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Review Article

Emerging Role of Biorhythms in Optimizing Treatment of Diseases

VINAY PANDIT, SARASIJA SURESH*

Department of Pharmaceutics, Al-Ameen College of Pharmacy, Bangalore-560027, INDIA

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ABSTRACT

In this review, the concepts of biological rhythms, chronobiology, chronopharmacology, and chronotherapy for various diseases have been discussed. 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.

INTRODUCTION

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. This article focuses on understanding of these biological rhythms, their role in diseases and various chronotherapeutic aspects of diseases. A biorhythm is a hypothetical cycle in physiological, emotional, or intellectual well-being or prowess. "Bio" pertains to *life* and "rhythm" pertains to the *flow* with regular movement. Biorhythms theory has no more predictive power than chance and has been labeled a pseudoscience by skeptics. A biological rhythm is a self-sustaining oscillation of endogenous origin. It is defined by the characteristics of period, level, amplitude, and phase. Biological rhythms and the clocks that orchestrate them are adaptive traits. All endogenous biological processes and functions are programmed-in-time during the 24 h for the conduct of specific activities at discrete times [1].

Period is the duration of time required to complete a single cycle. The spectrum of biological rhythms is broad (Table 1). Short-period rhythms of a second or so are quite common; Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian (<20 h), circadian (>24 h), and infradian (>28 h) rhythms. Finally, long-period rhythms show oscillations of roughly a week, month and year.

Author for Correspondence:
Email: sarasija_s@hotmail.com

Table 1: Types of Biological Rhythms

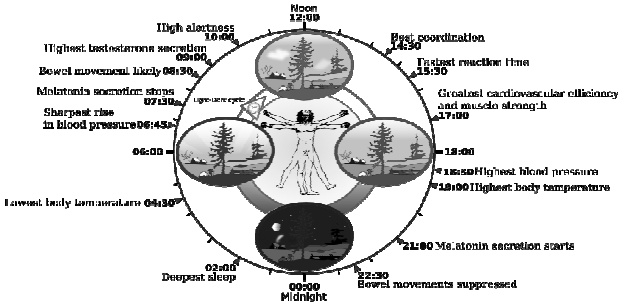
Period (τ)	Major rhythmic components
Short (τ <0.5h)	0.1s< τ <1 s τ≈min pulsatiles
Intermediate (0.5h <τ <6 days)	Ultradian (0.5h <τ <20h) Circadian (20h <τ <28h) Infradian (28 h <τ <6 days)
Long (τ >6 days)	Circasepatan (τ≈ 7 days) Circamensual (τ≈ 30 days) Circannual (τ≈ 1 year)

Level is the baseline around which rhythmic variation occurs. Amplitude is a measure of the magnitude of the predictable-in time variability due specifically to a biological rhythm. Some biological rhythms are of very high amplitude, accounting for 25– 50% of the total variability observed in a given process or function during the 24 h. The amplitude of rhythms may change with aging. For example, in diurnally active young adults the circadian rhythm in antidiuretic hormone (ADH), which regulates urine formation and volume, is of very high amplitude. Peak ADH concentration occurs during the nighttime to ensure reduced urine formation and volume during sleep; thus, in young adults urine formation and volume are much greater during diurnal activity than nocturnal sleep. However, with aging the amplitude of the ADH rhythm decreases; as a consequence, the peak of the circadian rhythm in urine formation and volume shifts to the middle of the night, resulting in frequent disturbances of sleep.

Phase refers to the clocking of specific features, such as the peak and trough values of a rhythm relative to the corresponding time scale. For example, the phase of the high-amplitude circadian rhythm of serum cortisol concentration is defined by its prominent morning peak (20 µg/dl) around 8 a.m. and its trough (as low as 0 µg/dl) during nighttime sleep [1-3].

Biorhythmic time structure

The results of numerous biological rhythm studies help define the temporal organization of human beings.



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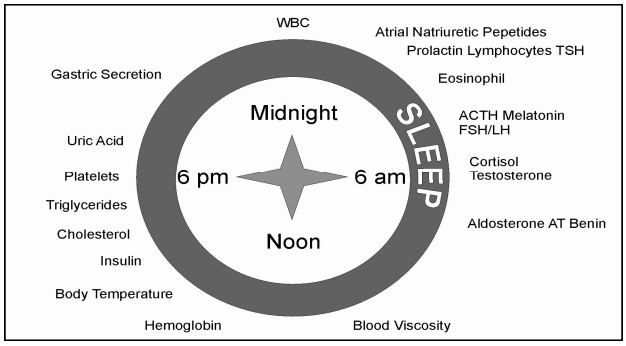

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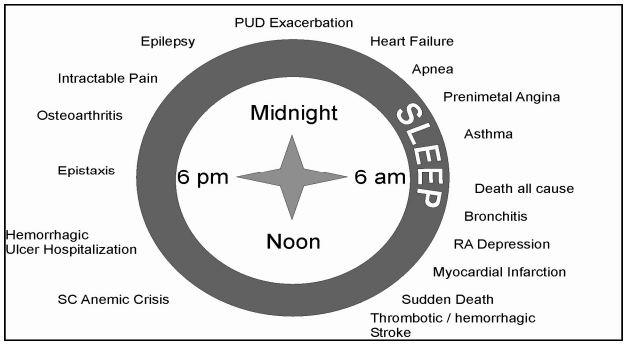

c)

Figure1: A 24 h clock diagram:

a) Peak time of selected circadian rhythms
b) Peak time of selected rhythms w.r.t secretion of various hormones
c) Peak time of chronic medical conditions relative to sleep and activity

One means of illustrating the human biorhythmic time structure is to depict the peak time of 24 h rhythms on a clock-like diagram like that shown in Fig. 1. Late at night, basal gastric acid secretion, white blood cell count, and atrial natriuretic peptides (which are potent vasodilators) begin to rise. Later in the sleep cycle, growth and thyroid-stimulating hormone, blood lymphocyte and eosinophil number, and plasma concentrations of melatonin and prolactin start to peak, as do adrenocorticotropic hormone, follicle-stimulating hormone, and luteinizing hormone. Plasma cortisol, renin, angiotensin, and aldosterone crest in the morning, as do arterial compliance, vascular resistance, platelet aggregation, and blood viscosity. Hemoglobin and insulin concentrations are greatest in the afternoon, whereas serum cholesterol and triglycerides are highest in early evening. Clearly, these data are compelling that human biochemistry and physiology are not constant; rather, they vary in a predictable manner during the 24 h time period. It seems plausible that timing of certain medical conditions and life-threatening emergencies may parallel these physiochemical circadian variations. Osteoarthritis worsens during the course of daily activities, being most bothersome in the evening; heart failure worsens nocturnally; and depression can flare in the early morning hours. From large database analyses and epidemical studies, we know that acute myocardial infarction (MI), 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 [2-4].

Biorhythms and disease conditions

Through a number of clinical trials and epidemiological studies, it has become evident that the levels of disease activity of number of clinical disorders have pattern associated with the body's inherent clock set according to biological rhythms. In fact just as the time of day influences normal biologic processes, so it affects the pathophysiology of the disease and its treatment. Many chronic and acute medical conditions exhibit prominent circadian patterns of symptom manifestation and severity as shown in Table 2. Predictable biological rhythms can be useful in diagnosis of certain diseases. For instance, when evaluating a patient suspected for 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 [5, 6].

Chronopharmacology: Concept and definitions

The science dealing with the phenomenon of biological rhythmicity in living organisms is called chronobiology. The branch dealing with the pharmacologic aspects of chronobiology is termed chronopharmacology, which may be subdivided into chronotherapy, chronopharmacokinetics and chronotoxicity. Chronopharmacology is the study of the manner and extent to which the kinetics and dynamics of medications are directly affected by endogenous biological rhythms, and also how the dosing time of medications affect biological timekeeping and the features (period, level, amplitude, and phase) of biological rhythms. Studies show that the time of drug administration, especially with reference to biological or circadian rhythms, can impact the kinetics and dynamics of various classes of medications. Chronokinetics refers to dosing-time, i.e., rhythm-dependent, differences in the absorption, distribution, metabolism, and elimination of medications. Circadian rhythms in gastrointestinal pH can affect drug dissolution, and circadian rhythms in gastric emptying, motility, and blood flow can affect the rate, and in certain cases the amount, of drug absorption.

Table 2: Biological Rhythm and the manifestations of clinical diseases

Biological System	Disease/ Syndrome	Biological rhythmicity
Respiratory	Allergic rhinitis,	Worse in morning/upon rising
	Asthma	Exacerbation more common during sleep period
Inflammatory	Rheumatoid arthritis,	Symptoms are more intense upon awakening
	Osteoarthritis	Symptoms worse in the middle/later portion of the day
Neoplastic	Various forms of cancer	For breast cancer, surgery not recommended for the first phase of menstrual cycle.
Cardiovascular	Hypertension	Incidence greatest in the early morning between 4-6 am.
	myocardial infarction	Incidence greatest in the early morning
	Strokes	Incidence higher in the morning
	Sudden Cardiac Death	Incidence higher in the morning after awakening
	Angina Pectoris	Chest pain and ECG changes more common in early morning
Gastrointestinal	Peptic ulcer disease	Worse in late evening and early morning hours
Endocrinology	Hormonal deficiency, Diabetes	Glucose level is highest at night time, insulin secretion highest at wee hours of morning.

Moreover, circadian rhythms in hepatic blood flow and enzyme activity can significantly affect drug biotransformation and metabolism, and rhythms in hepatic bile function and flow as well as renal blood flow, glomerular filtration, and tubular function can affect drug elimination.

Chronodynamics refers to dosing-time, i.e., rhythm-dependent, differences in the effects of medications. Such administration- time differences are due to rhythms in the free-to-bound drug fraction, number and conformation of drug-specific receptors, second messenger and ion channel dynamics, and rate limiting step(s) in metabolic pathways. Both the desired/ beneficial and undesired/adverse effects of medications can vary significantly according to their administration time. Many examples of chronodynamics can be cited. One is the constant infusion over 24 h of ranitidine, an H_2-antagonist prescribed to treat duodenal ulcer disease. The therapeutic effect of ranitidine — inhibition of gastric acid secretion and increase (alkalinity) of gastric pH—is poorer during the overnight hours of drug infusion than during the daytime hours of drug infusion, indicating that there might be a partial nocturnal resistance to H_2- receptor blockade .

Chronotoxicology, is an aspect of chronodynamics; it refers specifically to dosing-time, i.e., rhythm-dependent, differences in the manifestation and severity of adverse effects and thus intolerance of patients to medications. Classes of medications that have high risk of adverse effects and relatively narrow therapeutic range, in particular, are likely to show significant dosing-time differences in safety (i.e., chronotoxicologies). Circadian rhythm experiments conducted more than 50 years ago clearly showed a major adverse effect — adrenocortical suppression of potent synthetic anti-inflammatory glucocorticoid medications, such as methylprednisolone, triamcinolone, and prednisolone, can be significantly attenuated, or even averted, if correctly timed to circadian rhythms.

Chronesthesy means medications and other chemical substances typically exhibit dose and/or concentration–response relationships. However, chronopharmacology studies sometimes reveal great differences in their effects with different biological times of application, even through the pharmacokinetics and concentration are the same. This phenomenon is termed chronesthesy. It is another new concept in pharmacology, and it refers to rhythm-dependent differences in the sensitivity of target systems to medications that cannot be explained by corresponding administration-time differences in pharmacokinetic phenomena. Chronesthesies are demonstrable by the direct application of medications to their sites of action and by differences in the blood/tissue concentration–biological response to medications when administered at different times during the 24 h. The mechanisms of chronesthesies have yet to be fully elucidated.

Chronotherapeutics is the purposeful delivery of medications in unequal amounts over time, for example, during the 24 h. Chronotherapeutics takes into account biological rhythm determinants in (i) disease pathophysiology (chronopathology), (ii) chronopharmacology (chronokinetics, chronodynamics, chronesthesy, and chronotoxicology) of medications, and (iii) attributes (period, phase, amplitude, and level) of the human biorhythmic time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects. In some instances chronotherapeutics could entail the delivery of medication, especially neuroendocrine analogues, in a (typically high) frequency-modulated mode to mimic the 'language' of the neuroendocrine system in order to improve therapeutic outcomes. Chronotherapeutics may also entail the resetting or reorganization of a disordered or desynchronized circadian timekeeping system or time structure by a special class of medications termed 'chronobiotics'. An example of a type of chronobiotic is melatonin. The

judicious choice of the melatonin ingestion time, for example, by diurnally active persons, can result either in a phase advance when dosed in the afternoon or early evening or phase delay when dosed in the morning around awakening of the circadian temporal structure. Thus, melatonin, when properly timed, is able to accelerate the adjustment (phase shift) of the circadian system and lessen the duration and severity of 'jet lag' symptoms in persons rapidly displaced by jet aircraft across time zones.

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 correct target organ at the most appropriate time. Table 3 lists the various drugs that have been studied or are under study as chronotherapeutics [7-14].

CHRONOTHERAPHY OF HYPERTENSION

Hypertension is a common chronic condition affecting up to 35% of human adults. This condition is an important risk factor for strokes, heart attacks and other vascular and renal diseases. Pharmacologic treatment of high blood pressure (BP) reduces the incidence of these complications and prolongs life.

In man, blood pressure does not remain constant during day and night. Early in the morning blood pressure begins to rise from the low levels reached during sleep. Increases in blood pressure are accompanied by increases in heart rate caused by the chemicals generated by the body and delivered into the blood stream. Epidemiological studies have indicated that the greatest incidence of heart problems such as stroke, heart attack, myocardial ischemia and sudden cardiac death occur during the early morning waking hours when the blood pressure is rising in response to the natural circadian rhythm. After normally rising in the morning, blood pressure remains elevated during the day until generally early evening when it starts to fall to its lowest level during sleep.

Abnormally high blood pressure, i.e., hypertension, which is not a disease but a major risk factor for cardiac and vascular disease, displays different circadian patterns in different patient groups. The pattern seen in normotension and simple, uncomplicated essential hypertension is one of elevated pressure during daytime activity and reduced pressure, by 10 to 20%, during night time sleep. However, the pattern is different in secondary hypertension (high blood pressure occurring secondary to another coexisting medical condition, e.g., diabetes and renal diseases); the 24 h pattern in this situation is characterized by a blunted decline or even a rise in blood pressure to a higher level during nighttime sleep than found during daytime activity.

Thus, the treatment of hypertension not only includes the usual clinical goal of reducing mean blood pressure level, but also the normalization of the entire blood pressure circadian pattern. The predictable day–night variation in the symptoms of chronic medical conditions, risk of severe life-threatening cardiovascular events, and in medical conditions that are predisposing to serious disease presents the opportunity for a new, i.e., chronotherapeutic, treatment strategy that involves the delivery of medications so they are synchronized in time to biological need that varies according to the chronobiology of the targeted tissues. Thus, future applications of drug-delivery systems ought to be based on release-response to high and low concentrations of analytes/markers of disease activity as an innovative means of realizing optimal chronotherapeutic systems.

Table 3: Various classes of drugs used for chronotherapy

Class	Examples
Cardiovascular drugs	Verapamil, propanolol, diltiazem.
Antiasthmatic drugs	Theophylline, albuterol, terbutaline
Anticancer drugs	Cisplatin, doxorubicin, Methothrexate, Folinic acid
Anti Ulcer agents	Omeprazole, famotidine, ranitidine, cimetidine
Anticholesterolemic agents	Lovastatin, simvastatin
Non stereoidal anti-inflammatory agents	Tenoxicam, ketoprofen, indomethacin, ibuprofen
Others	Diazepam, haloperidol, vitamin D_3

A 24 h Ambulatory blood pressure (BP) measurement present a close correlation with target organ damage and cardiovascular events, including myocardial infarction, stroke and cardiovascular mortality. With the use of this measurement technique, a significant circadian variation has been shown to characterize BP. This circadian BP variation, although affected by a variety of external factors, represents the influence of internal factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, and hematologic and renal variables. The features of the circadian BP profile have direct implications for improving the drug-delivery of antihypertensive therapies as well as the qualification of patients for medication trials and assessment.

Currently available once-daily, extended-release antihypertensive medications provide safe and effective BP reductions over a 24 h dosing interval, but their static pattern of drug release may not be tailored to suit daily physiologic BP variations. The same can be said regarding once-daily antianginal medications. True chronotherapeutic agents impart a dynamic element to drug delivery by providing larger drug concentrations during the critical morning period and smaller amounts during the night time, thereby minimizing the risk of excessive nocturnal BP drops. Currently, 3 chronotherapeutic calcium channel blockers are available on the market for the management of certain cardiovascular diseases. When administered at bedtime, all 3 agents provide a peak effect coinciding with the rise in BP and HR in the critical time period of 6:00 am to noon, and trough concentrations during sleep.

Approved by the FDA in 1996 for hypertension and angina, Covera-HS (verapamil HCl) was initially developed and marketed by Searle until Pfizer obtained

the company in 2001. Covera- HS uses the controlled-onset, extended release (COER) delivery system, which mirrors the gastrointestinal therapeutic system (GITS) used in extended-release Procardia XL (nifedipine). The tablet consists of multiple layers or coats. The outermost coat is composed of a semipermeable membrane that regulates the amount of water that can penetrate into the tablet. Water from the gastrointestinal (GI) tract will continue to saturate this layer at a fixed rate until the second coat is reached. This second coat will continue to absorb water but temporarily impedes any fluid from reaching the inner core of active drug. After 4 to 5 hours, fluid eventually penetrates to the third coat, which osmotically expands, pushing verapamil out of the tablet at a constant, fixed rate. This continued osmotic expansion allows the extended release of verapamil over the 24 h time period.

Approved by the FDA in 1998 for hypertension, Verelan PM (verapamil HCl), marketed by Schwarz Pharma, and uses the chronotherapeutic oral drug absorption system (CODAS) technology. This technology incorporates a 4 to 5 h delay in drug delivery followed by extended drug release. Peak concentrations occur 11 hrs after the drug is administered, with trough concentrations occurring approximately 4 hrs post-dose. Each capsule contains pellets consisting of an inert core surrounded by active drug and rate-controlling membranes composed of water-soluble and water-insoluble polymers. Moving through the GI tract, the coated pellets are bathed in water, which in turn dissolves the water-soluble polymer, permitting the drug to diffuse through pores along the outer coating. The controlled release of the drug throughout the 24 h time period is dependent on the water-insoluble polymers, which impede immediate dispersion of verapamil.

Approved by the FDA in 2003 for hypertension and angina, Cardizem LA (diltiazem HCl), marketed by Biovail, employs a unique graded extended release tablet delivery system. Each tablet consists of polymer-coated, compressed beads. This particular polymer creates a lag time in tablet dissolution, allowing for detectable plasma concentrations within 3 to 4 h and maximal concentrations within 11 to 18 h post-dose.[39] Pharmacists frequently ask how the LA and CD formulations of Cardizem differ. First, as previously mentioned, bedtime dosing of Cardizem LA provides peak diltiazem concentrations within 11 to 18 hours, whereas bedtime dosing of Cardizem CD provides peak diltiazem within 10 to 14 hours. To obtain possible chronotherapeutic benefits with Cardizem CD during the 6:00 am to noon time period, the patient would have to administer the capsule at about 2:00 am. Second, when dosed at bedtime, Cardizem LA demonstrates a 1- peak plasma concentration profile, as opposed to the CD formulation, which exhibits a 2-peak profile, with decreasing plasma concentrations during the early morning hours. Finally, the polymer technology of the LA formulation allows for a longer diltiazem halflife of 6 to 9 h, compared with 5 to 8 h with the CD preparation [15-26].

CHRONOTHERAPHY OF ASTHMA

Normal lung function undergoes circadian changes and reaches a low point in the early morning hours. This dip is particularly pronounced in people with asthma. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours.

Several chronotheraphies have been proposed. Daily or alternate-day, morning dosing of glucocorticoids medications such as methylprednisolone (Medrol) significantly moderates the side effects and enhances therapeutic benefits. Oral prednisolone administered at 3 pm instead of 8 am shown to be highly effective in the treatment of nocturnal asthma. One example is the bronchodilator Uniphyl, a long-acting theophylline preparation manufactured by Purdue Frederick Co. of Norwalk, Conn., and approved by FDA in 1989. Taken once a day in the evening, Uniphyl causes theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours. Writing in the April 15, 1996, issue of Hospital Practice, Richard Martin, M.D., who directs the division of pulmonary medicine at the National Jewish Center for Immunology and Respiratory Medicine in Denver, stated his belief that "the key to managing [asthma] cases is chronotherapy. I have found that unless treatment improves night time asthma, it is hard to improve its daytime manifestations." For people with severe asthma who wake up several times a night gasping for breath, a good night's sleep can be a dream come true [27].

CHRONOTHERAPHY OF ARTHRITIS

Chronobiological patterns have been observed with arthritis pain. People with osteoarthritis, the most common form of the disease, tend to have less pain in the morning and more at night. In contrast, for people with rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day wears on. Recent animal studies showing that joint inflammation in rats fluctuates over a 24-hour period support these observations by both patients and physicians. For osteoarthritis sufferers, the optimal time for a nonsteroidal anti-inflammatory 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. The exact dose would depend on the severity of the patient's pain and his or her individual physiology. Chronotherapeutic of various forms of arthritis has been discussed below:

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder. The cardinal signs of rheumatoid arthritis are stiffness, swelling and pain of one or more joints of the body characteristically most severe in the morning. Rheumatoid arthritis shows a marked circadian variation in its symptoms [28, 29]. A group of British volunteers self-assessed the pain and stiffness of affected finger joints every 2 to 3 h daily for several consecutive days. They also measured the circumference of the arthritic joints to gauge the amount of their swelling, and they performed grip strength tests to determine the effect of the arthritic condition on the hands [30, 31]. Ratings of the severity of joint pain swelling and stiffness were about 3 times higher between 08:00 and 11:00 am than at bedtime. In contrast, hand strength was lower by as much as 30% in the morning than at night. This is typical of rheumatoid arthritis sufferers [32-34].

The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting Non Steroidal Anti-inflammatory Drugs (NSAIDs) like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes or averts their side effects. 12-hour sustained-release NSAIDs that are taken twice a day must include a night or bedtime ingestion time to ensure adequate control of the prominent morning symptoms of rheumatoid arthritis. If the arthritic condition is severe, synthetic corticosteroids are often of benefit. Morning once-a-day dosing of these medicines is least likely to cause side effects especially if they are taken for a long period of time. Splitting the daily dose of medicine into several small ones for ingestion with meals and at bedtime or taking the entire daily dose at night is not recommended unless absolutely necessary. The risk of severe side effects from these medications increases when they are taken more than 8 to 9 h after the customary time of awakening, after 15:00 pm for most people. The later in the day these medications are taken, the greater the risk of side effects. If the relief from the morning symptoms of rheumatoid arthritis sufferers is not attained by a once-day morning schedule, an increase in the morning dose is recommended. The results of one study suggest an early afternoon once-a-day treatment schedule might be beneficial for those people who fail to get significant relief from the morning pain and stiffness of rheumatoid arthritis when taking medicine in the morning.

Osteoarthritis

The circadian rhythm of pain and stiffness in osteoarthritis differs from that of rheumatoid arthritis. Osteoarthritis is a degenerative disease of the joints and is the commonest of all joint diseases, affecting nearly everyone at least to some degree by age 70. The weight bearing joints of the hip, knee, back, toes and fingers are mostly affected.

The pain of osteoarthritis sufferers is typically less intense in the morning than in the afternoon or evening. This is illustrated by the findings of a Canadian study of 20 persons troubled with osteoarthritis of the knee. Participants did pain self-ratings 10 times daily for 7 consecutive days. For the group as a whole, pain intensity was rated about 40 percent higher on average between 20:00 pm and midnight than between 06:00 and 10:00 am. However, the exact nature of the 24 h pattern of pain differed from person to person. In 40 percent, pain was greatest between 14:00 and 20:00 pm, and in 25%, it was highest between 20:00 pm and midnight. In 15 %, it peaked at two different times of the day, and in 20 %, the level of pain exhibited no day-night variation whatsoever. Interestingly, 40 % of the people exhibited weekly rhythms in pain intensity, although the exact day of the week it was worse varied. In some, it was more intense at the end of the week and in others the beginning. In summary, the day-night cycle of pain in osteoarthritis varies from one individual to another. Some experience worse pain in the morning and others at night. Some experiences two peaks i.e. in the morning and evening, while still others experience pain of equal intensity throughout the 24 h. The successful treatment of osteoarthritis requires that medications be taken at the right time relative to the day-night pattern of pain in each person.

The temporal pattern of pain and stiffness in osteoarthritis sufferers differs between persons. Thus, an individualized chronotherapy of NSAIDs is necessary. The chronotherapy of osteoarthritis involves the administration of once-a-day forms of ketoprofen, indomethacin and other such medicines in relation to the time of day pain is worse. If pain is worse at night or early in afternoon, an evening once-a day NSAIDs schedule is recommended. If pain is worse in the afternoon or night, a once-a-day morning or noontime treatment schedule is best, providing the amount of side effects produced by the morning one, in particular, is minimal [35, 36].

Ankylosing Spondylitis

Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. In its occurrence it is an inherited disorder that is more common in men than women. One investigator used questionnaires to study daily cycles in the back symptoms of 39 people suffering from this disease. Overall, back stiffness and pain were a problem throughout the 24 h, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 and 09:00 am than between noon and 15:00 pm when each was least bothersome. The symptoms also exhibited a second less prominent peak between 19:00 and 21:00 pm. The findings of a French study of 26 people suffering from this medical condition were identical. Ratings of the intensity of back stiffness and pain were higher in the morning and evening than in the afternoon. Marked seasonal variation in ankylosing spondylitis was also prominent. The onset of backache and stiffness was 12 times more frequent in winter than summer. Moreover, reoccurrence of back problems occurs 2 to 3 times more often in winter than summer [37, 38].

CHRONOTHERAPHY OF DIABETES

Insulin levels and the counter regulatory hormones, which work against the actions of insulin, are in turn, influenced by the circadian rhythm. These hormones which include glucagon, epinephrine (adrenaline), cortisol, and growth hormones raise blood sugar levels when they need to be raised. During the middle of the nighttime hours, there is a surge in the amount of growth hormone the body will release, that is followed by a surge in cortisol. This increases blood glucose production by the liver. In a nondiabetic person, these processes are offset by the increase in insulin secretion by the pancreas. Blood glucose then, remains stable. In type 1 diabetics who don't make insulin at all, and in type 2 diabetics where the liver may not respond to insulin very well to stop glucose production, changes in blood sugar levels during rest can have a large effect on morning glucose levels. The dawn phenomenon occurs, and this is where sugar levels rise between 4 am and 8 am. The dawn phenomenon is a sudden 10–20 mg/dl rise in blood glucose levels in the early morning hours, 3–6 am.

While studying the metabolism of migratory birds, it was observed that they develop seasonal insulin resistance and dopamine plays a role in it. This novel observation lead to the development of new drug, bromocriptine mesylate which has been approved by FDA on May 5, 2009 to be used as an adjunct to diet and exercise to

improve glycemic control in adults with type- 2 diabetes mellitus, as a single morning dose. This drug acts by causing resetting of abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients [39-44].

CHRONOTHERAPHY OF CANCER

The circadian timing system controls drug metabolism and cellular proliferation over the 24 h through molecular clocks in each cell, circadian physiology, and the suprachiasmatic nuclei; a hypothalamic pacemaker clock that coordinates circadian rhythms.

Further understanding of the cancer cell cycle would be the next step. A few studies have shown that cancer cells function on a cycle independent of the rest of the body. Therefore, if researchers can pinpoint the best time to administer cancer-killing drugs, these treatments would be more effective and do less harm to the rest of the body. When cancer medications are given in a chronobiological manner, patients may be able to tolerate higher, more potent doses than would be possible otherwise.

The circadian timings down- regulates malignant growth in cancer patients. Programmable- in- time infusion pumps and rhythmic physiology monitoring devices have made possible the application of chronotherapeutics to more than two thousand cancer patients without hospitalization. This strategy first revealed the antitumor efficacy of oxaliplatin against colorectal cancer. In this disease, international clinical trials have shown a five-fold improvement in patient tolerability and near doubling of antitumor activity through the chronomodulated, in comparison to constant-rate, delivery of oxaliplatin and 5- fluorouracil - leucovorin. Here, there relevance of the peak time, with reference to circadian rhythms, of the chemotherapeutic delivery of these cancer medications. The incidence of severe adverse events varied up to five- fold as a function of the choice of when during the 24 h the peak dose of the medications was timed. The optimal chronomodulated schedules corresponded to peak delivery rates at 1 am or 4 am for 5 -fluorouracil – leucovorin, at 1 pm or 4 pm for oxaliplatin, and at 4 pm for carboplatin. Ongoing translational studies, mathematical modeling, and technology developments are further paving the way for tailoring cancer chronotherapeutics to the main rhythmic characteristics of the individual patient. Targeting therapeutic delivery to the dynamics of the cross-talk between the circadian clock, the cell division cycle, and pharmacology pathways represents a new challenge to concurrently improve the quality of life and survival of cancer patients through personalized cancer chronotherapeutics.

The survival rate in ovarian cancer may be quadrupled when doxorubicin is given in the morning and cisplatin in the evening. The optimal timing of cancer surgery, particularly breast cancer, has also come under study. 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 helps cancer spread. However, the need to time surgery is debatable [45-52].

CHRONOTHERAPHY OF PEPTIC ULCER

In peptic ulcer patients, pain, gastric distress and acute exacerbation of the disease are most likely in the late evening and early morning hours. Ulcer pain typically occurs after stomach emptying, following daytime meals and in the very early morning, disrupting sleep. This is attributed to high gastric secreation and slows gastric motility and emptying at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Once daily nocturnal administration of H_2 antagonist or morning administration of proton pump inhibitor tablet medications not only reduce acid secretion more effectively but also promotes ulcer healing and reduce ulcer occurrence [52, 55].

CONCLUSION

In conclusion, there is growing evidence that circadian rhythmicity influences disease symptoms, diagnostic test results and even the body's response to drug therapy, but the concept is yet to be fully understood and adopted in the clinical practice. While technology is slowly being developed to help doctors administer medicine at the best times, more knowledge about chronotherapy is needed.

Further, from the regulatory perspective, proof that treatment efficacy is improved by a customized dosing regimen is needed to receive a strong label claim and to get intellectual property protection for an improved formulation. All of this makes development of chronotherapeutic, pulsatile-release products particularly challenging; however, getting the right drug to the right place at the right time can provide competitive differentiation in an increasingly crowded market place, where many companies are increasingly developing new formulations of the same drug. Thus it is concluded that by understanding the biorhythmic pattern the treatment for various diseases can be optimized.

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