

## Analysis of clinical relevance of chrono pharmacology in therapy of respiratory disorders in a tertiary care hospital- A prospective observational study

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### Abstracts

**Introduction:** Drugs following administration itself affect the biological rhythm or biological rhythm can affect the drug action. Administration of drugs according to biological rhythm helps in optimization and quantification of the drug effects and thereby aids in potentiation of desired effects while minimizing the undesired effects.

**Objectives:** To study the chronopharmacological relevance to time of drug administration in respiratory disorders in Medicine in-patients at a tertiary care hospital.

**Methodology:** A prospective non- interventional observational study was conducted on Medicine inpatients of a tertiary care hospital to study the relevance of chronopharmacology in respiratory disorders. Patients were included in the study based on inclusion and exclusion criteria. Data was recorded on a predesigned proforma

**Results:** Theophylline, montelukast, levocetizine, chlorpheniramine have been administered appropriately at bedtime and prednisolone accordingly in the morning in all the subjects thereby showing 100% relevance. However etophylline was administered according to chronopharmacology in 71% of subjects only.

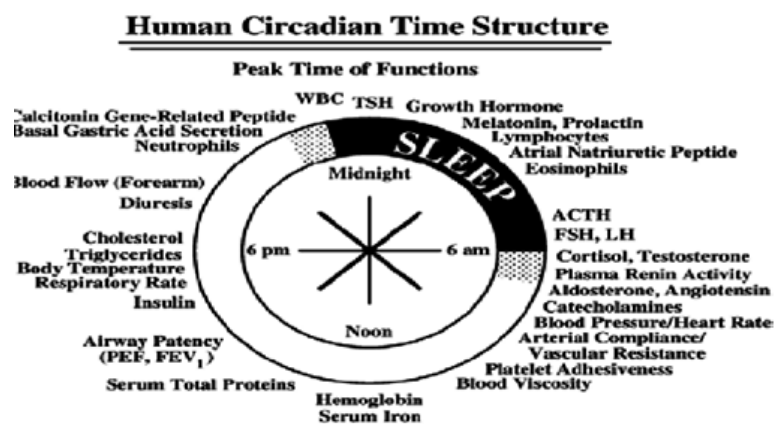
**Conclusion:** Most of the drugs recorded in the study were administered according to their relevance to circadian rhythm, while only a few drugs are lagging in the trend which needs to be addressed.

**Keywords:** Chrono pharmacology, Circadian rhythm, Respiratory disorders, Theophylline, Etophylline, Montelukast, Levocetizine, Chlorpheniramine, Prednisolone.

### Introduction

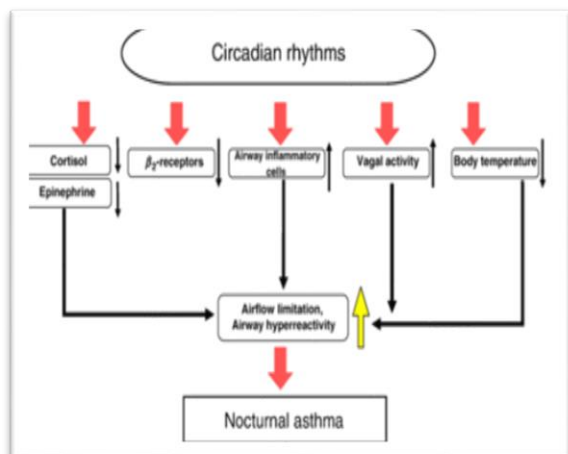
Chronopharmacology is the investigative science that elucidates the biological rhythm dependencies of medications. Chronopharmacokinetic studies of many drugs attempt to explain chronopharmacological phenomenon and demonstrate that the time of administration is a possible factor of variation in the pharmacokinetics of a drug. Time- dependent changes in pharmacokinetics may proceed from 24 hours

rhythms in each process of absorption, distribution, metabolism and elimination. Hence the quantitative as well as qualitative response of an organism varies with time of drug administration. Many disease patterns change according to physiological changes like asthma attacks precipitate in midnight and heart/ angina attacks are very likely at morning just within few hours of awakening and the treatment guidelines follow at the time of highest risk to alleviate the disease.<sup>(1)</sup>



**Fig. 1: Time of day when physiological or biochemical functions are at peak. PEF-peak expiratory flow rate; FEV-forced expiratory volume; WBC- white blood count; TSH-thyroid stimulating hormone; ACTH- adrenocortical tropic hormone; FSH- follicle stimulating hormone; LH-luteinizing hormone.<sup>(2)</sup>**

In the respiratory system, bronchoconstriction increases at midnight to morning because of increased parasympathetic tone, decreased adrenaline, decreased cortisol and increased sensitivity to allergens and irritants at night.<sup>(3)</sup> (Fig. 2).



**Fig. 2: Mechanisms underlying the nocturnal exacerbation of asthma. Airflow limitation and airway hyper-reactivity are caused by chronic airway inflammation, and are associated with changes of the parasympathetic nervous system and endocrine system at night. Because of the circadian rhythm of these factors, exacerbation of asthma often occurs in the early morning.<sup>(4)</sup>**

The findings of many studies clearly show that the nasal congestion and obstruction of allergic rhinitis can become so great during the night that the sleep of moderately and severely affected persons can be disturbed, compromising quality of life with difficulty in awakening in the morning, daytime fatigue, poor daytime concentration, poor work and school performance, and altered or depressed mood and irritability. Symptoms are likely to be much more intense nocturnally, during intended sleep, and/or in the early morning on awakening.<sup>(5,6)</sup>

The symptoms of sneezing, nasal itch, and rhinorrhoea, nasal congestion and obstruction are due to the exacerbation of inflammation of the nasal, sinus, and other tissue of the upper airway.<sup>(7)</sup> The release of inflammatory mediators like T cells, leukocytes, eosinophil, histamine, prostaglandins, and leukotriene, resulting in local vasomotor changes and local tissue oedema, inflammation, injury and mucus secretion. Most commonly eosinophil release is elaborated during midnight to morning.<sup>(8)</sup>

Respiratory symptoms could also involve key neuroendocrine circadian rhythms. For example, cortisol, which modulates tissue inflammation, attains peak blood concentration in the morning around the time of commencing daily activity and remains elevated throughout the waking span; Cortisol declines in the

late evening and reaches its lowest concentration of the 24 hour around the middle of the night-time sleep period. The circadian rhythms in adrenaline and noradrenaline may also be involved since they can play a role in controlling the trafficking of eosinophil and the stability of their membranes. The circadian rhythm in adrenaline could result in differential release of pro-inflammatory mediators during the 24 hour. In this regard, plasma histamine and other eosinophil derived mediators are in circadian rhythm in bronchial asthma subjects; Plasma histamine concentrations are greatest during the night when plasma adrenaline and noradrenaline concentrations are lowest.<sup>(9)</sup>

It is well understood by a previous study that nocturnal exacerbation of asthma, COPD, allergic rhinitis have circadian rhythm<sup>(4)</sup> and has thrown light upon the chronopharmacological approach to gain maximum effects. 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. The drugs used for treatment of respiratory disorders and having circadian rhythm are corticosteroids, methylxanthines, antihistaminic and leukotriene receptor antagonists.

Most of the drugs currently used for chronotherapy of asthma are administered once at night with the goal of preventing chronic airway inflammation or the onset of airflow limitation. A single dose at night contributes to improve patients' adherence and better self-management of asthma.

## Methodology

A prospective, non-interventional, observational study was conducted on the in-patients of the medical wards in a tertiary care hospital during the period December 2014 to June 2016. In the first month, a pilot study was conducted to assess feasibility of carrying out this study, to check availability of patients required for the study and if required to modify the proforma to facilitate the collection of relevant data.

Medicine inpatients aged  $\geq 14$  years, of either gender and treated for chronic disorders were included in the study. Outpatients, age  $< 14$  years, patients treated for acute infectious conditions, those requiring emergency treatment and pregnant women were excluded from the study. The patients were followed up for a period of 5 days of their hospital stay. Data collected from patients' case sheets were recorded in the predesigned proforma containing details of patients' demographics, onset and duration of illness, the drugs prescribed, dose, frequency, duration, timings and route of administration, comorbid illnesses, drug interactions and adverse effects any. The study was conducted after obtaining clearance from the Institutional Ethics committee.

Descriptive statistical analysis was done using Microsoft office excel 2010.

## Results

Over a period of nineteen months, 1064 inpatients from the Medicine wards were screened out of which 744 subjects were included in the study based on the inclusion and exclusion criteria. Among the study subjects 68.10% (n=506) were males and 31.98% (n=238) constituted females. The average age of male and female was found to be 55.97 and 55.96 years respectively.

Respiratory conditions seen in the wards were COPD, bronchial asthma, chronic bronchitis, pleural effusion, allergic broncho-pulmonary aspergillosis, lung fibrosis, sinusitis, pulmonary oedema, pulmonary TB and bronchiectasis. Out of the 114 drugs used in the treatment of various illnesses, 16 drugs were used in the treatment of respiratory disorders including steroids and autacoids. Out of these 16 drugs only 6 drugs having chronopharmacologic importance was studied. Levocetirizine (n=24) and chlorpheniramine are seen to be administered according to chronopharmacology at bedtime in all the 100% subjects. Similarly montelukast (n=72) and theophylline (n=4) were seen to have 100% relevance to their ideal time of administration at bedtime. However etophylline (n=138) was administered according to chronopharmacology in 71% of subjects only. Among the steroids, prednisolone (n=2), has been administered accordingly in the morning in all the patients. (Fig. 3)

## Discussion

In the current study out of the 12 drugs used in the therapy of respiratory disorders, only 6 drugs showed chronopharmacology. Theophylline, montelukast, levocetirizine have been administered appropriately at bedtime in all the subjects thereby showing 100% relevance. A study on motelukast reported a higher effectiveness after evening administration,<sup>(10)</sup> another study failed to find significant differences in its effect depending on morning versus evening administration.<sup>(11)</sup> A study on chronotherapy of a once daily evening dose of a new controlled release theophylline preparation, that achieves peak blood concentrations at 10-12 hours after dosage, effectively improved the values of PEF and symptoms of nocturnal asthmatics.<sup>(12)</sup> Acute nocturnal attacks may be prevented best by oral theophylline in retarded drug formulations or by inhalation of long-acting beta-sympathomimetic just before going to bed controls the nocturnal dip of bronchial potency.<sup>(13,14)</sup>

Antihistaminic drugs levocetirizine and chlorpheniramine are the most common group of drugs used in this study and are better administered at bedtime to decrease the midnight exacerbation of allergy. In the current study the same trend has been followed effectively in all subjects.

Etophylline used as either parenteral or oral route, was administered correctly at bedtime in only 71% of total subjects. Bedtime administration has better efficacy in

reducing the midnight exacerbation of the asthma, COPD or allergic rhinitis seen due to high sensitivity to allergy, high parasympathetic tone, so high bronchoconstriction and lesser protective cortisol at night. The other drugs recorded in the study like salbutamol, tiotropium, budesonide formoterol do not show chronopharmacological difference. Literatures have shown no significant difference in morning or evening doses of these drugs.<sup>(15)</sup>

Steroids have been used in various conditions like exacerbation of COPD, bronchial asthma, or lower respiratory tract infection as inhalational route. Besides respiratory, in osteoarthritis and rheumatoid arthritis steroids have a crucial role. It is better to prescribe them in the most appropriate time to derive its maximum effects with less or no side effects. In case of respiratory conditions prednisolone, ciclesonide or budesonide are usually used, but chronopharmacologic data is available only for methylprednisolone to administer in the morning to noon up to around 3 pm for maximum benefits.<sup>(16)</sup> A pioneer study evaluating the relationship between corticosteroid therapy and time of administration found that a dose of methylprednisolone (40 mg) was more effective on peak expiratory flow rate (PEFR) when administrated at 3 p.m. and less effective at 3 a.m. and 7 p.m.<sup>(17)</sup> In this study 100% of subjects followed chronopharmacology.

The current study adds scope for improvement in the therapeutic outcome if chronopharmacology is considered in treatment. In view of the current research and investigations, the chronopharmacologic aspect plays a major role for the optimal utilization of the available drugs to fetch an improved therapeutic effect when followed in clinical practice.

The study is limited by the fact that the dosage of each drug was not taken into consideration and was focussed mainly on the timing of drug administration. Also the beneficial effects of chronopharmaceuticals and identification of circadian oscillations at the protein level could be studied in the future.

## Conclusion

The current study depicts the correct application of chronopharmacology. Only a few drugs are lagging in the trend which needs to be addressed, while majority of the drugs have been administered at the right time. The study throws light on the importance of circadian rhythm in drug therapy. The knowledge of chronopharmacology and inclusion of this concept in prescribing medicine is crucial in understanding interactions between biological clock and drug for an effective therapy, a better patient outcome, and decrease in toxicities and the duration of hospital stay and to improve quality of life.

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### Conflicts of Interest

Nil

### Funding Source

Nil

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