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Chronopharmacology: Tailoring Therapy to Endogenous Rhythms

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Abstract:

Chronopharmacology aims at the use of biological rhythms in the clinical treatment so as to enhance both effectiveness and tolerance and minimize the side effects of a drug by determining the best biological time for its administration.

Chronopharmacology is useful to solve problems of drug optimization. In the human organs, the metabolic fate of a pharmacologic agent as well is not constant as a function of time. Thus, the chronobiological approach of drug administration involves a lesser risk of errors than the conventional homeostatic approach. Chronopharmacology is now used as a routine to treat various disorders like hypertension, angina, cancer and various psychotic disorders. The newer drug delivery systems that are designed with the chronopharmacological approach hold great scope for delivering better patient care in terms of efficacy, tolerance and safety parameters of the drug.

This review aims at introducing chronopharmacology, the role of the regulatory system of biological clock in pharmacotherapy and the benefits it has conferred in various clinical conditions.

Keywords: Chronopharmacology, Circadian rhythms, Chronobiology

Up to now, design of drug delivery systems has been governed by the homeostatic theory. This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g., heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function.[1] 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.

Jean-Jacques d'Ortous de Mairan described the concept of circadian rhythms in plants in the 18th century. Franz Halberg who coined the word circadian in 1960s, was considered as one of the founders of chronobiology. Historically, it was early recognized that rhythmic physiology resulted in rhythmic disease symptoms. Hippocrates already noticed ca. 400 B.C. that daytime sleepiness is indicative of disease, and night time sleeplessness can indicate pain and suffering. By medieval times, reports existed of daily variations in diseases such as bronchial asthma.[2] For over thirty years, it has been known that drug absorption and distribution is subjected to diurnal variation in rodents and humans. A twenty-four hour change in drug bioavailability has therefore been established for hundreds of drugs in rodents and humans.[3] For example, acetaminophen or theophylline show different pharmacokinetics in the morning compared to evening.[4] These changes are the results of several time-dependent modifications of physiological and molecular aspects that influence drug absorption and distribution.

Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs

over biological timings & endogenous periodicities. It is further subdivided into Chronotherapeutics, Chronokinetics, Chronesthesy, Chronergy and Chronotoxicity.

Chronotherapeutics is defined as the science that aims to increase the efficiency and safety of medications by proportioning their concentrations during the 24 hours in synchrony with biological rhythm determinants of disease.[2]

Chronokinetics on the other hand deals with time dependent and predictable changes in pharmacokinetic parameters i.e. deals with the study of the temporal changes in the absorption, distribution, metabolism and elimination due to time of administration of the drug.[6]

Chronesthesy is the study of circadian or other systemic changes in the susceptibility and sensitivity of the target system to a drug while chronergy is the study of rhythmic difference in effects of a drug on the organism as a whole which includes both desired and undesired effects.[7]

Chronotoxicity is the study of the toxic effects of drugs on the organism, which is undesirable and affects the rhythmic system.

Biological clocks and circadian rhythm:

Biological rhythms are innately determined rhythmic biological process or function and self-sustaining oscillation with the duration of time between successive repetitions (i.e., the period) being rather non-varying under normal conditions. A hundred different, measurable parameters in the human body exhibit rhythmic variability within 24 hours.[8]

Rhythms affecting our body are ultradian cycles shorter than a day e.g. msec. for a neuron to fire; Circadian-Circa- about a day, lasting for about 24 hours, e.g.,sleep and wake cycles; Infradian- cycles longer than 24 hours e.g. menstrual cycle. Seasonal-like seasonal affective disorder causing depression in people during the short day's of winter.

While 24-hour clock times and sleep/wake rhythms frequently overlap with the internal clock, they do not always match the circadian rhythm. There are a variety of methods to ascertain the timing of biological clocks. Melatonin provides the most reliable and consistent measure of the circadian pattern and can be measured in the plasma, saliva, or urine. Because secretion of the hormone is acutely suppressed by light exposure, the measurement of the time of onset of the daily melatonin rise during low-light exposure is a more reliable measure of the circadian phase. The dim-light melatonin onset (DLMO) has been used to assess alterations of circadian phase in a variety of diseases. Other markers, such as core body temperature, and cortisol may also serve as biomarkers for circadian rhythms.[9]

Circadian rhythms are particularly important in medicine. Physiological day is about 25 hours where the clock is reset daily by the environment night day social schedules.[10] Biologic rhythms are endogenous nature of circadian. Lack of external synchronizers leads to free running rhythms. The period of free-running rhythms is longer or shorter than 24 hours and is characteristic for each species. Our internal clocks are genetically determined.[11] An internal biological clock is located in mammals, in the suprachiasmatic nucleus of the hypothalamus (SCN), delivering its message of time throughout the body. It is responsible for circadian rhythms and annual/seasonal rhythms. The SCN uses its connections with the autonomic nervous system for spreading its time-of-day message, either by setting the sensitivity of endocrine glands i.e., thyroid, adrenal, ovary) or by directly controlling an endocrine output of pineal gland i.e., melatonin.[12]

Mechanism of Chronopharmacology:

The basic unit of circadian timekeeping is the cell. Even in very complex organisms, most cells contain autonomous circuitry for circadian oscillations. Generally speaking, this mechanism is comprised of negative feedback loops of transcription and translation: activation of a repressor gene results in its later repression by its own protein product, and the instability of this repressor insures this repression is short-lived, so that a new cycle can begin.[13] In mammals, the principal activators within this system are the CLOCK and BMAL1 proteins and their homologs, which dimerize and bind to cis-acting E-box elements (with the simple consensus DNA sequence CAANTG) to activate transcription of a large number of circadian genes.Among these genes are loci encoding the PERIOD and CRYPTOCHROME families of repressor proteins (PER1-3 and CRY1-2), whose products multimerize and suppress the CLOCK:BMAL1 activating complex. Also among the genes activated by CLOCK: BMAL1 is the *Rev-Erbα* gene, which encodes a nuclear orphan receptor protein that together with its sister protein REV-ERBβ represses *Bmal1* transcription in a parallel but interlocked loop. The ROR family of transcriptional activators likely competes with the REV-ERB family of repressors for the same binding sites, adding further cooperativity to the transition mechanism. At each of these steps, additional precision and regulatory finesse is achieved through interaction with a wide range of auxiliary proteins: kinases that phosphorylate clock proteins to modify their stability or activity.[14]

Chronopharmacological techniques ensure that drug levels in the blood are within therapeutic ranges during periods of maximal disease severity. An example of this is seen in how evening doses of antihypertensive therapy can be used to prevent morning rises in blood pressure. The evening dose of the drug may thus be well timed with diurnal changes in blood pressure, preventing diurnal worsening of hypertension.[15] Receptor changes and receptor holidays experienced during trough periods of drug activity may decrease tolerance to antiepileptic medications, thereby improving their efficacy during periods of greater need. The sensitivity of rats with experimental Parkinson's disease exposed to dopaminergic drugs [16] for example, can be temporarily enhanced following short term treatment withdrawal. In addition, medications may have a different effect based on the timing of the dose. The efficacy of ketamine, for example, has been shown to have varying efficacy based on the timing of dose despite reaching equivalent plasma concentrations, giving rise to the theory that some of these diurnal effects may be due to changes in receptors or secondary messenger systems. Chronotherapy may prevent up- or down-regulation of receptors during periods of lesser need allowing optimal efficacy during periods of disease exacerbation.

Antibiotics:

Important aspect of chronokinetics in antibiotics is that not only the efficacy of the drug may increase but also the toxicity of certain drugs may decrease at different time of day. For example in aminoglycosides[17], renal toxicity of aminoglycosides can be reduced by giving the drug as a single daily injection when patients are active (at day time or in other words in the activity period) e.g.: Gentamycin, Tobramycin, Amikacin.

Antihypertensive drugs:

It is known that blood pressure, stroke volume, cardiac output, blood flow are higher in morning and decrease later in the day. Cmax was found to be higher and/or tmax shorter after morning than evening dosing of the lipophilic drugs (nifedipine, oral nitrates, propranolol). ACE inhibitors were found to be safe and effective when administered at bed time when compared to morning.[18]

Anti-inflammatory drugs:

It is found that they have greater rates and extents of bioavailability when administered in the morning than evening.eg. Indomethacin, Ketoprofen.

Anticancer drugs:

The blood flow to tumors and tumor growth rate are each upto three fold greater during each daily activity phase of the circadian cycle than during the daily rest phase. Normal human bone marrow DNA synthesis peaks around noon, DNA synthesis in malignant lymphoma cells peaks near midnight.[19] Therefore by treatment at mid night, more tumor cell kill could be achieved with same dose of S-phase active cytotoxic therapy and with relatively little bone marrow damage.

Opiod analgesics:

Stronger analgesic effects were observed when Tramadol and Dihydrocodeine were applied in the evening to relieve painful stimuli. Peak morphine use occurred at 9 a.m. and least use at 3 a.m. A study of Meperidine reveals a circadian variation of Meperidine-induced analgesia in sickle cell anemia patients, with maximal analgesic effect occurring with the morning dose.[20]

Anti-hyperlipidemic drugs:

More cholesterol systhesis takes place in the evening than in the morning. The enzyme HMG Co-A reductase is required to reduce hydroxy 3-methyl glutaryl Co-A to mevalonate in the synthesis of cholesterol. This enzyme is competitively inhibited by HMG Co-A reductase inhibitors (statins).[22] Hence, short acting statins should be administered at evening rather than at morning for increased efficacy.

Anti-migraine drugs:

Sumatriptan is a drug of choice in migraine treatment. The mean peak serum concentration, area under curve was significantly higher following the 07:00 h administration than after the 19:00 h administration.[23]

Local anesthetics:

The duration of local anesthesia was longest when amide-type local anesthetic agents (Lidocaine, Ropivacaine, Mepivacaine and Betoxycaine) were applied around 3 p.m. Area under the Lidocaine plasma concentration curves (AUC) was largest in the afternoon. The plasma levels of Lidocaine were significantly higher in the evening than at any other time of day.[24]

Clinical applications:

Chronopharmacology of bronchial asthma:

Bronchial asthma is the chronic airway inflammation characterized by paroxysmal cough, wheeze and dyspnoea. Episodes of difficulty in breathing peak in the early morning hours. 70% of all deaths from asthma occur between midnight and 8.00 am. Bronchial potency peaks at 4.00 pm, decreases during sleep and reaches nadir at 4.00 am. Asthmatics' overnight fall in potency is exaggerated from 25% to 50%.[25] In asthmatics, increase in resistance is much greater during sleep because of sleep associated reduction in inspiratory muscle tone, decrease in pulmonary compliance, increased intrapulmonary blood pooling which promotes airway narrowing. The circadian rhythm of biological rhythms is particularly important in understanding the declined changes in lung function of asthmatics at night.[26]

Long-term oral administration of corticosteroids at 8:00am and 3:00pm are more effective in controlling nocturnal asthma. Inhalational corticosteroids (ICSs), with or without long-acting beta agonists (LABAs), continue to be the mainstay of pharmacological treatment for mild-to-moderate asthma. Inhaled corticosteroids of single daily dose at 5:30 p.m. (vs 8 a.m.) was nearly as effective as four doses a day. The majority of LABAs are inhaled as aerosols (the advantage being delivery directly to the target area with fewer systemic side effects). LABAs can also be administered orally as tablets and as a transdermal preparation in the form of patches. Terbutaline is a LABA tablet formulation that was one of the first to be

assessed in chronotherapy trials. Montelukast is recommended for ingestion once daily in the evening; a double-blind study showed that montelukast better improved FEV1 when dosed in the evening than morning.[27]

Oral corticosteroids should be administered around 3 P.M. to achieve peak pulmonary anti- inflammatory efficacy between 3 A.M. and 6 A.M. Chronotherapy of a once-daily evening dose of a new controlled-release theophylline preparation, which achieves to peak blood concentrations at 10-12 hours after dosage, effectively improved the values of PEF and symptoms of nocturnal asthmatics. Single night time dose of theophylline is recommended for nocturnal bronchospasm because reduction in FEV, is, only 9% compared to 28% with two or more doses. Evening dosing of special drug delivery forms of theophylline and morning methylprednisolone administration has proven to be beneficial. Controlled-release theophylline preparations, which achieve peak blood levels 10-12 hours after dosage, should be administered immediately after the evening meal to give greatest efficacy between 3 and 6 A.M. when airflow reaches its nadir.[28]

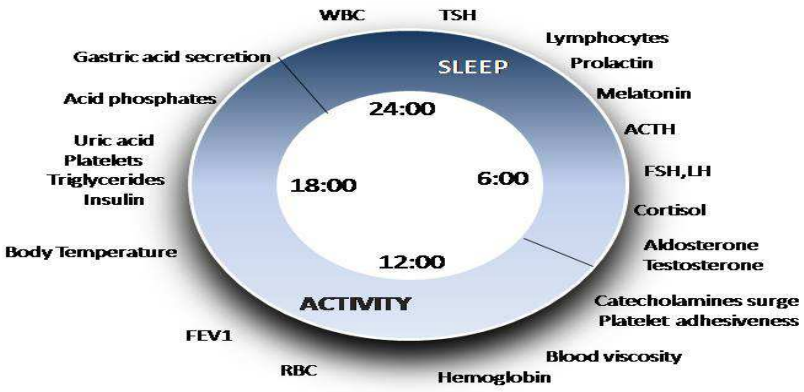

Image I: Display in the form of a 24 hr clock diagram of approximate time in humans following the diurnal activity/nocturnal sleep routine when symptoms of disease are worst [21]

Chronopharmacology of Gastic Ulcer: Under normal conditions, peak acid secretion occurs when other rhythms such as secretion of acid buffering substances, thickness of the protective lining and flow of blood naturally protects the mucosa.

Ulcer pain which is worst at night, usually 2 hours after food, wakes the patient in the night around 2 a.m. Stomach empties 2 hours after eating; residual acid and enzymes initiate ulcer, causing pain and discomfort.[29]

Also acid secretion peaks at night between 10 p.m. and 2 a.m. Antacids give temporary and partial relief by neutralizing stomach acid. Ulcer healing is directly related to how well acid secretion is inhibited during night time. Most of the drugs taken for this are lipophilic and are found to have higher rate of absorption in the early morning hours than any other time of the day. Omeprazole when given only in the morning before breakfast, or in two divided doses- morning and evening

or only at night before dinner, are all equally effective in preventing acid production during daytime but only B.D. and O.D. (evening dose) are effective in preventing night symptoms.[30]

Chronopharmacology of arthritis: Rheumatoid arthritis (RA), osteoarthritis (OA), ankylosing spondylitis (AS) and gout exhibit profound circadian rhythm in manifestations and intensity of symptoms.

a) Rheumatoid arthritis (RA):

It is chronic inflammatory autoimmune disorder with symptoms of stiffness, swelling and pain of one or more joints Severity of these are three times more between 08:00 and 11:00 am. Long acting NSAIDs like flurbiprofen, ketoprofen, indomethacin at bedtime ensure adequate control of morning symptoms of RA. Aspirin, non-acetylated salicylates, and numerous other nonsteroidal anti-inflammatory drugs (NSAIDs) are used in rheumatoid arthritis (RA) patients to decrease joint inflammation and improve function. Equivalent doses of aspirin and of non-acetylated salicylates are equally anti-inflammatory in RA.[31]

b) Osteoarthritis:

Pain is more intense between 2 p.m. and 8 pm. The temporal pattern of pain and stiffness varies from person to person. Individualized chronotherapy is necessary. If pain is worst at night, evening dose is recommended but if pain is worst in afternoon, morning dose is recommended.. Individualized chronotherapy is necessary, like once a day ketoprofen, indomethacin in relation to time of day when pain is worst. Solid dispersion of ketoprofen was found to be more effective in inhibiting progression of RA. The protective effect of ketoprofen and its solid dispersion was significantly higher when these were administered at 0800 hrs.[32]

Chronopharmacology of cardiovascular disorders:

Physiological functions as well as pathophysiological events– angina pectoris, myocardial infarction and sudden cardiac death- display pronounced circadian rhythms. Clinical studies also gives evidence for a circadian phase dependency in the pharmacokinetics of cardio-vascular active drugs. Ambulatory blood pressure assessment reveals marked circadian rhythms in blood pressure both in normotensive persons and hypertensive patients, whereas Holter monitoring substantiates day-night patterns in electrocardiographic events of patients with ischaemic heart disease.[33]

Blood pressure and heart rate in normotensives and essential (primary) hypertensive patients display highest values during daytime followed by a nightly drop and an early morning rise. In about 70% of forms of secondary hypertension (e.g. renal disease, hyperthyroidisms, hormonal diseases, gestational hypertension), however, this rhythmic pattern is abolished or even reversed exhibiting nightly peaks in blood pressure. This form of hypertension is accompanied by increased end organ damages. Thus, different subtypes of a disease (angina pectoris, hypertension) can display different circadian patterns in symptoms. These observations are a challenge for basic and clinical research to get a better understanding on the underlying mechanisms of regulation. Moreover, they call for a circadian time-specified drug treatment.

Epidemiologic studies document the heightened morning– time risk of angina, myocardial infarction and stroke. Circadian rhythms in coronary tone and reactivity, plasma volume, blood pressure, heart rate, myocardial oxygen demand, blood coagulation and neuroendocrine function, plus day-night patterns in the nature and strength of environmental triggers all contribute to this morning vulnerability. Circadian pattern of low blood pressure during night (resting span)- rather than day (active span) is called a dipper and inverse relationship is called as no dipper. Marked nocturnal fall of more than 80% of systolic blood pressure is more likely to have advanced silent

cerebrovascular damage than dipper or non-dipper. Furosemide when administered at 9 p.m. shows increase in urine volume and increased excretion of Na^+, Cl^- during first 60 minutes than when drug is administered at 9 a.m. Elevation of blood glucose concentration is more after an evening dose. For thrombolytics and heparin**,** minimal benefit for ischaemic events is during the early morning hours. Labetolol is more successful in controlling early morning rise in blood pressure.[34]

Chronopharmacology of cancer:

Cancer is regarded as a disease of malfunctioning internal clock because cancer cells lose their internal timekeeper and divide more rapidly than normal cells.[35] The chronomodulation of anti-cancer drugs arouses our interest as a method for cancer chemotherapy. Recent clinical studies reviewed regarding circadian rhythms in 1) target tissues: healthy and cancer tissues; 2) chronopharmacology of anticancer drugs; and 3) chronotoxicity of anticancer drugs

Studies suggest that chronobiological cycles for normal cells and tumour cells are different. Therefore, treatment goal is to time the administration of cancer drugs to the chronobiological cycles of tumour cells, making it more effective against cancer cells and least toxic to normal tissues. Studies in experimental models are required to understand the relation between tumor rhythms and antitumor treatments efficacy.[36] In healthy tissues, cell proliferation, and differentiation processes are regulated precisely and exhibit marked circadian rhythmicity. Experimental and human tumors can retain circadian rhythms or display altered oscillations. Healthy tissues can also display rhythm modifications, possibly related to cancer stage. Cellular rhythms modulate the metabolism of cytotoxic agents and the cellular response to them; hence, they determine the chronopharmacology of anticancer drugs. Results of laboratory animal studies have been extrapolated to the design of clinical cancer therapy trials involving a chronobiological approach.[37] Many physiological variables in hemato-oncology, e.g. the function of liver and kidney and hematopoiesis, show circadian changes. Consequently, the metabolism, elimination and toxicity of these drugs are subjected to circadian variations in animal and man. Moreover, preliminary clinical data suggest that an optimal circadian timing may even increase the efficacy of anticancer chemotherapy.

Chronopharmacology of Skin Disorders:

Similarly to other organs, the skin is under the influence of a coherent organization of circadian rhythms modulating various biological cycles which usually display wide amplitude.

Chronophysiology, chronopathology and clinical chronopharmacology may help reach optimal therapeutic decisions. Proliferation of skin cells varies up to 30 folds in 24 hours, being greatest at midnight and least at noon. Oil production by skin glands is twice as great at noon than between 02:00 and 04:00 a.m. [38]

Skin is more acidic during sleep than around midday. The cutaneous biorhythms in humans suggest that during daylight the skin boosts diverse protective functions with regard to environmental threats. In the evening and at night, the skin increases its renewal and diverse metabolic processes .In atopic dermatitis, itching is most intense late in evening because skin sensitivity to histamine is highest at night.

In psoriasis, cell proliferation rate of the affected skin is more than normal skin. Cell proliferation rate in areas of psoriasis is highest between 9 p.m. and 3 a.m. and least between 09:00 and 11:00 a.m. In dermis, cell proliferation is maximum at 9:00 a.m. and least at 03:00 a.m. Inflammatory activity is highest at night and least in the morning.[39]

Table I: Examples of disease states with chronopharmacology application[41]

THERAPEUTIC AREA	DISEASE OR CONDITION	CHRONO – PHARMACOLOGY RATIONALE
Cardiovascular	**Angina**	Angina (variant) attacks occur 30 times more often between 2:00 a.m. and 4:00 a.m. -> **Larger doses of Nitorglycerin early in the morning.**
	Heart Attacks and Strokes	Heart attacks and stroke are most likely between 6:00 a.m and Noon-> **Cardiovascular active drugs before waking.**
	Hypercholesterolemia	A circadian rhythm occurs during hepatic cholesterol synthesis, which is generally higher during the night than during daylight. Studies with HMG CoA reductase inhibitors suggest that evening dosing is more effective than morning dosing. **->Simvastatin in evening and during night.**
	Hypertension	Automatically and precisely release clonidine or other hypertension drugs in peak amounts to offset the peak symptoms associated with the dangerous morning symptoms**.->** **Clonidine, Captopril or other medication in the morning.**
CNS Degenerative Disorder	**Parkinson's Disease**	Automated dosing for patient compliance ->**Selegiline, Benztropine, Apomorphine**
	Alzheimer's Disease	Automated dosing for patient compliance ->**Rivastigimine, Mematine**
Diabetes	**Diabetes (Type II)**	Automated dosing for elderly patient compliance. Oral medication is poorly absorbed. **->.Miglitol before meals.Sulfonylureas 20-30 min before food, alpha glucosidase inhibitors: with food**
Epilepsy	**Epileptic seizure**	Epileptic seizures are most likely between 6:00 a.m. and 7:00 a.m. **->Gabapentan or other Epileptic drugs before waking up.**
Inflammation	**Rheumatoid Arthritis,**	Worst upon awakening. Cortisol and anti-inflammatory hormones are very low at night ->

	Osteoarthritis	**Indomethacin or Valdecoxib before waking up.**
Mental Health	**Depression**	Selegiline at night can create sleeping disorders (nightmares), but depression symptoms are high immediately upon waking up->**Selegiline before waking up.**
OTC	**Smoking Cessation**	Nicotine at night creates sleeping disorders (nightmares), but cravings are highest immediately upon waking -> **Nicotine before waking up.**
	Circadian rhythm sleep disorders and Morning Lethargy	Adrenaline is lowest in the morning, making early morning waking uncomfortable and difficult for many people. -> **OTC stimulant before waking**
	Insomnia	Some sleep medications induce drowsiness but do not provide for continuous sleep in sensitive patients. -> **Pulsatile and low dose delivery of sleep medication will provide continuous sleep.**
	Peptic ulcer disease	Gastric acid secretion increases in late afternoon and early night. Also, partial nocturnal resistance to H2- blockade has been noted. -> **H2- blockers (ranitidine, cimetidine, famotidine, roxatidine, nizatidine) during the night. Drugs other than H2- blockers or antibiotics during the night.**
	Jet lag Shift work	Melatonin can be used reset circadian rhythms.
	Colds and Flu	Heaviest symptoms overnight and in the morning. -> **Cold/ Flu medicine during the night. Triprolidine, Doxylamine.**
	Supplements/ weight loss	Vitamins and Supplements are best administered in low doses over the course of the day to be most effective.
Pulmonary	**Asthma**	Asthma attacks are 100 times more likely between 4:00a.m. and 6:00 a.m. Adrenaline and cortisol are virtually absent at night. ->**Albuterol or Tulobuterol in early morning.**
Pain	**Acute Pain**	Neurological pain is worst between 3:00 a.m. and 8:00 a.m. -> **Fentanyl in the middle of**

		night.
	Migraine Headaches and / or cluster headaches	Migraine headaches usually begin and occur between 8:00 a.m. and 10:00 a.m. Cluster headaches start earlier, around 4:00 a.m. ->**Zolmitriptan or dihydroergotamine in the middle of night.**
Women's Health	**Tocolytic Therapy**	Programmed – in – time administration of tocolytic medication relative to the circadian rhythm in uterine contractility to avert preterm labor and birth. ->**Nifedipine, Terbutaline or Ritodrine synchronized with uterine contractions.**

Chronopharmacology of Central Nervous System disorders:

Rhythms are present in the level of intracerebral neurotransmitters, receptors and second messengers. Each of these rhythms may cause other rhythms within each system of neurotransmitters, which in turn induces a rhythm in the susceptibility to drugs. The effects of many kinds of psychotropic drugs have been shown in animal studies to follow a circadian rhythm. Trials for the clinical application of this circadian rhythm have already been undertaken. Although the mechanisms underlying this phenomenon are still unclear, chronological changes in the levels of drugs in the blood and brain suggest that it is primarily due to rhythms in the brain's susceptibility to drugs.[40]

The conception of the specific activity of antidepressants is considered from the chronobiological positions. Depression can be based on phasic dissociation between different periods. Various antidepressants modified biorhythms and promoted their resynchronization. This action probably depended on its influence on the activity of the cerebral pacemaker structures (Suprachi asmatic nuclei, hypothalamus and pineal gland).

Role of Pulsatile drug delivery system:

These delivery systems helps in diseases having predictable cyclic rhythm and timing of medication can improve the outcome of desired effect. Nowadays, greater attention is given on development of sustained, controlled, and delayed release system.Conditions demands release of a drug as a pulse after a lag time and rapid drug release after a lag time is required.

Different types of them are available like Enteric-coated systems, Pulsin cap systems. Osmotic systems, Diffucaps, Time-controlled explosion systems (TES) and Press-coated systems.

Enteric coated system: Enteric coatings have traditionally been used to control the release of a drug in the stomach. Enteric coatings are pH sensitive and drug is released when pH is raised above 5 in the intestinal fluid. These formulations can be utilized in time-controlled drug administration when a lag time is needed.

They contain a core which is film coated with two polymers, first with HPMC(hydroxyl propyl methyl cellulose) and then with a gastro-resistant polymer.The duration of the lag phase in absorption can be controlled by the thickness of the HPMC layer.

Pulsincap: It is a delivery system which releases drug contents at a predetermined

time or at a specific site within the gastrointestinal tract. Each capsule is composed of a water insoluble body and a water soluble cap, and also contains the drug dose 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.

The dimension of the plug and its position in the capsule can be varied and the system delivers drug at exactly the programmed time, 1 to 10 hours after drug administration, to various regions of the gut.[42]

Osmotic system: Elementary osmotic pumps can be useful for delivering drugs based on chronotherapeutic requirements. Device consists of a drug layer and a push layer, are two membranes. The first is a semi-permeable insoluble membrane while the second is a release delaying hydrophilic polymer coat. Gastrointestinal fluid penetrates the semipermeable membrane, and as it enters the drug layer and push layer via the hydrated coat (within 4 to 5 hours), the push layer expands, pressing against the drug layer and causing drug release at a constant rate for 18 hours. If taken at bedtime, the system provides optimal drug concentration when the patient wakes up and during day time. Example: Salbutamol, initially at a constant delivery rate, then as a final pulse dose. Such a system could deliver a dose during a nocturnal asthma attack. Controlled onset extended-release (COER-24) verapamil formulation was tailored to the circadian rhythm of blood pressure and heart rate to better cover early morning symptoms of cardiovascular diseases.[43]

Diffucaps: In this one or two impermeable or semipermeable polymeric coatings (films or compressed) is applied on both sides of the core. It is a three-layer tablet system to allow biphasic drug release.The two layers both contain a drug dose. The outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug.

Example- L- dopa/benserazide used in the treatment of Parkinsonism.

Time controlled explosion system: These have been developed for both single and multiple unit dosage forms. In this, the core contains the drug, an inert osmotic agent and suitable disintegrants. Individual units is coated with a protective layer and then with a semipermeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. As water reaches the core, osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of the formulation can also be achieved through the use of swelling agents. Lag time is controllable by varying the thickness of the outer polymer coating.[44]

Press coated system: Delayed-release and intermittent-release formulations can be achieved by press-coating. Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat.

Materials such as hydrophilic cellulose derivatives can be used and compression is easy on a laboratory scale. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process.Ex- Diltiazem, furosemide, ibuprofen and salbutamol.[45]

In these ways, newer drug delivery systems have helped in utilization of property of chronopharmacology of various drugs in day to day clinical practice.

Conclusions:

The last decade has witnessed the emergence of chronopharmaceutical drug delivery systems against several diseases.

The increasing research interest surrounding this may lead to the creation of a new sub-discipline in pharmaceutics known as chronopharmaceutics. Future development in chronopharmaceutics may be made at the interface of other emerging disciplines such as System biology and Nanomedicine. Such novel and more biological approaches to drug delivery may lead to safer and more efficient disease therapy in the future.

The ever expanding field of chronopharmacology has opened many doors in research and development for designing better ways to align and administer the therapy for various diseases. In order to translate research data into clinical application, significant progress in the characterization of circadian variations in protein expression and activity in humans is absolutely necessary. Therefore, the knowledge of chronopharmacology is not limited to the biologists, pharmacologists and scientists but also to clinicians so that there is better delivery of patient care.

References:

1. Lemmer B, Labrecque GC Chronopharmacology and Chronotherapeutics. Chronobiol Int 1987:319-29.
2. Millar-Craig MW, Bishop CN, Reftery EB. Circadian Variation of blood pressure. Lancet 1978:795-99.
3. Van CE, Polonsky KS, Scheen AI. Roles of circadian rhythmicity and sleep in human glucose regulation: Endocr Rev 1997:716-38.
4. Watanabe H, Nakano S, Nagai K, Ogawa N. Time-Dependent Absorption of Theophylline in Man. J Clin Pharmacol 1984; 24: 509–15.
5. Evan RM, Marain C. Taking Your Medication: A Question of Timing. Chicago IL: American Medical Association 1996: 3-8.
6. Ura I, Shirachi D, Ferrill M. The Chronotherapeutic Approach to Pharmaceutical Treatment. California Pharmacist 1992: 46-53.
7. Lamberg L. Chronotherapeutics: implications for drug therapy. American Pharmacy 1991:20-23.
8. Lemmer B. Discoveries of rhythms in human biological functions: a historical review. Chronobiol Int 2009; 26: 1019–68.
9. Abraham U, Granada AE, Westermark PO, Heine M, Kramer A, Herzel H. Coupling governs entrainment range of circadian clocks. Mol Syst Biol 2010; 6: 438.
10. Smolensky MH, Labreque G. Chronotherapeutics Pharm News 1997:10-16.
11. Fujimura A Tateishi T, Ohashi K, Ebihara A. Differences of of chronopharmacokinetic profiles between propranolol and atenolol in hypertensive patients. J Clin Pharmacol 1993:756-61.
12. Lemmer B, Portaluppi R. Chronopharmacology of Cardiovasular Diseases: Physiology and Pharmacology of Biological Rhythms. Mannheim Springer Verlag 1997: 251-83.
13. Clench J, Reinberg A, Dziewanowska Z, Ghata J, Smolensky M. Circadian changes in the bioavailability and effects of indomethacin in healthy subjects. Eur J Clin Pharmacol 1981; 20 (5): 359-69.
14. Padmanabhan K, Robles MS, Westerling T, Weitz CJ. Feedback regulation of transcriptional termination by the mammalian circadian clock PERIOD complex. Science. 2012; 337: 599–602.
15. Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nature reviews. Neuroscience 2010; 11: 589-99.
16. Savvidis C, Koutsilieris M. Circadian rhythm disruption in cancer biology. Molecular medicine 2012; 18: 1249–60.
17. Panda S, Antoch MP, Miller BH, Su AI, Schook AB, Straume M et al. Coordinated transcription of key pathways in the mouse by the circadian clock. Cell 2002; 109: 307–20.

18. Storch KF, Lipan O, Leykin I, Viswanathan N, Davis FC, Wong WH et al. Extensive and divergent circadian gene expression in liver and heart. Nature 2002; 417:78–83.
19. Gachon F, Olela FF, Schaad O, Descombes P, Schibler U. The circadian PAR-domain basic leucine zipper transcription factors DBP, TEF, and HLF modulate basal and inducible xenobiotic detoxification. Cell metabolism 2006; 4: 25–36.
20. Elliott WJ. Timing treatment to the rhythm of disease. A short course in chronotherapeutics. Postgrad Med 2001; 110(2):119-22, 125-6, 129.
21. Smolensky MH, Labrecque G. Chronotherapeutics. Pharmaceutical News 1997; 4:10–16.
22. Martin RJ, Banks-Schlegel S. Chronobiology of asthma. Am J Respir Crit Care Med 1998; 158(3): 1002-07.
23. Anwar Y, White WB. Chronotherapeutics for cardiovascular Disease. Drugs 1998: 631-43.
24. Jouffe C, Cretenet G, Symul L, Martin E, Atger F, Naef F et al. The circadian clock coordinates ribosome biogenesis. PLoS Biol 2013; 11(1):e1001455.
25. McGlincy NJ, Valomon A, Chesham JE, Maywood ES, Hastings MH, Ule J. Regulation of alternative splicing by the circadian clock and food related cues. Genome Biol 2012; 13(6): R54.
26. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Thorax 2014:69.
27. Koike N, Yoo SH, Huang HC, Kumar V, Lee C, Kim TK et al. Transcriptional architecture and chromatin landscape of the core circadian clock in mammals. Science 2012; 338: 349–54.
28. Le Martelot G, Canella D, Symul L, Migliavacca E, Gilardi F, Liechti R et al. Genome-wide RNA polymerase II profiles and RNA accumulation reveal kinetics of transcription and associated epigenetic changes during diurnal cycles. PLoS Biology 2012; 10:e1001442.
29. Sanders SW, Moore JG. Gastrointestinal chronopharmacology: Physiology, pharmacology and therapeutic implications. pharmacology and therapeutics. 1992; 54(1):1–15.
30. Boardman PL, Hart FD. Clinical measurement of the anti-inflammatory effects of salicylates in rheumatoid arthritis. Br Med J . 1967; 4(5574): 264–68.
31.Vener KJ, and Archana Reddy. Timed treatment of the arthritic diseases: a review and hypothesis. Seminars in arthritis and rheumatism. WB Saunders 1992; 22(2).
32. Menet JS, Rodriguez J, Abruzzi KC, Rosbash M. Nascent-Seq reveals novel features of mouse circadian transcriptional regulation. eLife 2012; 1:e00011
33. Lemmer B, Portaluppi R., "Chronopharmacology of Cardiovascular Diseases", Physiology and Pharmacology of Biological Rhythms, Mannheim, Springer, Verlag; 1997, p. 251-283.
34. O'Neill JS, Maywood ES, Chesham JE, Takahashi JS, Hastings MH. cAMP-Dependent signaling as a core component of the mammalian circadian pacemaker. Science 2008; 320(5878): 949–53.
35. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annual review of physiology 2010; 72:517.
36. Yamazaki S, Numano R, Abe M, Hida A, Takahashi R. Resetting central and peripheral circadian oscillators in transgenic rats. Science 2000; 288:682–85.
37. Jin X, Shearman, LP, Weaver DR., Zylka, MJ, de Vries GJ. Reppert, SM. A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. Cell 1999; 96:57–68.
38. Kalsbeek A, Van Heerikhuize JJ, Wortel J, Buijs R M.. A diurnal rhythm of stimulatory input to the hypothalamo-pituitary-adrenal system as revealed by timed intrahypothalamic administration of the vasopressin V1 antagonist. J Neurosci1996; 16: 5555–65.

39. Zylka MJ, Shearman LP, Weaver D R, Reppert SM. Three period homologs in mammals: diŠerential light responses in the suprachiasmatic circadian clock and oscillating transcripts outside of brain. Neuron 1998; 20: 1103–10.
40. Ripperger J A, Shearman L P, Reppert SM. Schibler U. Clock, an essential pacemaker component, controls expression of the circadian transcription factor DBP. Genes Dev 2000; 14:679–89.
41. Kume K, Zylka MJ, Sriram S, Shearman LP, Weaver DR, Jin X, et al. mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. Cell 1999; 98:193–205.
42. Youan BB. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? J Control Release 2004; 98:337–53.
43. Ueyama T, Krout KE, Nguyen XV, Karpitskiy V, Kollert A, Mettenleiter T C, et al Suprachiasmatic nucleus: a central autonomic clock. Nature Neurosci 1999; 2: 1051–53.
44. Silver R, Lesauter J, Tresco PA, Lehman MN. A disusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. Nature 1996; 382: 810–13.
45. Arora S, Ali J, Ahuja A, Baboota S, Qureshi J. Pulsatile drug delivery systems: An approach for controlled drug delivery. Ind J Pharm Sci 2006; 68:295-300.

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