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Chronotherapeutic Drug Delivery System: A Novel Approach For Treatment Of Nocturnal Diseases.

Dubey Mahendrakumar Ramrang

Surya kiran society, Vasad, District-Anand 38806, Gujarat-India.

ABSTRACT

All functions in human are highly organized in time as biological rhythms of diverse periods, both in health and in disease. This represents a challenge for those involved in the development of drug-delivery systems to make possible the treatment of illness according to these physiological biological rhythms as a means of improving therapeutic outcomes. Pharmaceutical companies are experiencing obstacles in discovering new medications that represent significant advances in the treatment of disease. The current advances in chronobiology and the knowledge gained from chronotherapy of selected diseases strongly suggest that "the one size fits all at all times" approach to drug delivery is no longer substantiated, at least for selected bioactive agents and disease therapy or prevention. Thus, there is a critical and urgent need for chronopharmaceutical research (e.g., design and evaluation of robust, spatially and temporally controlled drug delivery systems that would be clinically intended for chronotherapy by different routes of administration).

KEYWORDS : Chrotherapeutics, chronobiological research, chronobiological rhythm.

INTRODUCTION:

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun [1].

One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated. The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The concept of chronotherapeutics is not new; the roots of clinical chronobiology date back to 1814, when Joseph Virey empirically recommended that opium should be dosed late in the evening, rather than in the morning. In the last few years recognition of the importance of the circadian rhythm to the health sciences has increased significantly. In fact the human circadian time structure presents peaks of actions directly related to the daily routine of most human beings. As human physiology and biochemistry predictably vary during a 24 hour period it is easy to understand that some medical conditions present prevalence at certain periods of the day.

There are numerous scientific evidences from basic chronogenetic/ chronobiological and clinical studies strongly suggesting that there is a critical and urgent need to revisit the formulation of both new and old drugs at least for selected diseases. Among other limitations in the fulfillment of this clinical demand, there are three major hurdles to widespread production and use of chronopharmaceutical drug products

It has become apparent that rhythmic processes are indispensable for the treatment of human diseases. Just as physiological functions vary over time, pathological states of disease have circadian rhythms. Epidemiological studies have documented the elevated risk of disease symptoms during the 24-hour cycle [2].

Chronopharmaceutics has been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy.[3] Chronotherapeutics is the purposeful delivery of medications in unequal amounts over time, for example, during the 24 h. Chronotherapeutics takes into account 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 circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects.[4-5]

There are number of conditions which show a circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Some of the conditions, which may be significantly benefited, are given below:

1. Myocardial infarction
2. Bronchial asthma
3. Cerebrovascular accidents
4. Arthritis
5. Hypercholesterolemia
6. Peptic ulcer
7. Hypertension

1). Myocardial infarction

Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 A.M. 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 [6,7].

2). Bronchial asthma

Bronchial 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. In one study [8], use of a timed-release formulation of theophylline (Theo- 24) achieved therapeutic drug concentrations during the night and avoided toxic levels during the day when the dose was ingested at 3 pm. Another study [9] 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. In addition, oral prednisone has been shown to be much more effective in improving several features of nocturnal asthma (i.e., overnight fall in forced expiratory volume in 1 second [FEV1], 4 am FEV1, and response to a standard dose of inhaled beta2 agonist) when administered at 3 pm rather than 8 am [10].

3). Cerebrovascular accident

The cerebrovascular accidents have been shown to occur on the first hours of morning between 10 A.M. and 12 noons, and the incidence declines steadily during the evening and the midnight. A major objective of chronotherapy for cardiovascular disease is to deliver the drug in higher concentration during time of greatest need and in lesser concentrations when the need is less. ACE inhibitors are more effective when administered during night. Atenolol, Nifedipine and amolodipine are more effective when administered at night. The night and avoided toxic levels during the day when the dose was

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4). Arthritis

The new cyclooxygenase-2 inhibitors effectively relieve osteoarthritis symptoms when taken in the morning; better results are obtained in rheumatoid arthritis when part of the dose is taken in the evening [11].

5) Hypercholesterolemia

When the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors were first introduced, morning dosing was recommended. This strategy was re-evaluated after the discovery of the circadian rhythm of cholesterol biosynthesis [12], in which higher rates of cholesterol intake and hepatic cholesterogenesis occur during the evening hours, even in the fasting state. One clinical study [13] 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 HMG- CoA reductase inhibitors failed to show a reduction in cardiovascular morbidity and mortality. However, the first primary prevention trial that studied evening dosing [14] 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 (Lipitor) may be an exception because of its long elimination half-life [14].

6). Peptic ulcer disease

In the past, histamine2 antagonists were administered at regular intervals around the clock, on the basis of pharmacokinetic properties. However, because maximal acid secretion, peptic ulcer disease pain, and perforation of gastric and duodenal ulcers are more common at night, administration of these drugs at bedtime is more effective. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer recurrence [15].

7). Hypertention

Heart rate and blood pressure are increased in the early morning hours (morning or A.M. surge). The blood pressure declines form mid afternoon and is minimum at midnight [16,17]. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or "a.m." surge [17, 18]. 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/hour8. Delivery of the drugs according to the variations is relatively a new practice. The first such agent developed for hypertension and angina is COER(R- Verapamil). Advantage of this formulation is that delivery of the active drug tailored to the typical circadian rhythms and heart rate, and the patients are better covered in the early morning when cardiovascular need appears to be greatest, and the effects of traditional medications seems to wane the timings of various antihypertensives and can be adjusted according to their onset of action, half life and duration of action.

The first chronotherapeutic therapy for hypertension and angina pectoris has recently been developed which matches drug delivery to the circadian pattern of blood pressure and rhythm of myocardial ischemia. Verapamil has been employed in this system where release is observed after 4-5 hours and continues for 18hours. Taken at bedtime, this provides optimal blood concentration between 4A.M. and 12 noons [19,20,21]. Data from recent studies demonstrate that antihypertensives and antianginal therapy can be designed to mimic the circadian rhythms. Future research will evaluate whether timings of drug delivery has an effect on the outcomes like control of hypertension, silent ischemia, myocardial infarction and quality of life

Table 1. Circadian Rhythms and the Severity or Manifestation of Clinical Disease.

Disease or Syndrome	Circadian Rhythmicity
Allergic rhinitis	Worse in early a.m./upon arising
Bronchial asthma	Exacerbations more common during sleep
Rheumatoid arthritis	Symptoms are most intense on awakening
Osteoarthritis	Symptoms worse in the middle/latter portion of the day
Angina pectoris	Chest pain and ECG changes more common during the early a.m.
Myocardial infarction	Incidence greatest in the early a.m.
Sudden cardiac death and	Incidence highest in ventricular tachycardia morning after awakening
Peptic ulcer disease	Symptoms worse in the early (sleep) a.m.
Allergic rhinitis	Worse in early a.m./upon arising.
Stroke	Incidence greatest in the early a.m.

Table 2. Drugs with different onset of action and duration of action.

Drugs	Onset of action	Duration of action
CalciumChannel Blockers		
Amolodipine	2-6 hrs.	2-4days
Nifidipine	30-60mins.	3-12hrs
ACE Inhibitors		
Enalapril	1hr.	24hrs.
NSAIDs		
Naproxen	1hr.	Up to 12hrs.
Ketoprofen	30mins.	6-8hrs.
Peptic ulcer		
Ranitidine	Within 1hr.	12hrs.

Overview of the current status of chronopharmaceutical drug delivery.

The chronopharmaceutical technologies based on physical and or chemical activation for controlled drug release that is intended for different route of administration have been described in detail elsewhere [22,23,24]. Examples of technologies that may be used for parenteral routes in chronotherapy include chronomodulating infusion pumps (i.e. MelodieTM, PanomatTM V5, SynchromedTM, RhythmicTM) and controlled release microchip strategies. Examples of technologies intended for oral administration include ContinTM, ChronsetTM, CodasTM, CeformTM, DiffucapsTM, TIMERx®, ChronotopicTM, EgaletTM, Geo- ClockTM, PortTM, Three-dimensional printing (3DP)TM, methods involving physicochemical modification of the active pharmaceuticaL ingredient and/or the use of controlled release erodible polymer [22,23].Recently, a novel floating pulsatile system using high internal phase emulsion based porous material intended for chronotherapy have been reported[25]. In this floating system,drug loading using a porous carrier, synthesized by high internal phase emulsion technique using styrene and divinylbenzene, was achieved via solvent evaporation method. The lack of chemical agent as release modifiers made this delivery system distinctfrom other technologies for chronotherapy. Overall, the concept of low density floating multiparticulate pulsed-release dosage forms have been extensively explored [26]. Moreover, the combination of floating and pulsatile principles to develop drug delivery system for chronotherapy in nocturnal acid breakthrough has been demonstrated by using a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating [27]. It is important to underscore that the clinical relevance or advantage of chronopharmaceutical formulation or delivery remains to be proven on case by case basis perhaps depending on the type of patientpopulation, disease and/or bioactive agent. For example, the bioavailability of the extended release tramadol (opioid analgesic) capsules for once daily administration was not affected by the time point of administration in pain management. The total and maximum exposure of the product was bioequivalent after intake in the morning and at night suggesting that the time-point of administration may be adjusted to the patient's needs without any

significant change in the invivo performance [28]. However, a recent clinical trial investigated the administration time dependent antihypertensive efficacy of the slow-release, once a day nifedipine gastrointestinal therapeutic system formulation .In this study, the blood pressure (BP) reduction after treatment and the number of patients with controlled ambulatory BP were significant larger bedtime than morning treatment. Moreover, the morning surge of BP (a risk factor for stroke) was also significant reduced only after bedtime administration of nifedipine. Therefore, the increased efficacy on ambulatory BP as well as the significant reduced prevalence of edema after bed time as compared to morning ingestion of this drug should be taken into account when not only during the design of novel delivery system for this application but also when prescribing such cardiovascular medication for patients with essential hypertension [29]. Moreover, in resistant hypertension, it has also been shown that the time of treatment may be more important for BP control and for the proper modeling of the circadian BP pattern than just changing the drug combination [30].

Conclusion:

One goal of this article is to educate biologists, clinicians, and pharmaceutical scientists of the importance of biological clocks and chronobiology to health and disease. A second goal is to stimulate further experimental and clinical research in the field of chronopharmacology. However, the most important goal of the issue is to motivate the development and applications of chronotherapeutics as a practical means of improving the outcomes and safety of medical treatment. In time where pharmaceutical companies strive to offer better solutions to the market the use of these intelligent systems could not only offer better therapeutic results but also increase patient's compliance.

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