

Study of Chronopharmacology and Drug Prescribing Pattern in Tertiary Care Hospital

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Abstract: ***Introduction:** Chronopharmacology is the science dealing with the optimization of drug effects and the minimization of adverse effects by timing medication in relation to the biological rhythm. In the treatment of several illnesses, including allergies and cardiovascular conditions, this chronopharmacological concept is applied. The study aimed to examine the application of the chronopharmacological approach in clinical practice by comparing the chronopharmacology of six medications with the physician's prescribing patterns. **Methodology:** This study was prospective and observational conducted by Department of Pharmacology in association with department of medicine and respiratory medicine at tertiary care teaching hospital over a period of 6 months from April to September 2023. Total 180 prescriptions were audited. Six commonly used drugs such as Beta blockers, ACE inhibitor, Insulin, Statins, Theophylline and Proton pump inhibitors were used. **Result:** Following is the chronopharmacological data of prescription as observed: Theophylline and statins have maximum matching pattern 100%, followed by ACE inhibitor and Beta blockers (96.66%), insulin (86.66%) and PPI (66.66%). **Conclusion:** The chronotherapeutic approach provides a more accurate determination of the time when patients are most at risk and require the most therapy. Patients may benefit from higher therapeutic effectiveness and fewer side effects if medications are given using a chronopharmacological approach.*

Keywords: Chronopharmacology, Prescribing pattern, side effects

1. Introduction

Chronopharmacology is the science dealing with the optimization of drug effects and the minimization of adverse effects by timing medication in relation to the biological rhythm ⁽¹⁾. It is the study of how the effects of drugs vary with biological timing and endogenous periodicities. The objective is to increase our knowledge of how desired effects (chrono effectiveness) and tolerance (chrono tolerance) of drugs vary periodically and are therefore predictable (e. g., circadian) ⁽²⁾. The term is derived from "chrono, " meaning time, and "pharmacology, " the study of drugs.

Many functions of the human body vary day by day and these type of variations cause the changes in both in disease state and in normal state ⁽³⁾. The dependence of our body functions in the certain diseased state depends on the circadian rhythm ⁽⁴⁾. Circadian rhythm, An approximately 24 - hour cycle of biological processes in plants and animals. In humans, the circadian "clock" is found in the suprachiasmatic nucleus, a cluster of cells located in a part of the brain called the hypothalamus. The circadian rhythm influences sleeping, eating, heart rate, blood pressure, body temperature, the levels of certain hormones, and the immune system ⁽⁵⁾

The science dealing with the phenomenon of biological rhythmicity in living organism is called chronobiology. The branch dealing with the pharmacological aspects of chronobiology is termed as Chronopharmacology.

Chronopharmacology further deals with ⁽⁶⁾

- Chronotherapeutics
- Chronokinetic
- Chronotoxicity

Chronotherapeutics: Combining evidence of circadian rhythms in the kinetics, effects, and safety of medications with knowledge of day - night and other prediction in time variations in the severity of symptoms and risk of acute exacerbation of disease forms the basis for a new pharmacologic approach to treatment. By adjusting drug concentrations throughout the day to correspond with biological rhythms that determine disease, it aims to improve the efficacy and safety of pharmaceuticals.

Chronopharmacokinetics: It deals with the study of temporary changes in absorption (A), distribution (D), metabolism (M), excretion (E) and thus considers how these various steps are affected by the time of administration.

Chrono toxicology: It is an aspect of chromodynamics; it refers specifically to dosing time i. e rhythm – dependent differences in the manifestations and severity of adverse effects and thus intolerance of patients to medication. ⁽⁷⁾

2. Method

This was a prospective and observational study conducted by Department of Pharmacology in association with department of medicine and respiratory medicine At Shri M. P. Shah Gov. Medical College & Guru Gobind Singh Government Hospital, Jamnagar over a period of 6 months from April to September 2023.

Sample Size:

180 Prescriptions of Six commonly used drugs such as: Beta blockers, ACE inhibitor, Insulin, Statins, Theophylline and Proton pump inhibitors were used.

Inclusion criteria

Prescriptions which include any of the above drugs

Volume 13 Issue 4, April 2024

Fully Refereed | Open Access | Double Blind Peer Reviewed Journal

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Patients who gave consent for study

Exclusion criteria

Prescriptions which didn't include any of the above drugs
Patients unwilling to give consent.

The ethical approval was obtained before the research was initiated. Before auditing the doctors' prescriptions, the physicians were informed of the study's purpose.

Percentages were used to calculate the results. To find out how far doctors are prescribing medications using a chronological approach, the number of prescriptions that followed a chronological pattern was calculated.

3. Result

The study was completed in six months from April to September 2023. When physicians were asked about chronopharmacology very few knew exactly about the term though all had some vague idea about it. The prescriptions were audited, and it was seen that physician didn't had much concept about chronopharmacological approach but depending upon their knowledge maximum physicians prescribed the drugs were chronological order except in case of Proton pump inhibitors.

Many cardiovascular events including myocardial infarction, stroke and sudden death occur during the initial hours of

morning activity between 6 A. M. and 12 noon. This pattern is linked to, higher blood pressure levels during wakefulness, mental and physical activity, and lower blood pressure values during sleeping and periods of minimal activity ⁽⁸⁾. This is why beta blockers prescribed in the morning.

Angiotensin converting enzyme (ACE) inhibitors: are available for the therapy of patients with hypertension and heart failure, these agents have some adverse effects such as angioedema and dry cough. Changing dosing time from morning to evening reduces the severity and frequency of the drug - induced dry cough in hypertensive patients.

Insulin: Patients with type 2 diabetes should receive a higher dose of insulin in the morning than in the evening because their tolerance to glucose increases during morning time ⁽⁹⁾.

Statins: Cholesterol is synthesized at its highest rate during the night, so statins, are most effective when taken right before bed.

Theophylline: Asthmatic patients experience a worsening of symptoms at night and early in the morning, so when we give theophylline at evening we can decrease rate of asthma attacks in night and early in morning.

PPI: As far as acid production is concerned, it has been stated that maximum acid production occurs during night between 10 pm to 2 am so, medication for acid peptic disease will be beneficial when given at night.

Table 1: Assess how far chronological approach translated to clinical practice.

Class of drugs	Timing of medication that is beneficial	Correctly prescribed	Not Correctly prescribed	% Of chronologically correct prescriptions
B - Blocker	Early morning	29	1	96.66%
ACE inhibitor	At night	29	1	96.66%
Insulin	Higher dose early morning than other part of the day	26	4	86.66%
PPI	At bed time	20	10	66.66%
Statin	At night	30	0	100%
Theophylline	Before dinner	30	0	100%

Statin and theophylline 30 out of 30 correctly prescribed prescriptions. In PPI 20 prescriptions were correctly prescribed and 10 were not correctly prescribed. Doctors preferred to prescribe PPI before breakfast rather than at bedtime. In β - Blocker and ACE inhibitors 29 prescriptions were correctly prescribed and 1 prescription in both drugs were not correctly prescribed. In Insulin 26 were correctly

prescribed and 4 were not correctly prescribed. (Table 1). This indicates a lack of implementation of the chronopharmacological approach of PPIs in clinical practice. Maximum percentage of chronologically correct prescriptions are of statin and theophylline are 100%. Minimum with PPI that is 66.66%. (Figure 1)

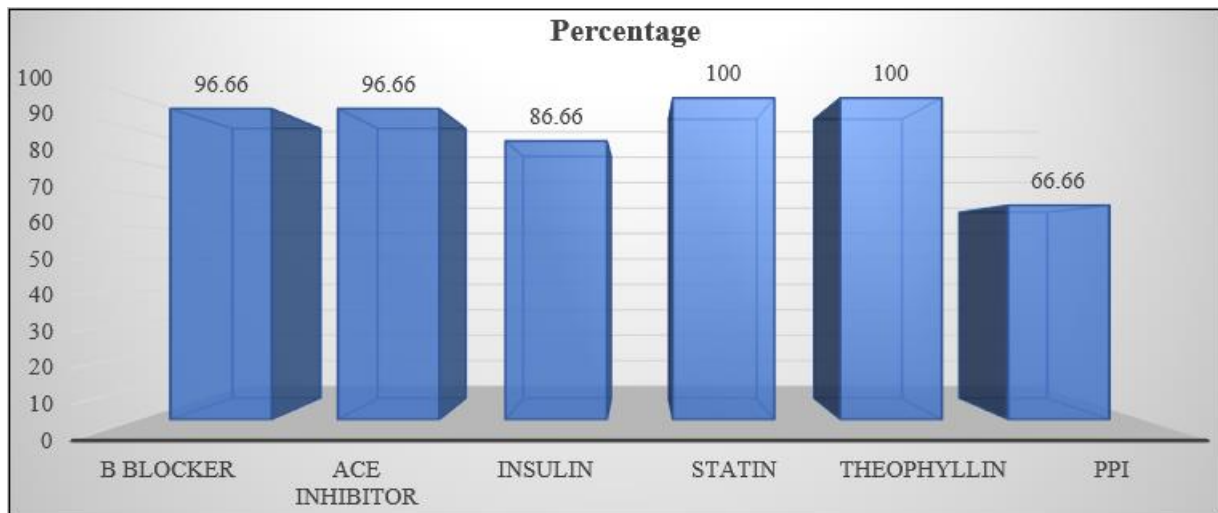


Figure 1: Percentage of correctly prescribed prescriptions of all 6 drugs

4. Discussion

In the present study, drug describing pattern of physicians in Guru Gobind Singh Government Hospital was compared to the chronopharmacological pattern in which various drugs should be prescribed in chronopharmacological order, so that patient gets maximum benefit and least side effects from the drug.

Chronopharmacology is necessary for monitoring therapy in order to restrict its duration, particularly when patients already have compromised liver, heart, kidney, or any other bodily function. Any kind of drug buildup in these organs results in increased toxicity, which may cause the organ to function less well. Chronopharmacotherapy becomes a very important part of treatment of several diseases particularly those effecting targeted body parts⁽¹⁰⁾. The American Medical Association review from 1996 states that the medical community as a whole is very much in favor of giving chronotherapy more thought in clinical trials. According to the survey's results, 75% of doctors support treating patients according to their daily or circadian rhythm⁽¹¹⁾.

From the different examinations, Between 6 a. m. and 12 p. m., the early morning hours of the day, a lot of cardiovascular events, such as myocardial infarction, stroke, and sudden death, are known to occur. And compared to other times of the day, this is significantly higher during this time. Early in the morning, blood pressure peaks sharply, which is significant because it corresponds with the peak of cardiovascular events. During the night, blood pressure continues to rise⁽¹²⁾. At the same time, heart rate increases in the late morning or early afternoon⁽¹³⁾. Platelet aggregation is increased in the morning and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper-coagulability of the blood.

In Diabetes: Tolerance to glucose increases from morning to evening hence in patients of type2 diabetes dose of insulin should be given in higher quantity compared to other part of the day.

It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that

they go to bed, as the rate of stomach acid secretion is highest at night⁽¹⁴⁾. The timing of administration of ulcer medications has a significant impact on their therapeutic effect

It has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day⁽¹⁵⁾. Many circadian - dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4: 00 am⁽¹⁶⁾. A research finding also reveals that theophylline absorption is slower at night⁽¹⁷⁾. The enhanced understanding of the chronobiological impact upon the pathology of asthma, and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care.

In our study maximum physicians were prescribing the medication as chronopharmacologically it can benefit the patient but as far as PPIs (Proton pump inhibitors) were concerned physician prescribed them before breakfast instead of prescribing it at bed time. This indicates a lack of implementation of the chronopharmacological approach in clinical practice.

5. Conclusion

It is concluded that Chronotherapeutic approach gives more accurate determination of the time when patients are at highest risk and in greatest need of therapy. If drugs are prescribed by following chronopharmacological approach it can prove beneficial to the patients as more effectiveness of the drug and lesser side effects.

Acknowledgements

We are thankful to the Dean, M. P. Shah Govt. Medical College, Guru Gobind Singh Government Hospital, Jamnagar for granting permission to carry out Present study.

Funding: No funding sources

Ethical approval: The study was approved by the Institutional Ethics Committee

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