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CHRONOPHARMACOLOGY

Pharma

KEYWORDS :

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ABSTRACT

Chronopharmacology is the study of the manner & extent to which the kinetics & dynamics of medication directly affected by endogenous biological rhythm & also how the dosing time of medications affects biological timekeeping & features (period, level, amplitude & phase) of biological rhythms. It includes chronopharmacotherapy, chronopharmacokinetics & Chronotoxity. Chronopharmacotherapy is the investigative science that elucidates the biological rhythm dependencies of medication. It is useful to solve problems of drug optimization i.e. to enhance the desired efficiency or to reduce its undesired effects. So Chronopharmacologic approaches involve a lesser risk of errors and or false information than the conventional homeostatic approach. The effectiveness & toxicity of many drugs vary depending on dosing time associated with 24 hours rhythm of biochemical , physiological & behavioural process under the control of circadian clock such chronopharmacologicalphenomenon are influenced by not only the pharmacokinetics but also pharmacodynamics of medication. Now a day Chronopharmacological principle are used in the therapy of various diseases. Biological rhythms not only impact the pathophysiology of diseases, but the pharmacokinetics and pharmacodynamics of medications. Chronopharmacotherapy is the investigative science that elucidates the biological rhythm dependencies of medications.

Introductionn

Many functions of the human body vary day by day and these types of variations cause the changes in both in disease state and in plasma drug concentration [1]. Cardiovascular functions such as heart rate and blood pressure show 24 h variation. The incidence of cardiovascular disease such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation since most of these disorders can induce fatal or severe outcomes. It is important to elucidate the precise mechanism of the onset of these diseases [2]. The dependence of our body functions in the certain diseased state depends on the circadian rhythm [1]. Circadian rhythm occurs in the certain diseased condition. The science dealing with the phenomenon of biological rhythmicity in living organism is called chronobiology. The branch dealing with the pharmacologic aspects of chronobiology is termed Chronopharmacology which may be subdivided into chronotherapy, chronopharmacokinetics &Chronotoxity [3]

a. Circadian Phase: The phase of circadian rhythm is defined with respect to an easily identifiable reference point of the endogenous circadian oscillation such as through of the body temperature rhythm or the onset of metabolism rhythm. Thus circadian phase shift can be determined by measuring the change in timing of the chosen phase maker from one cycle to the next. During ambulatory conditions, changes in environmental stimuli and behaviour (e.g. - Light/dark, rest/ activity and temperature) often obscure the endogenous component of the underlying circadian oscillation that is being measured. The amplitude of circadian rhythmrefers to the half distance from the maximumto the minimum of the observed rhythm [4] .Circadian clocks regulate a number of key behaviours in a wide variety of organisms it also helps organism to restrict their activity to species – specific times of the day, which enable them to find food escape predators & avoid undue competition between sympatric species e.g. – in drosophila parasitism activity peaks of different species occurs at different times of the day, which significantly reduces intrinsic competitive disadvantage for the inferior competitor and such temporal portioning is achieved at least partly with the help of circadian clocks [5] .In the evening, when less light enters in the eyes, the master clock triggers production of a hormone called melatonin which makes feel drowsy & helps stay in asleep. Circadian rhythm and their sensitivity to time may change as the age of the individual person increase [6].

Chronopharmacology is useful to solve problems of drugs optimization means to enhance the desired efficiency or to reduce its undesired effects. The chronopharmacologic approach involves a lesser risk of errors or false information than the conventional homeostatic approach. Many seasonal psychopharmacological drugs are useful in seasonal affective disorders though diazepam has fewer adverse effects and other selected drugs like phenobarbitone and chlorpromazine also have many adverse effects because of which they are leaving the market even though their pharmacological actions are potent. The need of the hour is to design strategies to ameliorate the side effects which make them more acceptable if the pharmacology and adverse effects of these drugs is circadian time dependant, it can be modulated by altering the time of administration of drugs. Any dependence of these drugs on the circadian time may provide a clue to ameliorate the major drawback of drugs [7].

b. Chronopharmaceutics:- Ithas been described as a branch of pharmaceutics devoted to the

design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy.

c. Chronopharmacokinetics: - It refers to rhythmic changes in drug bioavailability as well as excretion.

d. Chronotherapeutics: - Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to through rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs takes into account predictable administration time dependent variation in the pharmacokinetics of drugs as well as the susceptibility due to temporal organization of physiochemical process and function of body as circadian and others rhythms [8]. One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated [9].

e. Chronopharmacotherapy: -It is an area where the drug administration is synchronized with biological rhythms so as to maximize therapeutic effect. It involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. Circadian changes in the effect of various chemical agents have been documented such as histamine, sodium salicylate, acetylcholine, halothane, prostaglandin F 2 alpha, eserpine, Cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orcinprenaline and SCH 1000 (the latter being bronchodilators), Indomethacin, lignocaine, ACTH, cortisol and various synthetic corticosteroids.

Causes for Chronopharmacology

There are different reasons for this which may be summarized as:

Autoinduction: A repetitive dose of a drug induces or increases enzymes responsible for its elimination, thereby increasing its clearance. This is called as autoinduction. It is dependent on dose and concentration of the drug. It has a number of therapeutic consequences. It affects the time to achieve steady state and limits one's ability to use information from a single dose to predict kinetics after repeated dose or continous 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 with time.

Autoinhibition: it may occur during the course of metabolism of certain drugs. I this case, the matabolites formed increase in concentration and further inhibit metabolism of the parent drug. In biochemistry, this phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition.

Food effects: food is the major cause of diurnal variations. Gastric emptying is slowed or delayed by food, often resulting in a decrease in the peak concentration and an increase in the time of its occurrence following a single dose. It is a major cause of circadian variations in patients tending to eat more in the evening than at breakfast. When absorption is slowed by food, the rate of input into liver and concentration of drug entering liver are lowered and prolonged and thus metabolism is lowered. Hence, a concurrent intake of heavy food in evening and some drugs reduces bioavailability of the drug.

BIOLOGICAL RHYTHMS OBSERVED IN VARIOUS BIOLOGICAL SYSTEMS

The basic physiological process governing the drug action the absorption the distribution the metabolism and the excretion are controlled by the following systems of the body. Hence it is important to know the circadian rhythms in these systems and their effect on drug action.

Cardiovascular system

Most cardiovascular activities show a circadian rhythm, as do several electrophysiological phenomenon [10]. Under the influence of both external stimuli and endogenous homoeostatic mechanisms, cardiac electrophysiological properties change diurnally and enable the cardiovascular system adapt to rest-exercise cycles. For example when the case of blood pressure both the systolic and diastolic pressures is taken it seems that they are highest in the late afternoons and gradually decrease in the evenings to attain the lowest values at nights which can be attributed to the circadian rhythms in the nervous and endocrine system.Myocardial infarction (MI) occurs more frequently in the morning as a result of the concomitant infavourable timing of several physiological parameters and/or biochemical conditions. However, little is known about the possible influence of this circadian pattern on prognosis. During chronic oral treatment of hypertension patients with labetalol, an a, ß-adrenergic receptor blocker drug, observed that the mean steady state levels in patients were almost twice those predicted from a single oral dose. Even most of the cardiac ischemic conditions and acute myocardial infarctions occur usually between morning and the noon.

Urinary system

The urinary system which plays a pivotal role in the elimination of a drug has many instances of circadian rhythms altering either the clearance or the urinary flow causing nephrotoxicity. Amino glycosides can produce renal toxicity with chronic administration. Because these antibiotics are primarily eliminated by renal excretion, diminishing renal function with time may cause greater drug accumulation and more toxicity. There is clearly a need to monitor therapy to limit the duration of therapy [11], especially in patients who already have compromised renal function. Theophylline causes increase in the renal flow by increasing the clearance levels and thereby increase in the urine flow and renal excretion. Carbemazapine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration indicates that either oral bioavailability decreases or clearance increases with time. The latter has been shown to explain the observation caused by carbamazepine inducing its own metabolism. The elimination of diazepam is slower of the multiple dosing than following a single dose [12]. This change in clearance appears to be a consequence of the considerable accumulation of nor diazepam on the metabolism of diazepam. Gastrointestinal system The gastrointestinal motility, the intraluminal pH , blood flow to stomach and enzymatic action are not the only factors that influence the gastro intestinal absorption of the drug. It even depends on the circadian rhythms and all the above mentioned factors are also influenced by the time of the day [13]. Most of the drugs we generally take are lipophilic and they are found to have more rate of absorption in early mornings rather than any hour of the day.

Hepatic system

The anti-depressant nartryptalline which is injected to significant presystemic hepatic metabolism accumulates in a highly predictable manner on multiple oral dosing. The clearance levels of acetaminophen are decreased due to the effect of circadian rhythms and thus resulting in the hepatotoxicity.

DISEASES SHOWING DEPENDENCE ON BIOLOGICAL RHYTHMS

Cardiovascular diseases

Cardiovascular functions such as heart rate and blood pressure show 24h variation (14). The activity of the several components of the vascular systems appears to be diurnally regulated. En-

dothelial cell activation, Leukocyte and platelet interactions and lipoprotein metabolism all been shown to vary with time of the day, but whether these variations are due to the endogenous circadian clock, exogenous factors, such as the light dark circle, or an interaction between the two remains to be determined. In fact, the time of day of onset of platelet aggregability, nonfatal myocardial infarction, and sudden cardiac death had prominent circadian rhythms with a primary peak in the morning and a secondary peak in the evening. The blood pressure and the and essential (primary) hypertensive display highest values during daytime followed by a mighty drop and early morning rise(15). In about 70% of forms of secondary hypertension, however this rhythmic pattern is abolished or even reversed exhibiting nightly peaks in blood pressure.

Asthma

Chronic airway inflammation and limitation of airflow in the airways characterize bronchial asthma, and attacks begin with paroxysms of coughing, wheezing, and dyspnoea. Chronopharmacological studies statistically show that the development of asthma symptoms and many types of bronchospastic attacks is clearly more common from midnight to early morning from 2am and 6am every day. Chronopharmacotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. Several drugs for asthma have been developed based on chronopharmacology. One example is the bronchodilator uniphyl, a long-acting theophylline taken once a day in the evening causes theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours. Some studies have even proved that a single dose administered in those early hours is equally effective as four doses given in a day. In addition to bronchodilators, the inhaled glucocorticosteroid ciclesonide is now available with once-daily dosing, which also improves patient's compliance. Numerous investigations have demonstrated the usefulness of chronotherapy for asthma, especially for patients with nocturnal asthma (16).

Diabetes

Biologists have found that a key protein that regulates the biological clocks of mammals also regulates glucose production in the liver and altering the levels of this protein can improve the health of diabetic mice. Eric zhang the first author of this study feels that it is very surprising that the CRYPTOCHROME has a new function that no one has ever predicted since till date it was just supposed to be a just a key protein regulating the genes in a rhythmic way but now it is proved to have extra nuclear functions as well". The additional function of the cryptochrome is the regulation of gluconeogenesis according to the diurnal activity and feeding levels. So modulating cryptochrome levels can also help decrease the diabetic effect on the patients.

Arthritis

Chronobiological patterns have been observed with arthritis pain. The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting NSAIDs like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes or averts their side effects. People with osteoarthritis, the most common form of the disease, tend to have less pain in the morning and more at night. For osteoarthritis sufferers, the optimal time for a non-steroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. The overall, back stiffness and pain were a problem throughout the 24 hours, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 and 09:00 than between noon and 15:00.

Hypercholesterolemia

The circadian changes in lipid fractions in normal subjects and patients may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus it leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. Generally cholesterol synthesis is high during the night than daylight. The maximal cholesterol synthesis occurs early in the morning, i.e. 12 hour after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing.

Duodenal ulcer

The chronobiology, chronopharmacology and chronotherapeutics of duodenal ulcers have been extensively reviewed. Gastric acid secretion is maximum at night, while gastric and small bowel motility and gastric emptying are all slower at night. During night time, when gastric motility and emptying are slower, drug disintegration, dissolution and absorption may be slower. In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for an H2 antagonis.

Cancer

The tumour cells and the normal cells differ in their Chronobiological cycles. This fact is the basis for the chronopharmacotherapy of cancers (17). Based on study which suggested that the DNA synthesis in the normal human bone marrow cells has a peak around noon while the peak of DNA synthesis in lymphoma cells is near midnight, a s-phase active cytotoxic therapy at late nights was administered and it was found that there is a decrease in the tumour cell count with a little effect on normal cells.

Allergy

The allergic reactions both local and systemic are mediated through interactions of immune and inflammatory responses. Such responses during the day are usually coordinated by drenocortical function and steroid release with high amplitude daily rhythms. Scientists now believe that the symptoms of allergic rhinitis, and even the skin testing results, can vary according to the time of day (18). For sufferers of allergic rhinitis, the major symptoms of sneezing, runny nose, and stuffy nose are typically worsened in the evenings. Immunological reactions: In vivo immune responses vary with circadian rhythms including hypersensitivity reactions in the skin and lungs, acute graft rejection and humoral and cell antibody responsiveness. Circulating levels of immunoglobulin in normal animals and immune complexes in inflammatory states also vary with a predictable circadian pattern. Studies in the rat and in man have shown that the time of day at which an antigen is encountered has an influence on the expression of any subsequent cell-mediated immunity, when the responses measured after a fixed interval. This suggests that immune processes are modulated by intrinsic biological rhythms (19).. The study in rats demonstrated a circadian rhythm in delayed hypersensitivity to oxazolone. The response is T cell-mediated although there are B cells and possible serum components.

Future perspective of chronopharmacology

The basic expectations for the methods of human and animal biological rhythm research, both from the perspective of the fundamental criteria necessary for quality chronobiology investigation and from the perspective of human and ethical research on human beings and animals, have been extensively reviewed [20] All chronopharmaceutical and chronotherapy studies should conform to the respective policy and mandates of the Declaration of Helsinki and the Guide for the Care and Use of Laboratory Animals following the standards of good research practice. The foregoing information suggests that updated regulatory concern may be needed for chronopharmaceutical systems. There is a need for early interaction between the FDA and drug makers

to plan development more efficiently by appreciating the regulatory expectations for drug products intended for chronotherapy and chronoprevention of diseases, due to the new nature of the field.

Conclusion

The major objective of this review is to inform biologists, clinicians, pharmaceutical scientists and other professionals the importance of biological clocks and chronopharmacology to human health and disease. Other purpose is to trigger further experimental and clinical research in the field of chronopharmacotherapy. However, the most important issue of this article is to motivate the investigation, and development of chronotherapeutics as a practical means of improving the outcomes and safety of medical treatment with the older or already well established active pharmaceutical ingredients. In addition, the discoveries of small compounds or new drug substances that act on the peripheral clock will help us to establish chronopharmacotherapeutic approaches to more appropriate extend

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