Chronopharmacology: A Great Future for the Medicines

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***Abstract*: Chronopharmacology is helpful to solve problems of drug dose optimization i.e. improve the efficacy or reduce undesired effects. In the human the metabolic fate of a pharmacological agent is not constant as a function of a time. Thus during metabolic it is much useful chronobiological approach of pharmacological phenomena it includes a lesser risk of errors. Chronobiology is the branch of science which examines periodic phenomenon in living organisms and their adaptation to biological rhythm. These biological rhythms can be yearly, monthly, daily or more frequent. Daily (24hr) rhythms are called as CR. Chronopharmacology is the branch of science which take into account the influence of time. It is concerned with the effects of drug upon the timing of biological events and rhythms and the relation of biological timing and endogenous periodicities to the effect of drugs. It further deals with chronotherapeutics, chronokinetics, and chronotoxicity. The circadian rhythms in mammals are maintained and regulated by the master clock in brain called as Supra chiasmatic nucleus (SCN) present inhypothalamus. Circadian rhythms deal with the cyclic changes occurring in day and night which depends on absence and presence of light. When the light falls on the retina, the light sensitive ganglion cells act as receptors and sends signals to SCN through retinohypothalamic tracts. SCN either directly by influencing pineal gland which releases melatonin or indirectly by influencing autonomic nervous system regulates different physiological activities. Biological rhythms were affect on various system. Circadian rhythms are also exhibited by many diseases. Some drugs in absorption (A), distribution (D), metabolism (M) and excretion (E) in relation to time. During the CR hanges in ADME and takes into account the influence of time of administration on these different processes is called as chronopharmacokinetics either chronokinetics.**

***Keywords*: Chronopharmacology, Chronopharmacokinetics, Circadian rhythms (CR), Suprachiasmatic nucleus, Chronotherapeutics, Pulsatile drug delivery system.**

Introduction:

Various metabolic functions are changed in daily routine of the day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based changes leads to sleep-activity cycle, Chronopharmacology affects the body's functions day and night (24-hour period). The presence of 24-hour rhythms in receptors and cell metabolism explain why in the face of a constant concentration of a drug the cell response changes (Chronoesthesy)[1]. The dependence of body functions in certain disease conditions states on circadian rhythm is well known. For example number of hormones are released by the brain in the morning, while others are released during sleep. Blood pressure and heart rate both are highest during the hours of 6.00 a.m. to 12.00 noon. The normal working of all living creatures are influenced by change with time, result on affect on biological rhythms. Change in time at each level of an organism, whole body interactions. These are rhythms can be yearly (circannual), monthly, daily (circadian) or more frequent (pulsatile). Predetermined (biological clock) but can be influenced, modulated by environmental factors (time-trigger). Chronobiology is the branch of science which examines periodic phenomena in living organisms and their adaptation to biological rhythms. Chronotoxicology describes the daily changes in the activity of toxic agent on a given organism [2].

In case of Chronopharmacology it divides it to three in subtypes.

a) Chronophysiology

b) Chrono pathology

c) Chrono pharmacology

Chronopharmacology:-

Chronopharmacology is the branch of chronobiology concerned in this effect of drug upon the timing of biological events and cycles related to biological timing and endogenous periodicities to the effect of drugs. When a drug administered the pharmacological action of the drug can be predicted based on the body circadian rhythm. It is feasible correlate with body functions and time. In the same way as sleep – awake, feed hunger, joy depression are regulated by the biological clocks, the maximum efficacy and minimum toxicity of a drug can be achieved if it is administered at appropriate time i.e. right drug in the right form at right dose at right time.So the given drug acts synergistically with biological clock. Clock[3]. Pharmacology is based on circadian rhythms which are important in medicine. A circadian clock in the brain coordinates daily physiological cycle.

Choice of Chronopharmacology

Auto induction:-

Multiple, repeated dose increases enzymes responsible for its elimination there will be is known as auto induction increasing its clearance. This is called as auto induction. It depend on dose and concentration of the drug. It has a number of therapeutic consequences. It impacts the time to achieve steady state and limits one's ability to use information from a single dose to multiple dose taken kinetics continuous administration. Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration that either oral bioavailability decreases or clearance increases withtime.

Auto inhibition:-

It may occur during the metabolism of certain drugs. The metabolites formed from drug firstly increase in concentration and further inhibit metabolism of the parent drug. This phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition.

Chrono pharmacology further deals with[4]

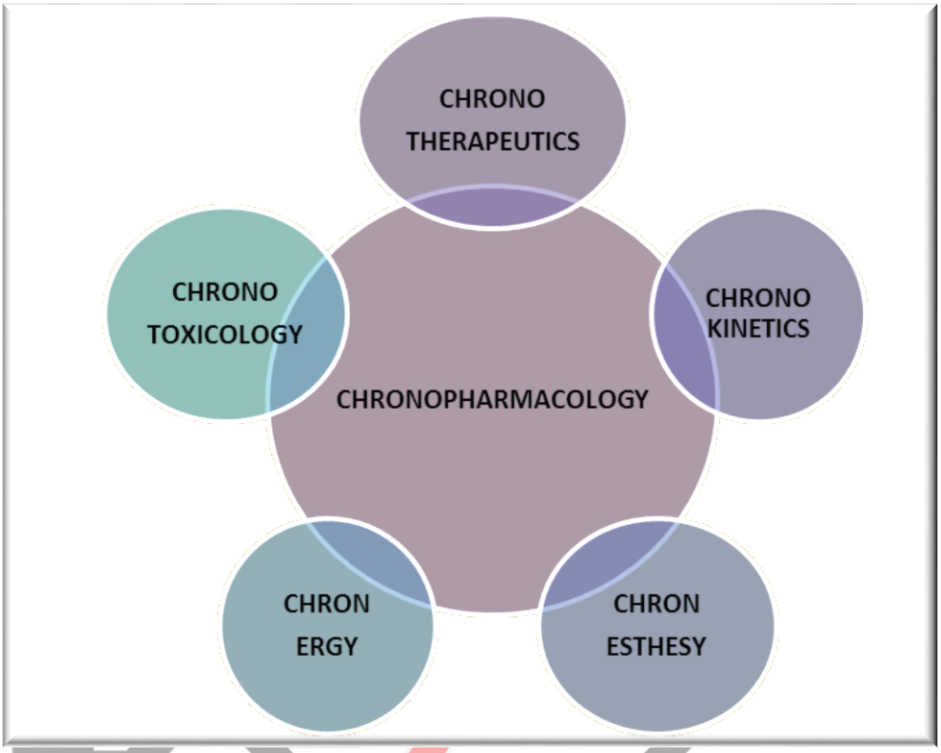

Fig. 1: Chronopharmacology and its disciplines.

Chronotherapeutics:

In this 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. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs. As more continues to be learned about chronobiology and chronotherapeutics, it is becoming increasingly more evident that the specific time that patients take the medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, attempt to maintain constant drug levels throughout a 24-hour period, may bechanging as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms[5]. One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated [6].

Advantages of Chronotherapeutics:

1. It prevents an overdosing of drug.
2. It makes the utilization of the drug more appropriate.
3. It reduces unnecessary side effects of a drug and helps in caring out the treatment for only a particular or limited period of time.

Need for Chronotherapeutics: -
It is required to observe therapy to limit the duration of therapy especially in cases where patients are already having renal, cardiac and hepatic other function of the body. Accumulation of drugs in these organs causes greater toxicity which may diminish function of the organ. Thus, the chronotherapeutics becomes a very important part of treatment of diseases particularly those effecting targeted body parts. According to the 1996 American medical association review, consideration of chronotherapy clinical trials is highly welcomed by the whole medical community.

Chronopharmacokinetics
Chronopharmacokinetics the study changes in drug absorption, distribution, metabolism and excretion. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity. Numerous chronopharmacokinetic studies been conducted over the last 20 years. The results of these studies demonstrate that time of administration affects drug kinetics. Studies in man have been reported, particularly in relation to cardiovascular active drugs, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, anticancer drugs, psychotropic drugs, antibiotics anti-asthmatic drugs. Most of the drugs seem to have a higher rate or extent of bioavailability when they are taken in morning than when they are taken in the evening.

Chronesthesy:
It deals with circadian or other systemic changes in the susceptibility and sensitivity of the target system to a drug.

Chronergy:
It deals with rhythmic difference in effects of drug on the organism as a whole which includes both desired and undesired effects.

Chrono toxicology:
It is an aspect of chrono dynamics; it refers specifically to dosing time i.e. rhythm dependant differences in the manifestations and severity of adverse effects and thus intolerance of patients to medication. The term circadian comes from Latin word circa means 'about' and dian means 'day'. Circadian rhythms are most important type of biological rhythms and are most significant for humans and animals. They play an important role in maintaining body temperature, heart rate, blood pressure, organ blood flow, pulmonary and kidney functions as well as for concentration of neurotransmitters, hormones, enzymes, electrolytes and glucose. Study of rhythms is important for pharmacotherapy[8]. Chronotherapy coordinate drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart diseases and cancer.

Mechanism of Circadian Rhythms
Circadian clock present in brain coordinates daily physiological cycle like
- Sleep wake cycle
- Digestion and temperature
- Hormones

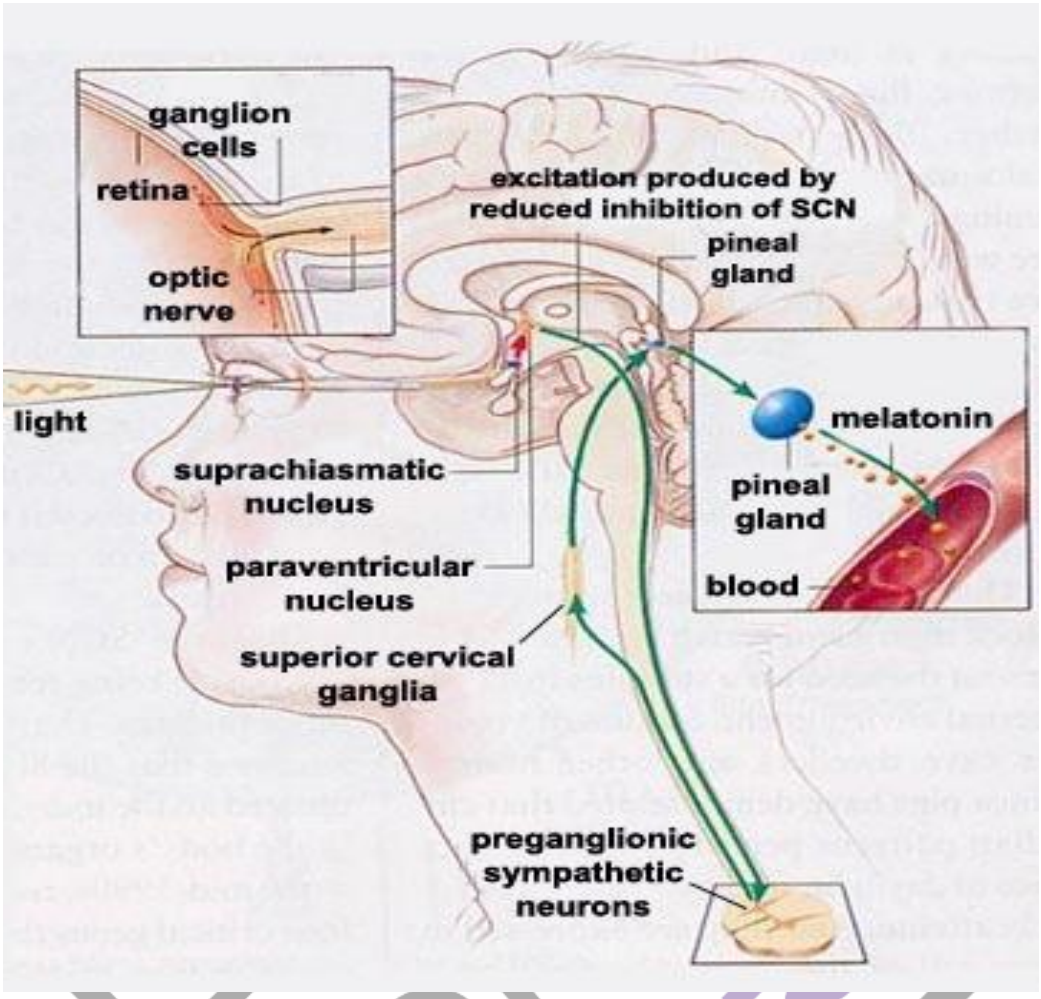

Fig 2: Supra chiasmatic nuclei (SCN) and pineal gland location.

Biological clock synchronises with environmental conditions, the circadian clock resides in two clusters of nerve cells called the suprachiasmatic nuclei (SCN), which are located in a region at the base of the brain called the anterior hypothalamus. Information on day light or its limitation by artificial illumination is received by retina cells and project via the retino hypothalamic tract into the SCN in the hypothalamus. Special light sensitive ganglion cells act in the retina as brightness receptors and send appropriate information useful for the regulation of circadian rhythms.

SCN uses its connection with the autonomic nervous system for its time of day message by setting the sensitivity of endocrine glands (thyroid, adrenal, and ovary) or by directly controlling on endocrine output of pineal gland (i.e. melatonin synthesis).Circadian rhythms are also reflected in the robustly rhythmic behavioural and physiological outputs, such as feeding, sleep-wakefulness, hormone secretion and metabolic homeostasis.

Rhythmic Components: -

Circadian major periodic components of biological rhythms are found around 24 hours (circadian) and 30 days (Circamensual) and one year (Circannual). Circadian rhythms are found in all the organisms; in fact the existence of circadian rhythms in living organisms was first established during a detailed study of leaf movement in plants more than 200 year ago. Biological rhythms possess both an internal as well as external components. Rhythmicity detected for a number of physiological variables like pulse, temperature, blood pressure, hormonal secretion via variation in effects of insulin on blood glucose [9].

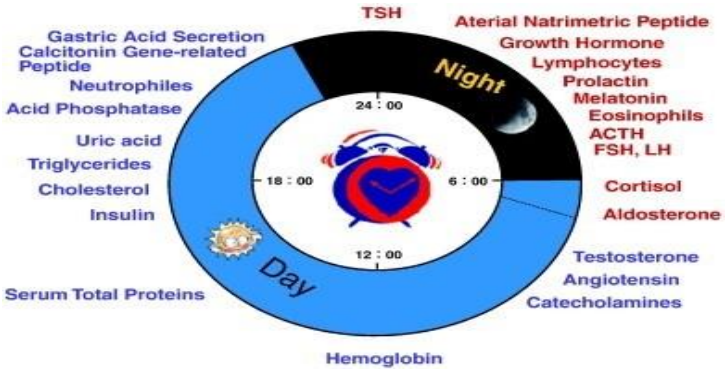

Fig.3 Human Circadian Time Structure

Symptoms of a disease play circadian variation, drugs release should also vary over time. Chronopharmaceutical drug delivery system gaining importance in the field of pharmaceutical technology as the system deliver right dose at specific time at a specific site. Various technologies such as time- controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chrono pharmaceutical drug delivery.[10] Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24- hours period [11]**.** Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy and this brought a new approach to the development of drug delivery systems [12].

Biological Rhythms Observed in Various Biological Systems

1. Urinary system

Circadian variations in urine volume, electrolyte excretion, micturition frequency, volume per void, and urine and output rates have been extensively studied. For example, water and electrolyte excretion is significantly low during the sleep phase compared with active daytime in healthy.

2. Gastrointestinal system

The gastrointestinal motility blood flow to stomach and enzymatic action are not the only factors that influence the gastro intestinal absorption of the drug. It also depends on circadian rhythms and it is influenced by time of the day. Biological rhythms are responsible for daily food intake; the period of hunger and satiety is controlled by the central pacemaker, SCN. It has been found that clocks in the GIT are responsible for the periodic activity (PA) of its various segments and transit along the GIT; they are localized in special cells, with unstable membrane potentials located between the longitudinal and circular muscle layers. The rhythm of slow waves is controlled in various segments of the GIT: in the stomach (about 3 cycles per min), in the duodenum (12 cycles per min), in the jejunum and ileum (from 7 to 10 cycles per min), and in the colon (12 cycles per min).

3. Hepatic system

Circadian regulation plays a large role in liver metabolism, as glucose, bile acids, lipids and cholesterol are all subject to timed circadian control. In normal humans, blood glucose and insulin levels in response to an oral glucose load vary over 24 h, with lower glucose response and higher insulin levels occurring in the morning, regardless of fasting duration, resulting in increased glucose tolerance in the morning compared to evening. Leptin a hormone which is secreted by the white adipose tissue displays a circadian rhythm. It regulates the sensation of hunger by binding to the receptors in the hypothalamus as well as those which are present on liver. Obesity is caused due to increase in the levels of leptin. Usually leptin is at its peak in the night than in the morning.

4. Cardiovascular system

CVS activities show circadian rhythm and cardiac electrophysiological properties change the cardiovascular system, exercise cycles. Blood pressures are highest in afternoon and decrease in evening and attain lowest values at nights which are due to circadian rhythms in nervous and endocrine system. Myocardial infarction occurs frequently in morning as a result of several physiological and biochemical conditions.

5. Hormones

Different hormones, like melatonin, cortisol, thyroid stimulating hormone (TSH), and prolactin (PRL), vary across the 24-hour day and are highly regulated by the circadian and sleep-wake cycles.Hormones, as well as other physiological rhythms like body temperature, play a role in sleep organization and can also be affected by sleep itself (or lack thereof) [13].

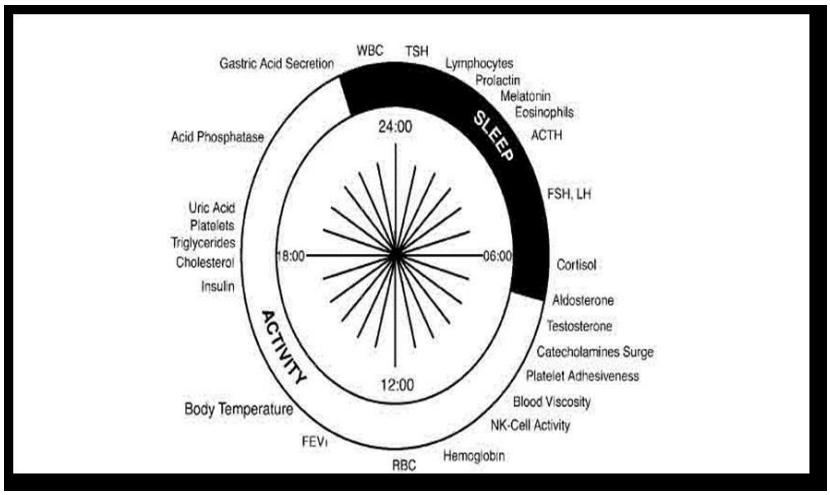

Fig 4: Hormones and different physiological activities showing circadian rhythms

Diseases exhibiting Circadian Rhythm

1. Allergic Rhinitis

Allergic rhinitis is associated with symptoms sleep disturbances, daytime somnolence and fatigue. These symptoms can interfere with sleep quality. The nasal congestion which causes sleep-disordered breathing is responsible for rhinitis related sleeps disorders. The severity of nasal decongestion is thought to be worst during night and in the early morning [14].

2. Bronchial asthma

Airway hyperresponsiveness and decreased lung function are exaggerated during night time and in the early morning. This is due to circadian changes in the neurotransmitters like epinephrine, AMP, Histamine and other inflammatory mediators, cortisol, vagal tone, body temperature, lower airway secretions favours nocturnal bronchoconstriction[15].

3. Arthritis

Clinical signs and symptoms in arthritis depend on the time. The symptoms of arthritis such as joint stiffness and pain are more prominent in the early morning. This is due to the diurnal rhythmicity exhibited by the production of proinflammatory cytokines which are at peak during night and early morning at the time when cortisol (anti-inflammatory) is lowest and melatonin (proinflammatory) is highest. Sex hormones also play a role in circadian rhythms of arthritis. The symptoms are common in luteal phase when the production of oestrogen and progesterone is higher than in the follicular phase [16].

4. Angina pectoris and Myocardial infarction

A number of physiological functions exhibit diurnal variations including Blood pressure, heart rate, coronary blood flow, platelet function, blood coagulability and fibrinolytic activity. The systemic BP and heart rate are increased in the early morning and therefore the oxygen demand of the heart is augmented. This can lead to sudden cardiac death.

5. Peptic ulcer disease

Stomach acid secretion is 2-3 times greater between 22:00 and 02:00 than in the day. In addition, eating and drinking immediately stimulates stomach acid production. Daytime heartburn symptoms arise from meal-triggered acid secretion, while night time ones result from the circadian rhythm of stomach acid production that peaks at night. Peptic ulcer disease exhibits 24 hours as well as weekly and annual cycles [17].

6. Stroke

The incidence of stroke is in similarity with other cardiovascular events showing high incidence rate in the early morning after awakening and lowest incidence during nocturnal sleep. This typical diurnal variation has been found in number of cardiovascular diseases like myocardial infarction, stroke (thrombotic or intracerebral or subarachnoid haemorrhage), angina (stable, unstable, or silent) and sudden death. Morning awakening is accompanied by an abrupt increase in sympathetic nervous system activity (as central mechanism) that results in an increase in blood pressure and heart rate, as well as platelet aggregability, and a reduction in fibrinolytic activity. These simultaneous changes cause vasoconstriction, an increase in wall resistance and thrombogenesis and can lead to stroke.

DRUGS UNDERGOING CHRONOKINETCS

1. Antibiotics

The important aspects of chronokinetics of antibiotics are followings-
a) Antibiotics show temporal variations in their pharmacokinetics in a 24hr cycle.

b) The efficacy of antibiotics is determined by the time at which the concentration is greater than minimum inhibitory concentration.

c) It not only increases the efficacy but also decreases the toxicity of antibiotics.

Examples

- **Amino glycosides:** the renal toxicity of aminoglycosides like amikacin and gentamicin can be reduced by giving the drug as a single daily injection when the patients are active i.e at day time or in the activity period [18].
- **Cephalosporins:** the toxicity of ceftriaxone is decreased by administering it at night as its total clearance value is highest during night and lowest during day time.
- **Floroquinolones:** the elimination of ciprofloxacin was found to be greater when the drug is administered at 10am than when it was administered at 10pm.
- **Ampicillin:** the renal and biliary clearance of ampicillin was greater at day time (activity period) than at night time.

2. Anti hypertensive drugs

- The rhythms in the blood pressure and heart rate depend on the time of the day. The kinetics of antihypertensive drugs also varies with the time of the day. The Cmaxwas higherand tmaxwas shorter when the drug was administered in the morning than in the evening. This is applicable to different lipophilic drugs like nifedipine, propanolol, verapamil etc.
- Angiotensin converting enzyme inhibitors (ACEIs) are found to be safe when are administered at bed time when compared to morning.
- Atenolol (hydrophilic drug) is not absorbed rapidly after morning administration.

3. Anti epileptic drugs

Valproic acid: Cmax was found to be higher, tmax was shorter and absorption rate constant ka was higher in morning than in the evening [19].

4. Anti inflammatory drugs

They have greater rate and extent of bioavailability when administered in the morning than in the evening. Ex: indomethacin, ketoprofen.

5. Anti migrane drugs

Cmax of Sumatriptan, drug of choice for migrane was higher when the drug was administered durin morning 7 am than after 7pm administration [20].

6. Anti cancer drugs

The renal toxicity of cisplatin was significantly reduced by evening administration rather than morning. 5-Floro uracil is intracellularly catabolised by an enzyme dehydropyrimidine dehydrogenase. The activity of this enzyme increases by 40% during midnight. Therefore the drug is highly tolerable when administered between 00:00 to 4 am [21].

7. Anti hyperlipidemic drugs

Cholesterol synthesis takes place in the presence of hydroxyl methyl glutaryl Co enzyme A reductase (HMGCoA reductase). More cholesterol is synthesized in the evening than in the morning. Therefore anti hyperlipidemic drugs like HMGCoA reductase inhibitors should be administered in evening for increased efficacy except atorvastatin which has a longer half-life.

8. Opioid analgesics

Stronger analgesic effects of tramadol and dihydrocodeine were observed when they were administered in the evening to relieve painful stimulus. Morphine fount to be highest peak of concentration at 09:00 am least to be found 03:00 am.

9. Heparin

The significant inhibition of blood coagulation by heparin was more pronounced at night. Even if it is given at constant infusion rate, risk of bleeding varies with hour of the day.

10. Topical steroids

The anti-inflammatory action of steroids is found to be maximum in afternoon.

11. Local anesthetics

Amide type local anesthetics like lidocane, ropivacaine, mepivacaine and betoxycaine were highly effective when are applied around 3:00pm the plasma levels of lidocaine were higher in the evening than any other time of the day.

12. General anaesthetics

- **Barbiturates**

Barbiturates like pentobarbital was highly effective when administered during the dark phase. This is because GABA ergic activity is highly pronounced during night time.

- **Benzodiazepines**

The elimination half-life of midazolam was found to be shortest at 14:00 hrs and is longest at 2:00 h. BZds like ketamine, etomidate, propolol are efficacious during night than during the day time.

12. Anti psychotic drugs

Chlorpromazine produces maximum sedative effect when administered at midnight and maximum anti psychotic effect when administered immediately after awakening. Haloperidol shows both sedative and antipsychotic effect when administered in the evening.

Chronotherapeutics is found to be useful in

1. Allergic rhinitis

As rhinitis is worst in the morning and evening, non sedative anti histaminic drugs are administered before bedtime to control the exacerbations during sleep. Oral corticosteroid therapy can be given in the morning for severe allergic rhinitis.

2. Bronchial asthma

- The risk of asthma is more pronounced during night and in the early morning. Therefore, sustained release formulation of theophylline is given at night time. It increases the efficacy of the drug, decreases its toxicity and also helps in avoiding multiple doses.

- High nocturnal cholinergic activity due to vagus nerve hyperactivity can be prevented by using cholinergic antagonist like Ipratropium bromide during night time.

- Corticosteroids should be administered during day time around 5:30pm so as to maximize their efficacy.

- Leukotriene receptor antagonist zileuton should be administered in night as LTB4 concentration was found to maximum during night time.

3. Peptic ulcer disease

As the maximal acid secretion, peptic ulcer disease pain, perforation of ulcers are maximum at night time, H2 receptor blockers like rantidine, famotidine are preferentially given at evening time.

4. Arthritis

The symptoms of Rheumatoid arthritis are worse in the morning while that of osteo arthritis are worse in night and less in the morning. Therefore NSAIDs like ibuprofen, ketoprofen and indomethacin are given at night in rheumatoid arthritis patients while are administered in the morning in osteo arthritis patients [22].

5. Cardio vascular disorders

The blood pressure is usually 20% high immediately after awakening due to increased physical activity, increased catecholamine activity, increased platelet aggregation, increased vascular tone, increased thrombolytic activity [23]. Therefore new COER Verapamil (Controlled onset extended release) is used in hypertension. It is formulated such that when it is taken at bedtime and it dissolves slowly and exerts its peak effect between 5 am and noon. There is also no dip in blood pressure during night. ACEIs like Ramipril and doxazosin are given at bed time rather than morning.

6. Diabetes mellitus

Morning hyperglycemia is common in patients with diabetes mellitus.

This can be explained by two phenomena

a) Dawn phenomenon

b) Somogyi phenomenon

a) Dawn phenomenon

Recurring abnormally high glucose levels in the morning before breakfast is known as dawn phenomenon. It occurs mostly between 3 am to 5 am. This is due to increase in growth hormone secretion[24] whic h has hyperglycemic properties during sleep [25].

b) Somogyi phenomenon

It is also called as rebound hyperglycemia phenomenon. It refers to blood sugar being high in the morning, after having been low (hypoglycemia). Hyperglycemia after hypoglycemia is a result of the insulin-antagonistic action of some hormones, especially those belonging to the hypothalamic-pituitary-adrenal axis. It is mainly caused by too much or long acting insulin. Because of insulin the glucose levels will be low at night or bed time, but later because of increase in growth hormone, cortisol and catecholamine levels during bed time causing hyperglycemia.Therefore, controlled release insulin (insulin pumps) should be preferred or should be taken at the time when there are more chances of hyperglycemia. Care should be taken so that insulin should not peak at the wrong time or in the middle of the night [26].

7. Oral contraceptives

Female sex hormones exhibit monthly cycle and oral contraceptives are prescribed as per menstrual cycle.

8. Cancer

Normal cells and tumour cells exhibit different biological rhythms. The tumor cells are fast growing at around 2 am and slow growing at 10.
The drugs are prescribed based on

- The duration of the phase of cell cycle
- Rate of cell proliferation

a. Colorectal cancer
Oxaliplatin is administered at daytime whereas 5-Floruracil at night.
b. Breast cancer
Treatment of these solid tumors is preferred during later half of the menstrual cycle as there is more clearance rate than early half of the cycle. Progesterone released in the later half cycle inhibits the enzymes which are responsible for the spread of cancer. Cyclo phosphamide toxicity was lower during the night and cure rate was higher. This means that it is possible to optimize the therapeutic index by carefully selecting the time of administration [27].

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