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Review

CHRONOTHERAPY: SCIENCE AND TECHNOLOGY OF DRUG SCHEDULING ON THE BASIS OF BIOLOGICAL RHYTHM

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Abstract

Drug delivery systems that precisely control the release rates or target drugs to a specific site have an enormous impact on the health care system. Over the past few years, pharmaceutical industry has focused its research in the development of various chronotherapeutic delivery systems. By choosing the optimal time to achieve the desired effect, treatment opportunities may arise, and undesirable side effects minimized. Hence the long term interest of both the public and the industry is to develop new and more effective methods on the current study focus – chronopharmaceuticals. The present article covers findings about the effects of biorhythms on various disorders, and their implications for drug therapy are discussed. Here we also reviewed the design of novel chronopharmaceutical drug delivery systems that might be able to release the therapeutic agents at predetermined intervals.

Key Words: Chronotherapy; circadian rhythm; biological clock; biological rhythm, hydrogels

Introduction

Coordination of biological rhythms with medical treatment is called chronotherapy. Chronotherapy considers a person's biological rhythms in determining the timing and amount of medication to optimize a drug's desired effects and minimize the undesired ones. Study of influence of biological rhythm on the effects of medication is known as chronopharmacology while the science of study of biological rhythms is known as chronobiology. With the understanding of biological time keeping the idea came that these rhythms must affect how the body responds to drugs administered over the course of the day.^{1,2}

Appropriate timing of administration can improve efficacy and diminish toxicity. Chronotherapy is relevant when the risk or intensity of the symptoms of disease vary with time as in the case of allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke and peptic ulcer disease (Table 1).^{3,4}

Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled/sustained release drug delivery systems, compared to immediate release preparations.^{5,6}

Some of the rhythms that affect our body are ultradian (cycles shorter than a day like firing of neurons take milliseconds), circadian (cycles lasting 24 h such as sleeping and waking pattern), infradian (cycles longer than a day like menstrual cycles) and seasonal rhythms (such as seasonal affective disorders causing more depression in susceptible individuals in winter). Circadian rhythm governs every process of our body.^{7, 8} The term circadian rhythm was first given by Halberg and Stephens in 1959.⁹ The 24 h clock pattern of diseases showing prominent day-night patterns when symptoms of disease are most frequent is shown in Fig. 1.

Table 1. Circadian rhythm of clinical diseases that have been well studied¹²

Disease / syndrome	Circadian rhythmicity
Allergic rhinitis	Symptoms worse in early morning
Bronchial asthma	Exacerbations more common during the sleep period
Arthritis, rheumatoid	Symptoms are most intense upon awakening
Osteoarthritis	Symptoms worse in the middle/latter portion of the day
Anti cancer agents	Doxorubicin, Cisplatin, methotrexate
NSAIDs	Ibuprofen, indomethacin, tenoxicam, acetylsalicylic acid
Angina pectoris	Chest pain and ECG changes more common during the early morning
Myocardial infarction	Incidence greatest in the early morning
Peptic ulcers	Symptoms worse after gastric emptying and in the early morning (sleep period)
Stroke	Incidence greatest in early morning

Endogenous rhythms of our body controlled by a molecular clock in the brain's suprachiasmatic nucleus (SCN). It is reset by a timer mechanism (daylight resets the clock to a 24 h rhythm). Biological rhythms concern to the control of biological functions including those of the autonomic nerve system, endocrine system, and

immune system, are fundamental in homeostasis and in protection against various diseases.¹⁰ The central pacemaker in mammals is in the suprachiasmatic nuclei of the anterior hypothalamus.⁸ Out of all the environmental stimuli, light is the most important. The pathways that detect light for the purpose of circadian synchronisation are different from those that are used for visual perception; because of this the blind human subjects have their circadian rhythm despite having no perception or awareness of light.¹¹

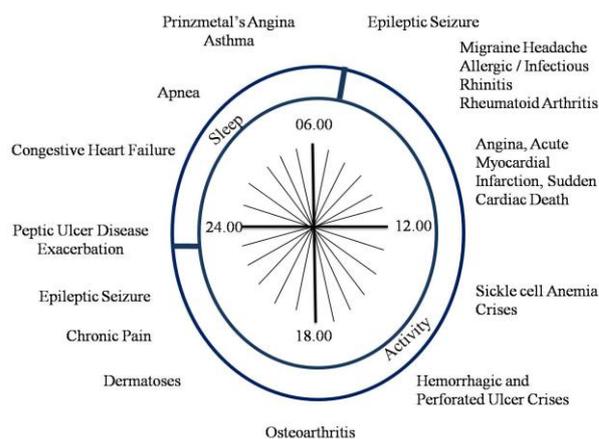


Fig.1. The circadian pattern of diseases

Chronotherapy of diseases

Chronotherapy of cardiac diseases

The chronobiological approach to physiology evaluates time-dependent changes in biological functions and considers those changes to be multifactorial. Chronotherapeutic approach gives more accurate determination of the time when patients are at highest risk and in greatest need of therapy. Circadian variations can occur due to myocardial ischemia, acute myocardial infarction, ventricular tachycardia, and sudden cardiac death. Factors affecting circadian variations in cardiovascular disorders include physiological determinants, such as heart rate, catecholamine release, and platelet aggregation which themselves vary cyclically and exogenous factors, such as mental stress, anxiety, and physical activity. In chronotherapy, circadian variations in disease states and in the pharmacodynamic properties of drugs are exploited to improve prevention and treatment. Chronotherapeutic approach may be advantageous in thromboembolism, hypertension, stable exertional angina, variant angina, sustained ventricular tachycardia, and acute myocardial infarction.¹³

Chronotherapy of Cancer

An important issue in the treatment of cancer is its tolerability by patients. Drugs having good therapeutic effect by killing tumour cells are always limited in their use by their toxicity on healthy tissues. So it is the greatest importance to find differences in the behaviours of healthy and cancer cells towards aggression by antitumour treatments. Experimental studies in cancer chronotherapy were initially performed by Halberg et al.¹⁴

Hrushesky et al, conducted research on chronotherapy for gynecological and genitourinary cancers including advanced renal cell carcinoma. These studies demonstrated the superiority of chronotherapy with respect to response and side effects when compared to conventional chemotherapy.^{15, 16}

In a laboratory test conducted on rodents, as a result of chronotherapy, the host tolerance and antitumor efficacy of anticancer drugs shows a large variation according to the dosing time. A specific technology (programmable-in-time infusion pumps) enables administration of chronotherapy to fully ambulatory patients. Phase I-III clinical trials showed chronotherapy significantly increases tolerance to high doses of anti-cancer drugs and improves antitumor activity in patients with metastatic colorectal cancer.¹⁷

Adler et al, conducted phase I clinical trial for chronotherapy of colorectal cancer in eight patients with 5-fluorouracil (initial dose of 500 mg/m²/day) and folinic acid (20 mg/m²/day] as a continuous intravenous infusion over five consecutive days. Compared with conventional Phase I/II trials using a five days infusion regimen, the maximal tolerated dose of 5 - fluorouracil and folinic acid was slightly higher. The results suggest that the circadian timing of 5-fluorouracil and folinic acid may not always allow the safe application of high dose levels.¹⁸ In a study, the chronotherapeutic schedules were used for safe activity of the combination of oxaliplatin, 5-fluorouracil, and leucovorin against metastatic colorectal carcinoma. The results offer that the chronotherapy concepts improve current cancer treatment.¹⁹

Chronotherapy of diabetes

The most widespread application of chronotherapy is insulin pump, which is used to administer insulin for the treatment of diabetes mellitus. With the

insulin pump, patients can customize insulin delivery to meet their particular requirements.

Several systems were developed to respond the change in glucose concentration like pH sensitive hydrogel containing glucose-oxidase enzyme immobilized in hydrogel. As the blood concentration of glucose rises, glucose-oxidase converts glucose into gluconic acid, which changes the pH of system. Due to change in pH, swelling of polymer takes place and this result into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to deswelling and hence decreasing the insulin release.¹²

Chronotherapy of renal disease

A repeated dosing study of high-dose active vitamin D3 in haemodialysis patients with secondary hyperparathyroidism was conducted. A higher dose (3 mg) was given orally to 13 haemodialysis patients at 08.00 h or 20.00 h for 12 months by a randomized, cross-over design with an 8-week washout period. Serum concentrations of calcium and inorganic phosphate were determined by orthocresolphthalein complex method, and ammonium molybdate method with an autoanalyser, respectively. The results indicate that a higher dose of oral D3 is more effective and safe after dosing at evening in patients with renal osteodystrophy.²⁰

Chronotherapy of Asthma

Asthma worsens at night and in the early morning, due to various circadian influences. Uninterrupted sleep, stable lung function over 24 h, and reduced and stable airways responsiveness are primary therapeutic goals in asthma. Asthma is well suited for chronotherapy, with beta 2- agonists and oral corticosteroids.²¹

Once-daily evening theophylline chronotherapy meets these goals, providing rising blood levels at night and in the early morning, when most needed. Theophylline chronotherapy is as well tolerated as more frequently administered methylxanthine preparations despite the relatively large single doses required by the prolonged dosing interval. Theophylline chronotherapy does not provide constant blood levels over the 24 h.²²

In a study, twenty patients with chronic obstructive bronchitis (COB) were examined. The peak expiratory flow rate (PEFR) for the assessment of daily rhythms of bronchial possibility was

determined. The test was conducted from 8.00 a.m. till 11.00 p.m., and additionally at 4.00 a.m., using the peak flow meter (Boehringer Ingelheim). Theophyllin 200 mg twice daily was prescribed for the chronotherapy during the periods of lower PEFr, measured individually for each patient. The daily average PEFr increased under the standard therapy on 4%, and on 10% under the chronotherapeutical approach. The results shows that the efficiency of the was increased by the chronotherapeutical approach.²³

Chronotherapy of sleep disorders

The circadian rhythm is not an immutable rhythm; it can be controlled by certain factors such as light and darkness, social interaction, sleep-wake schedule, timing for taking meals, etc. In the international classification published in 1990, sleep rhythm disorders such as non 24 h sleep-wake syndrome and delayed sleep phase syndrome are grouped together as circadian rhythm sleep disorder and treated as dyssomnias (Table 2).²⁴

Table 2. Classification of sleep disorders

Dyssomnias
1. Intrinsic sleep disorders
2. Extrinsic sleep disorders
3. Circadian rhythm sleep disorders
Parasomnias
1. Arosual disorder
2. Sleep – wake transition disorders
3. Parasomnias associated with REM
4. Other parasomnias
Sleep disorders associated with medical / psychiatric disorders
1. Associated with mental disorders
2. Associated with neurological disorders
3. Associated with other medical disorders

Chronotherapy of hypertension

Many antihypertensive drugs do not control the early morning blood pressure, when given once daily early in the morning.²⁵ Hermida et al, studied the impact of antihypertensive treatment and the time of therapy on the circadian pattern of blood pressure in 585 hypertensive patients with diabetes mellitus. Blood pressure was measured at 20 min intervals from 07:00 to 23:00 h and at 30 min intervals at night for 48 consecutive h. Blood pressure was reduced during diurnally active h, but not during nocturnal sleep, as compared to untreated patients (P<0.001). Results from this study indicate the need to establish a proper chronotherapeutic

scheme that could reduce BP and modify the altered circadian profile into a dipper BP pattern, associated to a lower cardiovascular risk.^{26, 27}

Koga et al, conducted a chronotherapeutic test for β – blockers to prevent the morning surge of hypertension by evening administration of carvedilol. In their study, they treated 12 male and 5 female patients with hypertension for 4 weeks at controlled blood pressure. The patients exceeding blood pressure 140/90 mmHg were treated with 10 mg/day carvediol as single dose in the evening. Results showed that the morning surge was suppressed with carvedilol and the 24 h mean systolic pressure was also reduced.²⁸

Chronotherapy of rheumatoid arthritis

The cardinal signs of rheumatoid arthritis are stiffness, swelling and pain of joints of the body characteristically most severe in the morning. Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. Taking long-acting NSAIDs like flubiprofen, ketoprofen and indomethacin once-a-day forms optimizes their therapeutic effect and minimizes or averts their side effects.^{29, 30}

Development of chronotherapeutic delivery systems

A basic chronotherapeutic system consists of a drug containing core and a barrier layer of polymer to control drug release from the core. Microchips can be used to control release of drug from the systems to obtain a controlled release program.³¹ Several techniques have been developed and applied to design chronopharmaceutic delivery systems for desired drug release. Different chronopharmaceutical technologies and marketed products are given in Table 3, and various US patents in the field of chronotherapy are given in Table 4. These techniques are broadly classified into following three major categories:

- Time controlled chronotropic systems.
- Stimuli induced pulsatile drug delivery systems
- Externally regulated pulsatile drug delivery systems

Time controlled chronotropic systems

The drug is released as a burst within a short period of time immediately after a predetermined off release period.

Time controlled chronotropic systems based on capsules

These systems are composed of an insoluble capsule body, swellable and degradable plugs made of hydrophilic polymers (like hydroxyl propyl cellulose, poly vinyl acetate, polyethylene-oxide), lipids and bioactive molecule. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap® a swellable hydrogel seals the drug contents into the capsule body. The hydrogel plug swells when the capsule comes in contact of fluid and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug.³²

Time controlled reservoir systems with rupturable polymer coating

The core is coated with a protective polymeric rupturable layer and an outer water insoluble semi permeable rate controlling membrane Pressure is requires to rupture the coating can be achieved by using swelling agents, gas producing effervescent agents or osmogens.^{33, 34, 35, 36} Swelling agent includes superdisintegrants like carboxy methylcellulose, sodium starch glycollate, L-hydroxy propyl cellulose. Polymers like polyacrylic acid, polyethylene glycol etc, and a mixture of tartaric acid and sodium bicarbonate is used as effervescent agent. Water ingress to system causes the coating to swell, rupture and release of drug occurs. Release of drug is independent of pH or solubility of drug. Lag-time can be varied by varying thickness of coating or by changing amount of plasticizers in the outermost layer. Rapid release of drug after lag-time can be observed with increase in the concentration of the osmotic agent. *In-vivo* studies of time controlled explosion system with an *in-vitro* lag-time of three h showed appearance of drug in blood after 3 h, and maximum level after 5 h.^{37, 38, 39}

A time dependent pulsed release system consisting of an effervescent core surrounded by consecutive layers of swelling and rupturable polymers were developed. The cores containing salbutamol sulphate as bioactive agent were prepared by direct compression method using different ratios of microcrystalline cellulose and effervescent agent and then coated sequentially with an inner swelling layer containing a hydrocolloid, hydroxyl propyl methylcellulose E5 and an outer rupturable layer having Eudragit RL/RS (1:1). The rupture and dissolution tests were studied using the USP paddle method at 50 rpm in 0.1 N HCl and phosphate buffer pH 6.8. The lag time of the drug release decreased by increasing the inner swelling layer and increased by increasing the rupturing layer level. Results suggest that osmotic pumping effect leads to the drug release.⁴⁰

Time controlled reservoir systems with soluble or eroding polymer coating

Ethylcellulose (EC) of varying particle sizes has been used as an outer coating layer to design a novel dry-coated tablet of sodium diclofenac by direct compression for time-controlled drug release. The drug release from dry-coated tablet exhibited an initial lag period depending on the particle size of the EC powder, followed by rapid drug release. The smaller the EC particle size used the longer the lag time obtained, suggesting the particle size of EC powder could modulate the timing of drug release from such a dry-coated tablet. The period of the lag time for sodium diclofenac released from dry-coated tablets was correlated with the penetration distance of the solvent into dry-coated tablet by an *in vitro* dye penetration study. The results suggest that these dry-coated tablets prepared with different particle sizes of EC powder as an outer coating layer might offer a desirable release profile for drug delivery at the predetermined time and sites.⁴¹

Table 3. Various developed chronopharmaceutic systems⁴⁶

Active pharmaceutical ingredient (API)	Proprietary name	Proprietary Chronopharmaceutic technology	Disease
Diltiazem HCl	Cardizem® LA	CEFORM® technology	Hypertension
Propranolol HCl	InnoPran® XL	DIFFUCAPS® technology	Hypertension
Verapamil HCl	Covera-HS®	OROS® technology	Hypertension
	InnoPran® XL	DIFFUCAPS® technology	Hypertension
	Verelan® PM	CODAS® technology	Hypertension
Famotidine	Pepcid®	Physico-chemical modification of the API	Ulcer
Simvastatin	Lipovas®	Physico-chemical modification of the API	Hyperlipidemia
Theophylline	Uniphyl®	CONTIN® technology	Asthama

Table 4. Various patents in the field of chronotherapy

Technology	Patent No.
Implantable electromechanically driven device	U.S. Pat. No. 4,003,379
Flexible system for timed controlled or position controlled drug delivery system	U.S. Pat. No. 7048945
Three Dimensional Printing [®] (3DP) technology	U.S. Pat. No. 5,490,962
Self-powered medication systems	U.S. Pat. No. 3,692,027
Implantable infusion device	U.S. Pat. No. 4,003,379
Pulsatile delivery	U.S. Pat. No. 6635277
Pulsatile technology	U.S. Pat. No. 5914134
Self-powered medication systems	U.S. Pat. No. 4,146,029
Pulsatile technology	U.S. Pat. No. 6217904
Microchip drug delivery devices	U.S. Pat. No. 5,797,898
Beads	U.S. Pat. No. 5439689

Pulsatile systems based on changed membrane permeability

Change in permeability of polymeric coating layer is responsible for drug release in presence of certain counter ions of surrounding media.⁴²

Stimuli induced pulsatile drug delivery system

The drug release from these systems is based on the physiochemical processes of body. These systems are meant for site specific targeted drug delivery by the induction of various physiochemical stimuli at target site. Biological stimuli like release of enzymes, hormones, antibodies, pH of the target site, temperature of the site, concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators) etc acts as stimuli to trigger the release of drug from these types of drug delivery systems. These systems are classified into following sub categories:

- Chemical stimuli induced pulsatile drug delivery systems
- pH sensitive pulsatile release chronotropic systems
- Enzyme catalyzed pulsatile chronotropic systems
- Temperature induced pulsatile drug delivery systems

Externally regulated pulsatile drug delivery systems

External stimuli like ultrasound, magnetic field, electrical effect and irradiation are required to control the drug release from these systems. When these external factors are applied on the delivery system, conductors present in the delivery system get sensitized to trigger the release of drug from the delivery system. Magnetic beads prepared by interfacial polymerization of polyamide

microcapsules shows this type of delivery mechanism.

Dosage forms used for chronotherapy

A number of commercially available chronotherapeutic drug-delivery systems have been developed for desired drug release. They are administered in the evening and delay the release of drugs until the early morning hours, when the symptoms of the disease are worst. Parenteral chronotropic systems are experiencing increased importance. The most widespread application is that of the insulin pump, which is used to administer insulin for the treatment of diabetes mellitus. Time scheduled regimens for cytotoxic drug delivery by intravenous infusion are also an example of chronotherapeutic system.

Core in cup tablets

These systems are made up of a core tablet containing active ingredient, an impermeable outer shell and a top cover layer-barrier of a soluble polymer. The cover layer erosion is responsible for drug release.⁴³

Compression coated/press coated tablets

Delayed release and intermittent release formulations can be achieved by press-coating or compression coating. Hydrophilic cellulose derivatives are used in these systems. The major drawbacks of this technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process.⁴⁴

Halsas et al, have developed a diltiazem hydrochloride formulation intended for use in the

treatment of time related symptoms of ischaemic heart disease and hypertension. The tablet consists of a core, which contains the drug, and a coat formed by compressing hydroxyethylcellulose. The results shows that diltiazem was rapidly released after a delay of several h.⁴⁵

Double coated hard gelatin capsules and double coated tablets

These are rupturable pulsatile drug delivery systems in form of hard gelatin capsules or tablets which releases the drug in time controlled manner. Capsules are filled with active pharmaceutical ingredient either for single pulse or multi-pulse release (in form of multiparticulates) and coated with a swelling layer followed by an external water insoluble semipermeable polymeric coating. A threshold hydrodynamic pressure due to water absorption is required to rupture the outer coating (rate controlling step) and allowing the release of contents in surrounding medium and fulfills the purpose of desired lag time required in chronotherapy of disease.⁴⁷

Chronomodulating infusion pumps

These system contains core having drug (low bulk density solid or liquid lipid material) and disintegrant. Core is coated with cellulose acetate polymer. When the system comes in contact with water, water penetrates the core, displaces the lipid material. After depletion of lipid material, internal pressure increases until a critical stress is reached, which causes rupture of coating and release of drug for chronotherapeutic applications.

Pulsincap systems

Pulsincaps are composed of a water insoluble body and a water soluble cap, and a drug which is sealed with a hydrogel plug. At a predetermined time after ingestion, the swollen plug is ejected from the capsule and the drug is then released into the small intestine or colon.⁴⁸

Controlled-release microchip

A microchip device is enable to store one or more compounds inside of the microchip in any form (solid, liquid, or gel), with the release of the compounds achieved on demand. The microchip contains a large number of reservoirs, each covered by a thin membrane of a material that serves as an anode in an electrochemical reaction. There are other electrodes on the surface of the microchip that serve as cathodes in an electrochemical reaction. Each reservoir is filled with a compound for release.

When release from a particular reservoir is desired, an electrical voltage (approximately 1 volt) is applied between the anode covering that reservoir and a cathode. The anode membrane dissolves due to an electrochemical reaction. This reservoir is now open, allowing the material inside to diffuse out into the surrounding fluid. Each reservoir on the microchip can be activated and opened individually, allowing complex release patterns to be achieved.⁴⁹

Hydrogels as carriers in chronotherapeutic systems

Hydrogels are used as chronotherapeutic carriers due to their physicochemical and biological properties. Hydrogels are three-dimensional structures that can imbibe a large amount of water. They are composed of swellable hydrophilic polymers. Hydrogels containing hydrophilic groups swell to a higher degree. Swelling of stimuli sensitive hydrogels can be affected by the change of the temperature, ionic strength and pH of the swelling medium. The swelling kinetics of hydrogels can be diffusion-controlled (Fickian) and relaxation-controlled swelling. Various hydrogels are used in the formulation of chronotherapeutic delivery systems like, stimuli-sensitive hydrogels, stimuli-sensitive hydrogels, temperature-sensitive hydrogels, physical stimuli, such as light, magnetic field sensitive hydrogels, chemical stimuli sensitive hydrogels, analyte-sensitive hydrogels etc.¹²

Conclusion

The effectiveness and toxicity of certain drugs depends on dosing time associated with 24 h rhythms under control of the circadian clock. The application of biological rhythm to pharmacotherapy may be correlated by the appropriate timing of dosing of these drug delivery systems to synchronize drug concentrations to rhythms in disease state. Applications of chronotherapeutic drug delivery systems are now better understood for selected disease such as cancer, peptic ulcer, sleep disorder, hypertension etc. The outcomes of these systems would be a more effective and can provide quality drug delivery device for real time and ambulatory disease monitoring systems. Development of some more technologies for the large scale production of chronotherapeutic systems needs to be initiated.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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