Chronopharmacology: The Biological Clock

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Abstract- *Chronopharmacology is the science that is of various types in the pharmacological activities of various treatment over organic timings and endogenous balance. Chronopharmacology is useful for solving problems of drug dosing optimization, i.e. improving efficacy or reducing side effects. Chronobiology studies cyclic phenomena in living organisms and their adaptation to circadian rhythms. These circadian rhythms can be annual, monthly, daily, or more frequent. Daily rhythm (24h) is called CR. Chronopharmacology is a branch of science that takes into account the effects of time. circadian clock regulates human biology. These clocks are present in most cells of the body, but are organized hierarchically. Interestingly, some aspects of physiology and behavior are directly controlled through a "master clock" in the superchiasmatic nucleus (SCN) of the hypothalamus, while others are controlled by "slave" vibrations in specific brain regions or body tissues.*

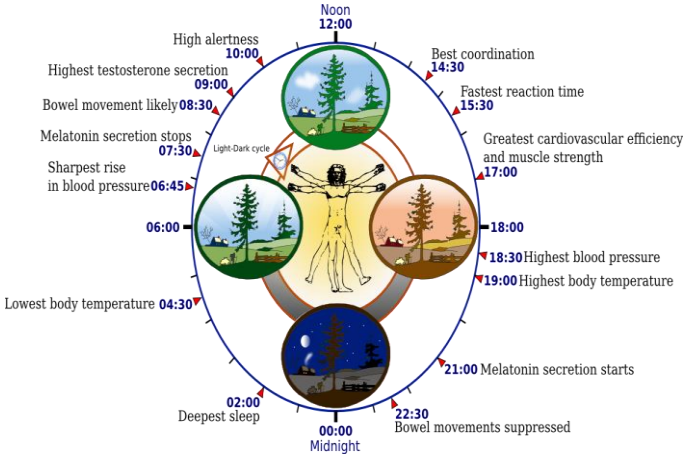
Keywords- Circadian rhythm, Chronobiology, Chronopharmacotherapy, Chronopharmacology, Biological clock.

I. INTRODUCTION

Chronopharmacology describes how the effects of drugs differ with circadian rhythm and endogenous periodicities. The motive is to improve our conception of periodic and thus predictable (e.g. circadian) changes in expected effects (chronoeffectiveness) and tolerance (chronotolerance) of medications. Chronotherapy is a treatment action in which in vivo drug availability is timed to meet illness rhythms, resulting in better therapeutic effects and fewer side effects. Dosing time-dependent changes in administration also include the quantification of parameters that characterize endogenous circadian rhythm, in terms of pharmacological effects, such as the adjusted average value of 24 hours mean (M), period (7`), amplitude (A, the difference peak through) and acrophase (4), the position of maximum time on the 24-hour scale). Chronopharmacology was only recognized as a field of scientific research in the early 1970s.

For pharmacologists with routine training, it is not clear that the predictable temporal changes in the action and disposal of drugs (for example, drugs, hormones, and toxic substances) are driven by endogenous biological rhythms, rather than external factors change driven. On the 24-hour scale (as well as annual scale), there are non-randomly distributed peaks and valleys of physiological variables; their respective positions correspond to the time organization controlled by a set of pacemakers (the so-called biological clocks). These pacemakers are probably interrelated and layered.

Organisms use periodic changes in environmental factors (zeitgebers or synchronizers) as signals and signals to reset biological clock. For many plants and animals, the notable zeitgebers (time givers) are the light dark cycle, the alternation of rest and activities related to work schedule restrictions, and/or human social habits.



Chronopharmacology and its disciplines:

1. Chronotherapeutics
2. Chronokinetics
3. Chronoesthesy
4. Chronergy
5. Chronotoxicology

Chronotherapeutics:

In this regard, it basically refers to the observation that every metabolic event changes rhythmically over time. The researchers concluded that all living organisms are composed of rhythms with different frequencies, which can change from a few seconds. It is based on the consideration that there is an independent relationship between peak rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and the pharmacokinetics of many drugs. With the increasing understanding of chronobiology and chronotherapy, it becomes increasingly clear that the specific time patients take the drug may be more important than previously recognized. The tradition of prescribing medications at intervals of evenly throughout the day, trying to maintain a constant level of medication within 24 hours, may be changing because researchers report that if the administration of certain medications is coordinated with day-night and biological rhythms, it may be possible will work better. One way to improve the effectiveness of drug treatment is to administer when the drug is most effective and tolerable.

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 necessary to adhere to treatment to limit the duration of treatment, especially in cases where the patient already has other kidney, heart and liver functions of the body. The accumulation of drugs in these organs causes greater toxicity that can impair organ function. Therefore, chronotherapy becomes a very important part of the treatment of diseases, especially those diseases, affects targeted body parts[1]. According to the 1996 American Medical Association review, the rating of chronotherapy clinical trials which was received very positively by the medical community as a whole.

Chronopharmacokinetics:

Absorption:

In humans, for drugs indicated orally, anabolism has been shown to be affected by circadian rhythm's gastric erosion and gastric pH, gastric motility, duration of stomach fatigue and changes of gastrointestinal blood flow as indicated by season of day. These developments may affect the temporal differentiation of drug assimilation. Again, gastric emptying time is another important factor in drug retention. Gastric elimination rate was estimated to be approximately between 8 a.m. and 8 p.m. in males, and gastric emptying (t ½) in evening meals was found to be substantially longer for solids but for liquids there is no contrast and those of morning meal. Likewise, prolonged night time gastric emptying time may delay achievement of peak plasma uptake for some drugs. Such genera can be identified with the physiochemical properties of drug, because most lipophilic drugs appear to be consumed quicker in the first part of the day when contrasted with night. The systems basic the chronokinetics of lipophilic medications include a quicker gastric discharging time and higher gastrointestinal perfusion in the first part of the day.

Distribution:

In natural fluids and tissues, biological alterations were identified with drug dispersion appearing to change at time points. Blood flow is dependent on a number of administrative factors, including the thoughtful and parasympathetic frameworks whose exercises are known to be circadian time-dependent with a dominating diurnal impact of the thoughtful structure. Therefore, daytime increments and evening diminish the bloodstream, and nearby tissue bloodstreams may clarify a conceivable contrast in medication appropriation relying upon dosing time[3,4].

Most human plasma protein fixations, including egg whites and a1- glycoprotein, collapse down to their least during the evening time, increment by day, and reach to most around early afternoon. Subsequently, everyday varieties have been accounted for medication protein authoritative. Touitou et al., (1986) have demonstrated that in youthful solid grown-up subjects, the circadian- abundance of plasma protein was fairly little (8-15%) contrasted and that of sound old subjects (normal age ~ 75 yr.).

A noteworthy night time fall was watched for the last mentioned (circadian adequacy of 20%), an outcome which recommends that the free part of medication typically bound to plasma proteins increments during the nighttime rest as a component of maturing. The impacts of circadian rhythm on the plasma protein authoritative of medications were first shown for cortisol, which spans to its most noteworthy level around early afternoon.

In addition, it was shown that analogs designed for cortisol are affected by circadian mood. Pglycoprotein, multi-drug resistance (MDO) added to the kidney, biliary tract and intestinal drug removal quality results, and intestinal H (+)/peptide 1 cotransporter (PEPT1) assumes important functions as supplements and drug transporters act as

xenobiological transporters and show the 24-hour variety. From a toxicological point of view, drugs with little volume of dissemination and extra high protein restriction limits and drugs which have a tight remedial record might be influenced by the progressions in circadian rhythm and wrong dosing of such medications in evening time may cause direct lethality.

Metabolism:

Hepatic medicines digestion appears to rely upon liver xenobiotic-using protein movement or potentially hepatic bloodstream. Circadian rhythms can affect the liberty of some medications, including propranolol.

Of the well-evolved organisms, a large portion of xenobiotic is utilized, the majority, in the liver. However, there is an additional extrahepatic metabolism in the cerebrum, kidneys, lungs, and various tissues. Xenobiotic digestion is consisting of three sets of protein with unmistakable capacities. Phase I Collection contains microsomal cytochrome P450 (CYP450) catalysts. Phase II, or the conjugation of compound, involves sulfotransferase (SULT), UDP-glucuronotransferases (UGT), NAD (P) H quinine oxidoreductases (NQO), epoxide hydrolase (EPH), Glutathione-S-transferase (GST) and Nacetyltransferases (NAT). The combination renders the lipophilic mixture sufficiently hydrophilic in this way to control and promote their excretion in the bile and feces and additionally urine.

After Phase II reactions, xenobiotic conjugates are applicable to organize reactions III. Very few types of oxidation reactions catalyzed by cYP450 compounds have been considered as substrates, for example, aminopyrine, paranitroanisole, hexobarbital and 4-dimethy-aminobenzene, aniline, benzphetamine, benzpyrene and imipramine. It appears that medication digestion coming because of oxidative microsomal responses achieves its crest during the action range and it's most minimal during the relaxation period. In contrast, the conjugation of sulfate was much faster at rest than that of during action period.

Excretion:

The circadian rhythm planning framework plays a key role in the development of drug lethality by affecting their digestion systems in the liver and digestive system, regardless of their elimination by bile and urine. Rodents with endless bile waste under the indomitable lighting plan (light on at 6 am and off at 6 pm) displayed a noteworthy circadian rhythm of bile stream, biliary obsession, and evacuative amount of bile salts, cholesterol and phospholipids. On the other hand, healthy volunteers found that of these polyamines had the highest elimination rate at the beginning of the day. The rate and level of ciprofloxacin released after 10 o'clock in the evening dropped significantly. The excretion of 18oxosteroids was likewise indicated to be impacted by circadian clock.

Chronoesthesy:

It distributes rhythmic change notification within the system. It has collectively created sensitive changes notice in parasites, bacteria, and tumors.

Chronergy:

Its response and aspect response rhythm changes, this is due to the kinetics of the drug and chronosthesy of different systems. It is crucial to acknowledge that plasma protein is evidence of unit beats of time.

Chronotoxicology:

This is an aspect of Chrono dynamics; it is particularly related to the time of administration i.e. the rhythm-dependent difference in performance and the severity of side effects of leads to the patient's intolerance to the drug. The term circadian rhythm comes from the Latin word circa, means "about" and dian means "day". Circadian rhythm is the most important type of biological rhythm, the most important for humans and animals. They play an important role in maintaining body temperature, heart rate, blood pressure, organ blood flow, lung and kidney function, and the concentration of neurotransmitters, hormones, enzymes, electrolytes, and glucose. Study of rhythms is important for pharmacotherapy. Chronotherapy harmonizes drug delivery with the body's biological rhythms and has tremendous involvement in pain management and treatment of asthma, heart diseases and cancer.

Chronotherapy in various diseases:

Cancer:

Man and animal studies suggest that chemotherapy can be more effective and less toxic if anti-cancer drugs are carefully administered at times selected that exploit tumor cell cycles, while less toxic to normal tissue. The rhythmic circadian variations in the bloodstream of tumor and cancer growth are relevant both when tumors are small and grow faster and, when they are bigger and are growing more slowly. Significantly circadian chemotherapy time concerns toxicity patterns and the severity of drugs, maximum tolerated doses, the average dose intensity, the quality of the tumor response and frequency and the survival of cancer patients.

The pharmacologic & pharmacokinetic property of the drug and, rhythmic changes in DNA and RNA synthesis, RNA translation activity and mitotic activity can affect tumor cell susceptibility. Chronogenetic cancer therapy was detected in the suppression of the tumors in vivo. For example, it has been shown that CLOCK genes dictate sensitivity to the anticancer drug cyclophosphamide.

Cardiovascular diseases:

In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decrease later in days. The increase in platelet aggregation and the decrease of the fibrinolytic activity in the morning leads to relative hypercoagulability of blood. In addition, BP is lower during the sleep cycle and rises to during the awakening early in the morning. These observations show that the myocardial ischemia, angina pectoris, acute myocardial infarction, congestive heart failure and sudden death are also distributed unevenly during the 2 hours with more expected events during the initial hours of the daily activity span, in the late afternoon or early evening.

Sympathetic activity and the Renin-angiotensin-aldosterone axis both peak in the early morning hours. External factors including physical activity, emotional state, meal and sleep/wake routine affecting ANS also contribute to variations. Currently, there are chronotherapeutic antihypertensive products such as oral nitrates, calcium channel blocker and β-adrenoceptor antagonist whose both pharmacokinetics and pharmacodynamics are influenced by circadian rhythm are available with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon after administration of medications at 10 pm.

Diabetes:

In type I diabetes the circadian rhythms of insulin and its action are of physiological interest and clinical importance. Thus, insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show its cyclic rhythmicity of 8-30 min which can show the optimal action. The modulators of insulin release and action are secreted in a circadian pattern and impress the mode of insulin release. Therefore, difference between maximum and minimum plasma insulin concentration has short-term rhythmicity and complex secondary circadian rhythm is variable early-morning and late-afternoon insulin resistance.

Alzheimer's disease:

The change of circadian rhythm is also observed in patients with Alzheimer's disease. Individuals with Alzheimer's symptoms show less diurnal motor activity and higher percentage of nocturnal activity showing lower inert daily stability of motor activity and activity pf macrophages peak time than normal healthy subjects. The core body temperature is also higher in patients and the circadian abnormalities are observed along with cognitive and functional impairment in this disease.

Arthritis:

Rheumatoid arthritis can be distinguished from osteoarthritis by the time of day when the patient's joints are more painful and morning stiffness is characteristic feature of rheumatoid arthritis while the symptoms of osteoarthritis are usually worse in the afternoon and evening. Non-steroidal antiinflammatory drugs are taken to relieve the morning pain and stiffness of rheumatoid arthritis, so the drugs are taken late night and are best for treatment. The new cyclooxygenase-2 inhibitors are effective in relieving the symptoms of osteoarthritis when taken in the morning and produce better results in rheumatoid arthritis when a small portion of dose is taken in the evening.

Chronotherapy for all forms of arthritis uses standard treatment that includes the non-steroidal antiinflammatory drugs and corticosteroids but in the treatment the dosages time are match with the rhythms of disease which are timed to ensuring that the highest blood levels of the drug coincide with peak pain.

Allergic Rhinitis:

Allergic rhinitis symptoms (e.g. nasal congestion, sneezing, running nose) are usually most severe in the early morning hours. If the administration of the drug can be matched with the biological time structure which have the peak pharmacologic activity are matching the time of greatest discomfort, optimum relief may be provided at the timewhen it is needed most to the patient.

II. CONCLUSION

Effectiveness and toxicity of a drug are not constant over 24hr period. Understanding the biological rhythms can optimize and individualize drug therapy to a great extent.

Thus it can help to decrease the drug related toxicity and enhance effectiveness.

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