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Original Research Article

Chronopharmacology: an insight into its knowledge among medical students

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ABSTRACT

Background: Chronopharmacology is the science which deals with the optimization of drug dose that promotes efficacy and minimizes the adverse effects by taking the medications in relation to the biological rhythm. Circadian rhythms can be manipulated to treat certain disorders through chronotherapy. The aim of the study was to explore this knowledge of chronopharmacology and to give an insight about it among medical students.

Methods: This was a cross sectional study conducted across students of different medical colleges in India by giving semi structured questionnaire.

Results: A total of 208 participants (74 males, 134 females) from different batches of MBBS were participated. Majority of them are aware about the term chronopharmacology but their lack of apprehension on chronotherapy was evident throughout the study.

Conclusions: There is an inadequate knowledge on chronopharmacology among medical students. Introducing this as a part of undergraduate curriculum can bring out a significant change in the practice of modern medicine.

Keywords: Chronopharmacology, Medical students, Circadian rhythm, Chronotherapy

INTRODUCTION

Chronopharmacology is the science dealing with the optimization of drug effects and minimization of adverse effects by timing the medications in relation to the biological rhythm.¹ This concept was first outlined by Alain Reinberg and Franz Halberg in 1971, the first scientific approach on the importance of synchronizing the therapy with the 'biological clocks' took place in 1814.¹

The goal is to improve our understanding of periodic and thus predictable (e.g.: circadian) changes in both desired effects (chrono-effectiveness) and tolerance (chrono-tolerance) of medications.² Our understanding of the relationship of biological rhythms in disease development and drug therapy is growing. Currently however,

chronopharmacology is a field that is relatively unappreciated, under-represented and under-utilized in the development of new drugs, drug regulation, and clinical practice.³

However, during the last couple of decades, much progress has been made in the field of circadian medicine, and the concept of biological rhythm is being viewed as a possible complement to homeostasis.⁴ It is important to maintain constancy in the blood concentration of drugs so as to maintain the constant efficacy of drug.⁴ Circadian oscillations in both pharmacokinetics and pharmacodynamic processes are known to affect efficacy and toxicity of several therapeutic agents.⁵ It may also be very important in influencing the responses to various medications. Many aspects of pharmacology and

toxicology also oscillate according to the same 24-hour clock.⁶

A thorough understanding of the circadian rhythm and its application for drug administration serves productive utilization of drugs. Thus, chronopharmacology is synchronization of drug therapy with the biological rhythm. However, knowing the temporal variability (ultrafine, circadian, infradian, circaseptan, circatrigintan, and circannual) of the manifestations and the security of drug utilization constitutes the reason of a new approach of the therapy - chronotherapy.¹

Pharmaceutical industries have come up with various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices in recent years for the delivery of synchronized drug concentrations to rhythms in disease activity. Some of the diseases where chronotherapeutics is employed currently are cardiovascular diseases like myocardial infarction, hypertension, congestive heart failure and stroke, bronchial asthma, peptic ulcer, cancer, chemotherapy, etc.^{1,2}

So far, there hasn't been a study done to explore the knowledge about chronopharmacology among medical students. The aim of the study was to analyze the knowledge of chronopharmacology among the medical students for the diseases which follow circadian pattern.

METHODS

This was a cross sectional questionnaire based study which was conducted across MBBS students of different medical colleges in India, after obtaining prior approval from the ethics committee of Sri Siddhartha Medical College, Tumkur. The study was conducted during the period of December 2021-October 2022.

The participants who are interested and willing only were enrolled into the study after taking informed consent. A semi structured questionnaire was developed after reviewing the literature to assess the subjects' knowledge about chronopharmacology. Few questions were related to demographic characters like sex and status of student. Q1 and 2 are related to terminology, Q3-5 related to GIT disorders, Q6-8 related to respiratory disorders, Q9-11 related to cardiovascular disorders and Q12-14 are related

to miscellaneous disorders. The data obtained were entered in Microsoft excel and analyzed using statistical software. Only completed questionnaire were used for analysis. Scores of minimum of 50% or more correct responses were considered to have adequate knowledge.

RESULTS

A total of 208 participants belonging to different phases of MBBS responded to the questionnaire with majority from 3rd year. Males were 74 and females were 134 of the total participant as depicted in Table 1.

Table 1: General characteristics of study participants.

Characteristics	Frequency (%)
1st year MBBS	50 (24.0)
2nd year MBBS	61(29.3)
3rd year MBBS	80 (38.5)
4th year MBBS	11 (5.3)
Intern	6 (2.9)
Male-74 (35.6)	Female- 134 (64.4)

A set of questions depicting the effect of chronopharmacology on major systems in human body were formulated and the data was collected and analyzed as depicted in Table 2. Among the total participants, (88%) knew the term Chronopharmacology and (81.7%) knew that circadian rhythm is associated with 24 hr time frame. But the majority was unaware (69.7%) about the diurnal variation of gastric acid production which occurs more during night time. Similarly (67%) didn't know that PUD symptoms worsen during night time and that the best time to administer H₂ blocker is during night time (76%). Only 35.1% were correct that bronchial asthma exacerbates during night and 20.2% were correct about the effectiveness of inhalational corticosteroids during the night time. Similarly, only 19.2% were right that there is an increased risk of myocardial infarction during morning (6 am-12 pm), also only 24.5% and 23.1% were right about administering ACE inhibitor in night and calcium channel blocker in the morning respectively. Administering oxaliplatin at 4 pm was found to be more effective in treating bowel cancer but only 22.1% participants knew this. The knowledge about physiological synthesis of cholesterol which occurs mainly during night was known to 41.3% and only 22.1% knew that statins can be administered any time during the day.

Table 2: Frequency of responses related to chronopharmacology.

Terminology	Frequency (%)	
The study on effect of drugs which vary with biological timings and endogenous periodicities is called	Chronopharmacology	183 (88.0)
	Chronobiology	9 (4.3)
	Chronometry	8 (3.8)
	Chronogram	8 (3.8)
Circadian rhythm is associated with	6-hour time frame	15 (7.2)
	8-hour time frame	8 (3.8)
	12-hour time frame	15 (7.2)

Continued.

Terminology	Frequency (%)	
	24-hour time frame 170 (81.7)	
GIT		
In which part of the day is gastric pH least in human body?	Early morning	70 (33.7)
	Mid-day	52 (25.0)
	Night	63 (30.3)
	Remains same throughout	23 (11.1)
During which part of the day would symptoms of peptic ulcer disease worsen?	Early morning (6-8 am)	58 (27.9)
	Mid-day (11 pm-1 pm)	58 (27.9)
	Night (11 pm-1 am)	68 (32.7)
	Remains same throughout	24 (11.5)
Ideal time to administer H2 blockers like ranitidine in peptic ulcer is	Before breakfast	88 (42.3)
	Before lunch	44 (21.2)
	Before dinner	50 (24.0)
	Anytime	26 (12.5)
Respiratory system		
The symptoms of bronchial asthma particularly exacerbate during	Early morning	74 (35.6)
	Mid-day	36 (17.3)
	Night	73 (35.1)
	Any time	25 (12.0)
Bronchodilators like theophylline or salbutamol sustained release preparations is more effective at	Morning	55 (26.4)
	Noon	61 (29.3)
	Evening	33 (15.9)
	Night	59 (28.4)
Administering a single daily dose of inhalational corticosteroid will be more effective at what time during the day	Morning	61(29.3)
	Afternoon	61 (29.3)
	Evening	42 (20.2)
	Night	44 (21.2)
CVS		
There is an increased risk of Myocardial Infarction between	6am - 12 pm	40 (19.2)
	12 pm - 6 pm	53 (25.5)
	6 pm - 12 am	78 (37.5)
	Same at all intervals	37 (17.8)
ACE inhibitor: enalapril are highly effective in reduction of blood pressure if given in	Morning	59 (28.4)
	Afternoon	51 (24.5)
	Night	51 (24.5)
	Evening	47 (22.6)
The ideal time to administer calcium channel blocker nifedipine in the treatment of hypertension-	Morning	48 (23.1)
	Mid-day	58 (27.9)
	Evening	40 (19.2)
	Bed time	62 (29.8)
Miscellaneous		
The ideal time to administer platinum based chemotherapy agent oxaliplatin for treating bowel cancer is	8 am	57 (27.4)
	4 pm	46 (22.1)
	12 pm	50 (24.0)
	Any time	55 (26.4)
Cholesterol synthesis occurs mainly during	Morning	35 (16.8)
	Afternoon	48 (23.1)
	Night	86 (41.3)
	Same throughout	39 (18.8)
When do you think administration of statins would be more efficacious	During morning	42 (20.2)
	During afternoon	52 (25.0)
	During night	68 (32.7)
	Remains same throughout	46 (22.1)

DISCUSSION

In the present study we considered chronopharmacology of diseases which show strong association with circadian rhythm. These are ubiquitous phenomena that recur daily in a self-sustaining, entrainable, and oscillatory manner, and orchestrate a wide range of molecular, physiological, and behavioural processes. Circadian clocks are comprised of a hierarchical network of central and peripheral clocks that generate, sustain, and synchronize the circadian rhythms.⁵

Drug transport and diffusion is highly dependent on gastric pH that regulates drug ionization and hydrophobicity. In most animal species including man, gastric pH presents a strong circadian pattern influencing drug solubility.⁶ There is an increase in gastric acid secretion in the evening and at night and hence the ideal time to administer H₂ blockers is during bedtime.⁷

Similarly bronchial asthma is a common disorder with largest circadian variation with the symptoms exacerbating during night.⁸ Serial recordings of peak expiratory flow in a patient with asthma shows sharp overnight fall (morning dip) and subsequent rise during the day. Administration of glucocorticoids in the night improves the PEF rate and reduction of morning dip.^{8,9} This emphasizes that the drugs need to be administered during the night which was lacking in the present study.

Similarly the knowledge was lacking with regards to cardiovascular disorders. This system exhibits dramatic time-of-day dependent rhythms, for example the diurnal variation of heart rate, blood pressure, and timing of onset of adverse cardiovascular events such as heart attack and sudden cardiac death.¹⁰ This is confirmed by three fold elevation of CK-MB in myocardial infarction peaking at 9 am.¹¹ Blood pressure and heart rate are highest during daytime followed by a nightly drop and an early morning rise.¹² Calcium channel blocker should be administered in the morning for its peak effect and bedtime administration of ACE inhibitor is the appropriate chronopharmacology.¹

The platinum-based chemotherapy agent oxaliplatin used in bowel cancer failed in early clinical trials due to its severe toxic effects. Later the studies revealed that giving Oxaliplatin at certain times of the day- ideally at 4 pm rather than early morning dosing led to a significant reduction in its harmful effects. It then progressed through development and its use is now widespread.³ Cholesterol biosynthesis follows a circadian rhythm and is principally produced between 12:00 am and 6:00 am. But there was low quality evidence about the influence of chronotherapy on lipid levels with the use of statins.¹³ The respondents were poorly aware about the importance of drugs exhibiting chronopharmacological properties. Various studies claim that the timely administration of the drugs can result in better efficacy and decreased adverse effects.² Based on the above results, it is clearly evident that the poor knowledge among the participants about

chronopharmacology increases the chances of morbidity and which can lead to unnecessary prescription of drugs increasing the cost of treatment.

Limitations

The current study did not include postgraduates or practising physicians. The questionnaires could cover only limited drugs and diseases related to circadian pattern; however, it gives an idea regarding the status of knowledge on chronopharmacology among medical students and interns. There is a need for more researches to fully realise the clinical potential of chronopharmacology.

CONCLUSION

Our understanding on the relationship of biological rhythms in disease development and drug therapy is growing. 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 reaching patients more rapidly. Treatments already in existence may be optimized by taking chronopharmacological approaches into consideration. Lack of knowledge about chronopharmacology among medical students is very much evident in the present study. By addressing this issue in the undergraduate curriculum can bring about a huge change in modern medical practice.

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