

Assessment of Knowledge, Attitude and Practice of Chronopharmacology among Doctors

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Abstract: Background: Chronopharmacology is a field of science focusing on studying the effect of biological rhythms on pharmacotherapy, i.e., a branch of pharmacology studying the dependencies between the timing of drug administration and its effect. Chronopharmacology is frequently overlooked and poorly studied aspect of therapy rationalization. This study was planned to assess the knowledge, attitude and practice (KAP) of chronopharmacology among doctors. Materials & Methods: It was a questionnaire based cross sectional, descriptive study. Total 200 participants were enrolled after taking consent and subjected to a structured KAP questionnaire & data was expressed in percentage. Questionnaire consisted of 22 questions. Results: 55% of participants have answered that they have heard the term chronopharmacology. 67% of participants have chosen yes for the question that chronopharmacology is concerned with the effects of drugs on timing of biological events & rhythms like circadian rhythm. 77% of participants answered yes for the question that chronotherapy could reduce the incidence of adverse drug effects. 81% of participants have answered yes for the question that correct timing of drug administration is always mentioned in your prescription. Conclusion: Most of the participants have not heard the term chronopharmacology but they have knowledge that biological clock is related to diseases & they believe counselling of patients regarding chronopharmacology should be done. Doctors should be educated more about chronopharmacology.

Keywords: chronopharmacology, knowledge, attitude, practice

1. Introduction

Chronopharmacology refers to the study of biological rhythm dependencies of drugs to optimize drug therapy by selecting the appropriate time of drug administration, which is associated with maximum efficacy and minimal adverse effects⁽¹⁾. In other words, if we take our medication according to our body clock, the medicine can be more beneficial & cause minimal side effects. Ex: In relation to our body clock, maximum synthesis of cholesterol takes place at night. Hence, drugs used to lower cholesterol, like statins, will prove beneficial when prescribed at bedtime⁽²⁾.

Chronotherapeutics refers to the treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes & minimize side effects. It is indicated when the risk of severe medical events or the intensity of diseases and their symptoms is known to vary predictably during 24 hrs & other time periods⁽³⁾.

The term "Chronopharmacology" was introduced by Halberg in the 1960s & in 1971 Reinberg & Halberg reviewed the early studies on this subject. It involves both investigation of drug effects as a function of biologic timing & investigation of drug effects upon rhythm characteristics⁽⁴⁾.

Biological rhythms are innately determined rhythmic biological process or function and self-sustained oscillation with the duration of time between successive repetitions being rather non varying under normal conditions. Rhythms that affect our body are:

Ultradian- Cycles shorter than a day e.g., msec. for a neuron to fire.

Circadian- Lasting for about 24 hours, e.g., sleep and wake cycles.

Infradian- Cycles longer than 24 hours e.g., menstrual cycle.

Seasonal- Seasonal affective disorders causing depression in people during the short days of winter⁽³⁾.

The most important rhythms are the circadian rhythms⁽⁵⁾. The word 'circadian' was coined by Franz Halberg⁽⁶⁾ from the Latin words *circa* meaning 'about' & *diem* meaning 'a day'. As the name suggests, this is a cycle that runs for approximately 24 hours. This rhythm is run by a sophisticated series of internal clocks controlled by a master clock in the brain called the suprachiasmatic nucleus⁽⁵⁾ (SCN), located bilaterally in the anterior part of the hypothalamus, right above the optic chiasm.

The activity of SCN is mostly modulated by sunshine⁽⁶⁾. The SCN uses its connections with the autonomic nervous system for spreading its time-of-day message, either by setting the sensitivity of endocrine glands (i.e., thyroid, adrenal, ovary) or by directly controlling an endocrine output of pineal gland (i.e., melatonin synthesis)⁽³⁾. The circadian rhythm mechanisms of newborn babies are under-developed⁽⁵⁾.

Internal rhythm is influenced by many external factors, the most important being light and dark. Our behaviours can also alter our circadian rhythms, causing our bodies to be out of sync with what nature has intended, such as jet lag, by staying awake all night and following daylight saving clock changes.

Factors affecting chronopharmacology are inherited factors of direct relevance to chronopharmacology (genetic

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variability, gender related differences) as well as age- related differences, interindividual difference in chronoeffectiveness related to disease (e.g., various types & stages of cancer) as well as to drug-dependent alteration (phase shifts, distortion) of biological rhythms⁽³⁾.

The pathophysiology of many conditions, such as bronchial asthma, ulcer disease, rheumatic conditions & depression is connected with disturbances of endogenic biological rhythms. An increase in risk of onset of selected diseases at a specific time of the day, for instance, cardiovascular episodes in the morning or exacerbation of peptic ulcer disease at night.

The main genes regulating the activity of the biological clock include *Clock* (Circadian Locomotor Output Cycles Kaput) & *Bmal1* (Brain-muscle Arnt Like-1)⁽⁷⁾. The discovery of the basics of circadian functioning of the biological clock & genes controlling it, connected with adaptation to the environmental conditions changing on a cyclic basis, was awarded the Nobel prize in Physiology & Medicine in 2017.

Advantages of Chronopharmacotherapy:

- It prevents overdosing on a drug.
- It makes the best use of any drug taken.
- It decreases the excessive use of a drug at the same time & facilitates the time- dependent release of the drug.
- It decreases the unnecessary adverse effects of a drug.

Ideal characteristics of Chronopharmacotherapy:

- The application of chronopharmacotherapy helps make the drugs non-poisonous by cutting off the factors causing them to behave so.
- It has an actual time & a specific biomarker for each diseased state.
- It works on a command framework.
- It is biodegradable & biocompatible.
- It can be manufactured at an economical expense.
- It can easily monitor the sufferers & improve consistency in their drug routine ⁽²⁾.

2. Materials & Methods

Study design:

This was a cross-sectional, descriptive survey, conducted through pre-validated structured questionnaire.

Study population:

The study population was doctors of either gender in Tirupati.

Study period:

This was conducted in October 2022. The study was conducted in S.V Medical college, Tirupati.

Study sample:

A non-probability sampling technique (convenience method) was employed to reach to the representative population. A total of 200 doctors in our institution were recruited randomly. The purpose of the study was explained and informed oral consents were taken.

Study instrument:

The questionnaire consisted of four sections. First section was about respondent's personal information including gender, age. Second section included questions related to participants knowledge towards chronopharmacology. Third section included questions related to participants attitude towards chronopharmacology. Fourth section included questions related to participants practice towards chronopharmacology. The questionnaire consisted of 22 questions out of which one was open ended & remaining were close ended.

Data collection method:

Data collection was done through online forms. Participation in survey was voluntary. The questionnaire was provided in English only.

Data analysis:

All returned questionnaires were double-checked for accuracy and then the collected data were feed into an excel spreadsheet dataset. 200 participants completed the questionnaire satisfactorily.

Ethical considerations:

Oral informed consent was obtained from all the respondents. Participation was voluntary. The Ethical approval was received from Institutional ethics committee.

3. Results

- Among the participants, 55% are males & 45% are females.
- Most of the participants are between the age group 20-40 years.

Questions related to participant's knowledge	Yes (%)
Have you heard the term chronopharmacology & chronotherapeutics?	55%
Chronopharmacology is concerned with the effects of drugs on timing of biological events & rhythms like circadian rhythm.	67%
Chronopharmacology is concerned with relation of biological timing to the effects of drugs.	74%
Chronotherapeutics is an area where dosing regimen is synchronized with biological rhythms.	76%
Circadian rhythm variation can affect drug disposition in the body.	77%
Any perturbation in circadian rhythm can lead to pathological alterations in the body.	58%
Biological rhythms could be a determinant of pharmacokinetic properties such as absorption & biotransformation of a drug.	74%
Biological rhythms have their implications in:	
• Neurosciences	81%
• Jet lags	68%
• Diseases like asthma, diabetes & obesity	68%
• Low work performance	67%

- 55% of participants have answered that they have heard the term chronopharmacology.
- 67% of participants have chosen yes for the question that chronopharmacology is concerned with the effects of drugs on timing of biological events & rhythms like circadian rhythm.
- 74% Of participants have chosen yes for the question that chronopharmacology is concerned with relation of biological timing to the effects of drugs.
- 76% of participants have chosen yes for the question that chronotherapeutics is an area where dosing regimen is synchronized with biological rhythms.
- 77% participants have answered yes for the question that circadian rhythm variation can affect drug disposition in the body.
- 58% of participants answered yes for the question that any perturbation in circadian rhythm can lead to pathological alterations in the body.
- 74% participants answered yes for the question that biological rhythms could be a determinant of pharmacokinetic properties such as absorption & biotransformation of a drug.

Questions related to participant's attitude	Yes (%)
Chronotherapy could reduce the incidence of adverse drug effects.	77%
Chronotherapy could increase the efficacy of a drug.	64%
At therapy initiation, counselling should be done to the patients about more effective 'circadian-time windows' for drugs, where this is applicable.	82%
Counselling the patients about taking their medication at more effective 'circadian-time windows' for a particular drug may lead better cost effectiveness, where this is applicable.	82%
Chronotherapeutic information should be included in drug references.	83%

- 77% of participants answered yes for the question that chronotherapy could reduce the incidence of adverse drug effects.
- 64% of participants answered yes for the question that chronotherapy could increase the efficacy of a drug.
- 82% of participants answered yes for the question that 'at therapy initiation, counselling should be done to the patients about more effective circadian time windows for drugs, where this is applicable.
- 82% of participants answered yes for the question that counselling the patients about taking their medication at more effective circadian time windows for a particular drug may lead better cost effectiveness, where this is applicable.
- 83% of participants have answered yes for the question that chronotherapeutic information should be included in drug references.

Questions related to participant's practice	Yes (%)
Correct timing of drug administration is always mentioned in your prescription.	81%
Proper patient counselling regarding timing of drug intake is essential part of your practice.	81%
Such type of counselling is wastage of time.	28%
Such type of counselling is essential but your overburdened schedule does not allow to do so.	78%
Have you ever been taught chronopharmacology/ chronotherapeutics during your medical education.	43%
Do you realize a need for including chronopharmacology/ chronotherapeutics in medical education curriculum.	65%
Have you ever encountered a situation where drug prescribed was not effective enough due to incorrect timing of intake?	72%

- 81% of participants have answered yes for the question that correct timing of drug administration is always mentioned in your prescription.
- 81% of participants have answered yes for the question that proper patient counselling regarding timing of drug intake is essential part of your practice.
- 28% of participants have answered no for the question that such type of counselling is wastage of time.
- 78% of participants have answered yes for the question that such type of counselling is essential but your overburdened schedule does not allow to do so.
- 43% of participants have answered yes for the question that chronopharmacology/ chronotherapeutics have been taught during their medical education.
- 65% of participants have answered yes for the question that there is need for including chronopharmacology/ chronotherapeutics in medical education curriculum.
- 72% of participants have answered yes for the question that 'have they ever encountered a situation where drug prescribed was not effective enough due to incorrect timing of intake'.

4. Discussion & Analysis

Most of the participants have not heard the term chronopharmacology & chronotherapeutics. Majority of the participants who have heard the term know it by reading books & journals. But they have knowledge about the relation between the biological rhythm and diseases.

Majority of the participants have positive attitude about chronopharmacology. They believe chronotherapy could reduce the incidence of adverse effects & could increase the efficacy of the drug. They also believe counselling the patients regarding biological rhythm is essential & information regarding chronotherapy should be included in drug references.

Majority of the participants are mentioning correct timing of the drug intake. Most of them think counselling of patients regarding time of drug intake is essential but they are unable to do it due to their overburdened schedule. Only few participants have been taught about the chronopharmacology

during their medical education & they think it should be included in medical education curriculum.

The discovery of biological clock has changed many established concepts & hypothesis in pharmacology and medicine. Diseases born due to disturbances or deregulation of biological clock are set right only by setting the clock right. There are many natural & life style factors which deregulate the clock.

A study by Pushkala K stated that chronic disruption of one of the day/night cycle leads to weight gain, impulsivity, slower thinking & other physiological & behavioural changes in mice, similar to those observed in people who experience shift work or jet lag.

The drug therapy can be optimized by tailoring the dosing schedule based on chrono -biological pattern. The safety & efficacy of the drug is achieved by coordinating the peak plasma concentration of the drug with circadian rhythm of the body.

Earlier it was difficult to treat the diseases borne due to deregulation of biological clock. However after the understanding of this clock it was possible to formulate some drugs through the study of chronopharmacodynamics of some chemical compounds and manage such diseases so as to get some relief to the patients⁽⁴⁾.

Chronopharmacology is a field that is relatively unappreciated, under-represented & under-utilised in the development of new drugs, drug regulation & clinical practice. Given the vast financial costs and time associated with drug development, chronopharmacology could provide ways to improve the efficiency of this process, which would ultimately ensure effective medicines reach patients more rapidly. There is a need for more evidence to fully realise the clinical potential of chronopharmacology⁽⁶⁾.

Chronopharmacology paves the way for investigating each drug in regards to biological timing & its effects on a rhythmic pattern. It holds the promise of drug safety & enhances the treatment process for a particular disease. The recently evolving discipline of chronopharmacology has opened several ways for managing higher procedures & special illnesses.

Identification of rhythmic markers for selecting dosing time & further research in the field of chronopharmaceuticals will lead to improved progress & diffusion of chronotherapeutics. It will offer a further dimension for research for safer & efficient disease therapy in future⁽⁷⁾.

5. Limitations of the Study

This study has been conducted at a single center and hence the sample size is very small. Similar studies should be conducted at different areas.

6. Conclusion

There is a need to educate & train doctors about chronopharmacology by conducting CME's etc. A more

detailed knowledge is required not only of how clocks control physiology, but also of how clocks in different organ systems contribute to different organ systems contribute to different processes relevant to PK/PD. After the understanding of the biological clock, it was possible to formulate some drugs through the study of chronopharmacodynamics of some chemical compounds & manage such diseases so as to get some relief to the patients.

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References

- [1] Anandabaskar N. Chronopharmacology. In Introduction to Basics of Pharmacology and Toxicology 2019 (pp. 261-270). Springer, Singapore.
- [2] Dallmann R, Brown SA, Gachon F. Chronopharmacology: new insights and therapeutic implications. Annual review of pharmacology and toxicology. 2014 Jan 6;54:339-61.
- [3] Tamilanban T, Mohamedmajeed A, Chitra V. Overview of chronopharmacology. Research Journal of Pharmacy and Technology. 2020 Sep 1;13(9):4457-63.
- [4] Gupta PD. Chronopharmacology: A new approach for drug delivery schedules. Clinical Research and Clinical Trials. 2021;3(1).
- [5] Patil AA, Kengar MD, Mane SA, Waggmare SA, Nirmale DM. Chronopharmacology: A Great Future for the Medicines.
- [6] Bairy LK. Chronotherapeutics: A hype or future of chronopharmacology?. Indian Journal of Pharmacology. 2013 Nov;45(6):545.
- [7] Dobrek L. Chronopharmacology in therapeutic drug monitoring—dependencies between the rhythmic processes and drug concentration in blood. Pharmaceutics. 2021 Nov 12;13(11):1915.