapamil would be absorbed during the night, but by 8-12 h later when the patient was likely to be awakening, there would be abundant delivery of verapamil.

A second biopharmaceutical preparation of verapamil using the CODAS™ (chronotherapeutic drug absorption system) technology has recently been introduced into the US marketplace (Verelan PM, Schwarz Pharma, USA). This formulation is also taken at bedtime and is delivered using a multiple-bead pharmaceutical system. Each non-pareil bead is coated with a non-enteric release-controlling polymer that delays the delivery of verapamil into the gut for 4-5 h after administration, and thereby provides a morning peak concentration, with little absorption during the night.

Graded-release diltiazem HCl extended release (GRD) administered once daily at bedtime (10 pm) significantly reduces BP and heart rate over the 24-h interval. Greater reductions are obtained between 6 am and 12 pm, when circadian BP is highest, compared to morning administration of the same dose. Propranolol CR (Innopran XL™, Reliant Pharmaceuticals, USA) is a novel chronotherapeutic formulation of propranolol designed for nighttime dosing, and has appropriate pharmacokinetics to provide maximum cardio protective effect in the morning. Peak drug levels are reached between 4 am and 10 am.

Asthma[35-42]:

Research has proven that normal lung function undergoes circadian changes. Airway resistance, bronchoconstriction and exacerbation of symptoms increase progressively at night in asthmatic patients. Risk of asthma attack is 100-fold greater during nighttime sleep than during daytime activity. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during early-morning hours.

Several chronotherapies have been proposed. Daily or alternate-day, morning dosing of glucocorticoid medications such as methylprednisolone (Medrol) significantly moderates side effects and enhances therapeutic benefit. Oral prednisolone administered at 3 pm rather than 8 am has been shown to be highly effective in the treatment of nocturnal asthma. Findings demonstrate that conventional β_2 agonist aerosol medications administered at 3 pm rather than 8 am result in further optimization of asthma chronotherapy. In one study, use of a timed-release formulation of theophylline (Theo-24) administered at 3 pm achieved an elevated theophylline level overnight, thereby reducing the risk of an acute episode of asthma. Evening, once daily dosing of controlled-release theophylline tablets (Uniphyl 400 mg tablets) showed chronotherapeutic potential in the treatment of nocturnal and early-morning asthma.

Arthritis[43-45]:

Circadian variation in pain, stiffness and manual dexterity in patients with osteo and rheumatoid arthritis has been studied, and has implications for timing antirheumatic drug treatment. Symptoms of rheumatoid arthritis are most intense when awaking from nighttime sleep, while those of osteoarthritis are worse in the evening or at night. For osteoarthritis sufferers, the optimal time for a non-steroidal antiinflammatory drug such as ibuprofen would be around noon or mid-afternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal.

Chronopharmacologic studies of once-daily sustained-release indomethacin preparation for the treatment of osteoarthritis have indicated that time of dosing influences tolerance and effectiveness. Evening ingestion was most effective in patients with predominant nocturnal or morning pain; conversely, morning or noon ingestion was most effective in patients with maximum afternoon or evening pain. Varying the ingestion time resulted in a 4-fold improvement in tolerance and doubling of analgesic effectiveness.

Peptic Ulcer[46-53]:

In peptic ulcer patients, pain, gastric distress and acute exacerbation of the disease are most likely in the late evening and early morning hours. This is attributed to high gastric acid secretion and slow gastric motility and emptying at night. Supression of nocturnal acid is an important factor in duodenal ulcer healing. Once daily nocturnal administration of H_2 antagonists or morning administration of proton pump antagonist tablet medications not only reduce acid secretion more effectively but also promote ulcer healing (as documented by endoscopy) and reduce ulcer recurrence (Axid, Pepsid, Tagamet, Zantac, Prilosec).

Hypercholesterolemia[54-58]:

Diurnal variation in human cholesterol synthesis has been studied. It has been observed that cholesterol synthesis increases during the night. Free cholesterol levels are reported to be lowest at 2 pm to 6 pm and peak at 6 am.

Chronotherapy can be achieved by timing the medication in accordance with circadian rhythm for hypercholesterolemia. Morning versus evening administration of HMG-CoA-reductase antagonists (Lescol, Mevacor, Pravachol and Zocor) showed that evening dosing of these medications is more effective than morning dosing.

Cancer[59-66]:

Studies so far suggest that there may be different chronobiological cycles for normal cells and tumor cells. If it is true, the goal would be to time the administration of cancer drugs to the chronobiological cycles of tumor cells, making them more effective against the cancer and less toxic to normal tissues. Acute lymphoblastic leukemia is one of the first diseases studied that showed improved clinical outcomes with chronotherapy. Probably the most impressive results were obtained in a clinical trial involving patients with colorectal cancer. The patients were randomly assigned to receive identical doses of oxaliplatin, fluorouracil and folinic acid given by either continuous infusion over 24 h, or specially designed pumps that provide oxaliplatin during the daytime and the other two agents at night. The group receiving the chronotherapeutic regimen had much lower rates of adverse effects, and the effects were generally less severe. Statistically significant differences in complete and partial remission rates between the chronotherapy group and the constant-infusion group were also observed.

The optimal timing of cancer surgery, particularly breast cancer, has also come under study (www.fda.gov/fdac/features/1997/397_chrono.html). 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. Many experts believe that any improved outcome is hormone-related. In the first half of the menstrual cycle, estrogen levels are high and progesterone is not produced. In the second half, progesterone rises and estrogen falls. It is believed that progesterone may inhibit the production of some enzymes that help cancer spread. However, the need to time surgery is debatable.

CONCLUSIONS

Recent reports linking circadian patterns to the development of symptomatic and asymptomatic diseases such as myocardial ischemia, sudden cardiac death, hypertension, cancer, peptic ulcer and asthma raise important questions concerning the mechanisms of disease activity in patients, and they have implications for prognosis, therapy and further research. Chronotherapeutics presents new challenges to pathophysiology and disease treatment. The major objective of chronotherapy is to deliver the drug in higher concentrations at the time of greatest need and in lesser concentrations when the need is less. This concept has several advantages, notably maximum therapeutic benefit, minimum harm, improved patient convenience and compliance.

The recognition of circadian rhythms in both normal human biologic function and disease has heightened the awareness that the timing of conventional drug regimens may have an important impact on the effectiveness of treatment. Specialized drug delivery technology is increasingly being relied upon to time treatment to the rhythm of the disease. Specialized technologies will give pharmaceutical companies competitive and financial advantages and provide improved medications to patients. Pharmacists must realize the need to develop and dispense such medications that have potential therapeutic benefit. It is hoped that the experts in various branches of pharmacy will collaborate together to use the new knowledge of biological rhythms to optimize and individualize drug use in patients.

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