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Chronopharmacology: A Review

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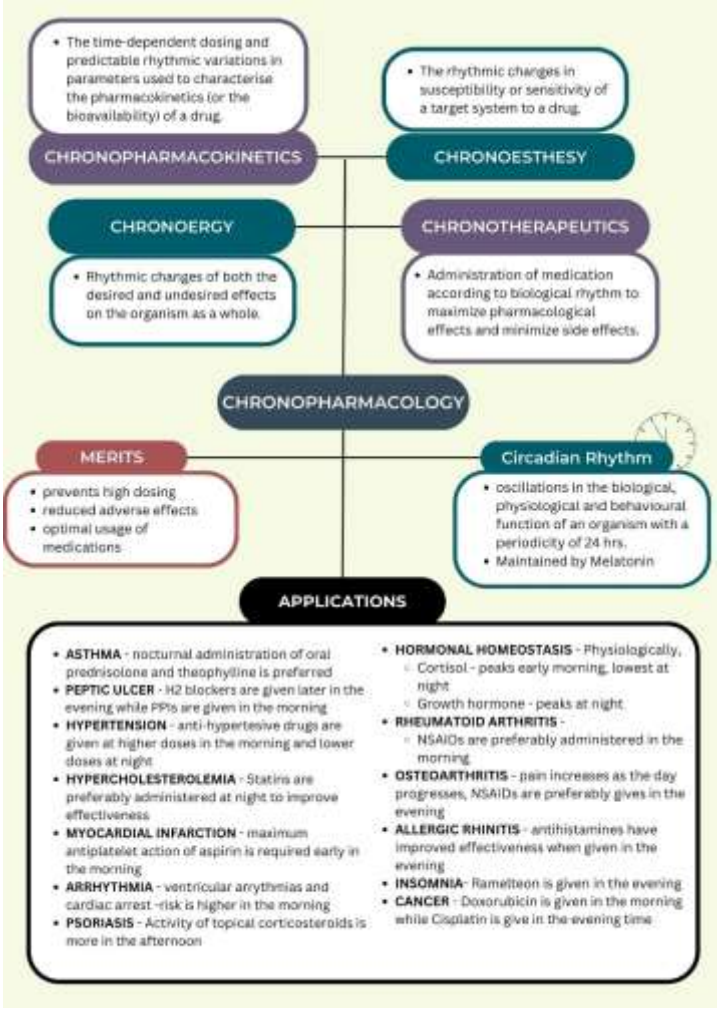
Illustrative Abstract



Introduction

The biological function of all living organisms including humans is influenced by the change of time in a rhythmic pattern that results in biological rhythm. Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. The goal should be to

enhance our comprehension of the predictable (e.g., circadian) and periodic variations in the tolerance (chrono tolerance) and intended effects (chrono effectiveness) of drugs.

Concept of Chronopharmacolgy:

Chronobiology: is the branch of science, which examines periodic phenomena in living organisms and their adaptation to biological rhythms. Under the impact of time, three disciplines are considered in medicine. Chronophysiology, Chronopathology and Chronopharmacolgy. Chronopharmacology is the science that deals with the optimization of drug dose that promotes efficacy and minimizes the adverse effects by taking medications about the biological rhythm. Simply put, medicines can be beneficial and have fewer side effects if we take them by our body clock.[1]

There are four divisions under Chronopharmacolgy:

1. Chronopharmacokinetics: deals with the study of the temporal changes in the pharmacokinetics of the drugs with respective time. Study of absorption, distribution, metabolism, and excretion of drugs according to the time of the day or year.
2. Chronesthesy: The rhythmic changes in susceptibility or sensitivity of a target system to a drug.
3. Chronergy: Rhythmic changes of both the desired and undesired effects on the organism as a whole.
4. Chronotherapeutics: administration of medication according to biological rhythm to maximize pharmacological effects and minimize side effects.

Merits of Chronopharmacotherapy:

· It prohibits higher than required dosing of each class of drug.

· It decreases unnecessary side effects of a medicine and thereby helps to reduce the duration of hospitalization.

· It generates usage of the medicine most suitable and the value of the medicine is an increase.[2]

Chronopharmacokinetics

Human circadian rhythms may influence drug pharmacokinetics and cause pharmacological circadian variation. Chronopharmacokinetics is defined as dosing time-dependent and predictable rhythmic variations in parameters used to characterize the pharmacokinetics (or the bioavailability) of a drug.[3]

In humans, it has been demonstrated that the circadian rhythm influences drug absorption when taken orally since the time of day affects factors such as gastrointestinal blood flow, motility, pH and acidity of the stomach and gastric emptying time.[4,5]

Chrono kinetics of lipophilic drugs involve a faster gastric emptying time and a higher gastrointestinal perfusion in the morning. This leads to a higher C_{max} and shorter T_{max} during morning administration. Several drugs, such as nifedipine, propranolol, and verapamil, presented a reduced bioavailability after evening administration compared with morning administration.[4,6]

Circadian variation in the pharmacokinetics of nelfinavir (1250 mg b.i.d.) results in higher relative bioavailability (220%) for evening dosing compared with morning dosing.[7]

Albumin and acid glycoprotein are at the lowest peak during nocturnal rest and highest in the morning. Therefore, drugs bound to plasma protein, like valproic acid, carbamazepine, diazepam, lignocaine, prednisolone show increase in free fraction at night.

Based on serum levels, rifampicin's pharmacokinetics demonstrated circadian rhythmicity, but the kinetics of sulphanilamide and sulfamethoxazole's urinary excretion demonstrated circadian rhythms.[8] Continuous infusion of amikacin in neutropenic patients, significantly achieves higher drug level in the early morning than in the evening. Gentamicin, amikacin has higher clearance when injected during the activity period and longer serum half-life after evening dosing. Excretion chronokinetics of these acid medications are explained by diurnal oscillations in urine pH, which is lower at night. Single dose of ciprofloxacin taken orally at 10 am, is eliminated from urine more quickly and completely than when it is taken after 10 pm.[9]

Circadian rhythm

The term "circadian" comes from the Latin words for about (circa) a day (diem). Circadian Rhythm is defined as oscillations in the biological, physiological and behavioural function of an organism with a periodicity of 24 hrs.

Circadian rhythm is controlled by a molecular clock located in almost every cell. The master clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus, while the peripheral clocks are found in each organ or cell. Through the autonomic nervous system, humoral mediators, and other unidentified mechanisms, the central clock controls physiological processes.[10]

The circadian rhythms throughout the body are connected to an internal clock located in the brain. Clock genes in the SCN deliver signals to control bodily activity at different times of the day. Because the SCN is so sensitive to light, light is an important external cue that affects the signals the SCN to

the body to synchronize circadian cycles. Circadian rhythms are strongly related to day and night. The master clock in the SCN consists of about 100,000 neurons in humans. It is the only molecular clock that the retina sends light signal to. Internal clocks are harmonized with light depending on the time of day.[11,12]

Melatonin is the main circadian hormone and the central clock coordinates all of the body's peripheral clocks. Melatonin plays a critical role in maintaining the circadian rhythm, depending on when it is light or dark.[13]

The daily circadian rhythm of the metabolism is regulated by the combined action of central and peripheral clocks.[14]

When the stimuli for the central and peripheral clock systems do not coincide the two clock systems become desynchronized because the phases of each clock are influenced by different stimuli. This mismatch disrupts the metabolism because the two clock systems coordinate interlinked metabolic pathways. Circadian rhythm mismatch increases the risk of developing metabolic diseases.[15,16]

A higher risk of cardiovascular disease is one of the disorders that might result from the lack of synchronization.[17]

Applications of Chronopharmacolgy

Asthma: is a disease with a strong circadian rhythm. Symptoms of asthma frequently show exacerbation in the early hours of the morning, at around 4 am. Sudden death in asthma also tends to occur at this time.[18] Pulmonary functions such as FEVI are circadian phase-dependent with lower values at night. The lungs are also more sensitive to bronchoconstrictor substances such as acetylcholine, histamine, housemite dust, and grass pollens at nightly hours than during daytime. In individuals suffering from nocturnal asthma, a decrease in lung function over-night is linked to heightened airway hyperresponsiveness and inflammation, resulting in nighttime symptoms including cough and dyspnea that interfere with sleep. Administration of glucocorticoids in the night improves the peak expiratory flow rate and reduction of morning dip.[19]

Theophylline was one of the first drugs for which daily variations in its pharmacokinetics were reported. Numerous research findings indicated that Theophylline might be dosed higher during the night than during daytime hours, or even a single evening dose might be used--to overcome the nocturnal decrease in pulmonary function adequately.[18] Clinical evidence suggests that terbutaline, a beta 2-sympathomimetic, has circadian phase dependent pharmacokinetics and effects on peak expiratory flow. Oral prednisone is much more effective in improving several features of nocturnal asthma and response to inhaled β-2 agonists when administered at 3 PM rather than 8 AM.[20]

Peptic Ulcer: Many components of the digestive system are subject to circadian cycles; e.g. the amount of acidic stomach secretion increases in the evening. Around dusk, there is a decrease in stomach motility and a decrease in gastric exhaustion. Highest acid production happens at night, between the hours of 10p.m. and 2a.m., so the ideal time to administer medication for acid reflux disease at night will be helpful. H_2 blockers (ranitidine, cimetidine, famotidine, roxatidine, nizatidine) should be taken once a day in the late afternoon or early night when acid secretion is increasing, independently of whether the compounds have a short or a long half-life.[21,22]

In contrast to H_2blockers proton pump inhibitors (PPI) should be dosed in the morning since the increase by lansoprazole and omeprazole in intragastric pH is more pronounced after morning than evening administration.[23]

Hypertension: Hypertension poses a significant risk of heart attacks, strokes, and other vascular and renal diseases. BP rises rapidly in the early morning hours; this rise in BP corresponds to increased secretion of catecholamine's and increased plasma rennin activity.[24]

Standard guidelines for the chronotherapy of hypertension state that antihypertensive

medications should be given at higher doses during the early morning postawakening period, when blood pressure is at its highest, and at lower doses d uring the middle of a sleep, when blood pressure is at its lowest.

Administration of angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists at night deciphered to better hypertension control in comparison with drugs administered in the morning. Similar results have been observed for thiazide diuretics when used in hypotensive monotherapy in the evenings. When given in the evening, the fixed combination of captopril and hydrochlorothiazide was more successful in lowering nocturnal BP.[25] However, compared to an evening dosage, using beta-adrenolytic drugs in the morning enhances the effectiveness of hypotensive treatment.[26]

α- blockers are more effective in reducing peripheral resistance compared to other times of the day or night. A single dose of doxazosin taken at night lowers BP and heart rate during the day and night, although the biggest reduction occurs in the early hours of the morning.[27]

Several trials that examined the differential effects of morning vs. evening administration of CCBs reported that sustained-release formulation of diltiazem was found to be more effective in controlling the 24-hour BP mean, morning administration of amlodipine lasting for 24h; may be effective for morning surge and the better effect of Nitrendipine is seen if administered in the evening.[28]

Hypercholesterolemia: Elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) play an important role in the development of atheromas and, therefore, in Cardiovascular diseases. Cholesterol is produced more during nighttime and evening hours due to increased cholesterol consumption and hepatic-cholesterogenesis. When an HMG-CoA reductase inhibitor is taken in the evening rather than the morning, serum cholesterol levels are lowered more. The HMG-CoA enzyme, a cholesterol-rate limiting enzyme, shows a circadian rhythm in humans. This enzyme peaks at night, so it is recommended to take cholesterol-lowering drugs such as statins at night to maximize their effectiveness.[29]

While statins with a longer half-life may be just as effective when taken at any time of day, those with a shorter half-life (one to five hours) might be more beneficial if taken in the evening. This is because the peak of cholesterol biosynthesis would coincide with the period of maximal action for short half-life statins (lovastatin, simvastatin, etc.). Simvastatin administration in the evening is recommended to get the best reduction in LDL-C levels, according to a systematic review that evaluated the effect of statins on blood cholesterol levels depending on when they were taken (morning versus evening).[30,31]

Myocardial Infarction: The risk of myocardial infarction is highest between 6 am and noon.[31] Homeostatic changes, gene expression changes, and external triggers can cause a stressful environment and cause damage to the atherosclerotic plaque in the coronary arteries in the morning when prothrombin is increased.[32] A reduction in fibrinolytic activity results in a hypercoagulable state that could elicit the morning onset of thromboembolic events. Studies suggest that the autonomic nervous system plays a major role in the circadian variation of the onset of Acute Myocardial Infarction. Many studies demonstrated the existence of circadian variation in the efficacy of thrombolytic therapy, with marked early morning resistance and significantly better late daytime results.[33] Myocardial infarction incidence peaks in the morning, and again in the late hours of the night.[34] Beta blockers prevent increased sympathetic activity, catecholamine concentration, heart rate, blood pressure, and cardiac oxygen deprivation.[35,36]

The maximum antiplatelet effect of Aspirin is seen in the morning. Thrombolytics and Heparin ↓ benefit during early morning hours. Atenolol works better in the daytime. Labetalol is more effective in the early morning hours. After taking a morning dose, enalapril exhibits peak effects in the afternoon.

Arrhythmia: Atrial & ventricular refractory periods are strongly affected by the autonomic nervous system, in which sympathetic activity shortens it and parasympathetic activity elongates the period. Therefore, fluctuations in the activity of autonomic nervous system within a day can be a major trigger of circadian onset of cardiac arrhythmia. Multiple reports concluded in term of peak paroxysmal supra ventricular tachycardia (PSVT) from morning to midnight. Continuous halter monitoring of ECG revealed a 24 h variation in the occurrence of ventricular premature beats with a peak between 6 am & 12 noon.[37]

The presence of a circadian onset of ventricular premature beats (VPBs) depends on left ventricular function. Only patient with a left ventricular ejection fraction greater than 30 % have a circadian variation of VPB.[38] Ventricular arrhythmias and sudden cardiac death risk increases during the early morning. In individuals with sinus rhythm, Ivabradine lowers average daily heart rate while attenuating daily heart rate variability, indicating a local effect at the local sinus node clock. Ventricular arrhythmias' morning peak and circadian pattern are lessened by beta-blockers. Amiodarone lowers heart rate variability, which may indicate that the heart's autonomic nervous system is being suppressed. [39]

Hormonal homeostasis: is impacted by the circadian clock, with several hormones exhibiting daily fluctuations. During daytime and feeding, insulin is released to ensure the uptake of glucose, lipids, and amino acids.[40] While growth hormone is released at night to promote release of insulin-like growth factor 1 and the oxidation of fatty acids.

Due to a decreased glucose tolerance during the day compared to the night, the rise in plasma glucose concentrations is substantially smaller in night (particularly between 3:00 and 5:00 a.m.) than it is in the morning. Hyperglycaemia in T2DM patients usually occurs in the morning. Hepatic Glucose Production (HGP) in the morning before breakfast has been associated with a prolonged overnight fast, which results in a surge of counterregulatory hormones (cortisol, growth hormones, and norepinephrine) as well as a circadian modulation of HGP. Cortisol- Highest secretion is just before awakening and, in the morning, lowest at midnight. Growth hormone- Peaks during sleep. Testosterone- Peaks early morning.[41,42]

Rheumatoid arthritis (RA): The symptoms and intensity of Rheumatoid arthritis (RA), osteoarthritis (OA), ankylosing spondylitis (AS), and gout all show a strong circadian cycle. Pathological symptoms in RA follow a circadian rhythm, with priming of symptoms in early morning, abatement during the noon and then increasing from late evening.

It is chronic inflammatory autoimmune disorder with cardinal signs - stiffness, swelling and pain of one or more joints Severity of cardinal signs is three times more between 08:00 and 11:00 am. When NSAIDs are administered in the morning, pain is typically reduced throughout the day. Long acting NSAIDs like flurbiprofen, ketoprofen, indomethacin at bedtime ensures adequate control of morning symptoms of RA.[43]

Cortisol synthesis inhibits the rise in concentration of IL-6 in RA patients. Circadian fluctuations in the peripheral metabolism of endogenous glucocorticoids also play a role in the early morning onset of RA symptoms. Consequently, to exploit this biorhythm low dose of glucocorticoids can be given at around 2:00h rather than the same dose at 7:00h in the morning, which significantly improved the condition of RA patients. [44] Numerous studies establish the best timing to provide methotrexate to patients with RA, can be in the morning 10am or evening 6pm. It was found that there was almost no difference in the pharmacokinetic study of the drug except for the creatinine clearance level in the subjects who received it at 10:00 h 18:00 h.[45]

Osteoarthritis: Pain worsens from 2:00 to 8:00 p.m. Morning dose for afternoon worsening, evening dose for night time worsening.

Allergic Rhinitis: Both local and systemic allergic reactions are mediated through interactions of immune and inflammatory responses. Such responses during the day are usually coordinated by adrenocortical function and steroid release with high amplitude daily rhythms.[46] The severity of nasal congestion follows a circadian rhythm, being worst at night and in the early morning. Chronotherapy studies in allergic rhinitis suggest there are benefits to nighttime dosing of antiallergy medications. Antihistamine has shown improved efficacy when administered in the evening compared with morning dosing.

When leukotriene receptor antagonists are given in the evening, nighttime rhinitis symptoms are greatly reduced. Intranasal corticosteroids administered in the morning have proved efficacy in improving nighttime symptoms.[47]

Skin disorders: Psoriasis: The rate of cell proliferation peaks between 3am and 9pm. Inflammatory activity is highest at night, least in the morning. **Atopic dermatitis:** sensitivity to histamine is highest at night. Activity of topical corticosteroids in the afternoon is higher than that in the morning.

Insomnia: Melatonin is a hormone produced in the pineal gland under control of the circadian system in the hypothalamic suprachiasmatic nucleus (SCN). Melatonin level often peak in the evening as bed time draws near and remain low during the day. Melatonin secretion reaches its plateau phase during the night and then starts to fall around the daybreak, when most people wake up. Thus, the increase in melatonin facilitates the onset of sleep and also strengthens the circadian rhythm. Ramelteon, melatonin receptor agonists used to treat insomnia.[48,49]

Cancer: 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. So, an s-phase active cytotoxic therapy at late nights should be more advantageous. Administration of Doxorubicin in the morning (e.g., at 6 am) and cisplatin in the evening (e.g at 6 pm) in patients of advanced ovarian cancer causes fewer complications and less renal toxicity.[50]

Conclusion

Chronopharmacolgy is a scientific field that examines when and how to dose medications to maximize their effectiveness. The severity of some disorders can be effectively reduced in accordance with the drug's circadian rhythm of delivery. Chronopharmacology is slowly, but surely, garnering more interest in therapy to improve health outcomes. It is an underrated concept that is overlooked during prescribing by physicians and it would be beneficial to incorporate the topic into the undergraduate curriculum. Taking chronopharmacology into consideration during the process of new drug development also has immense potential.

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