

Perspective

Chronotherapeutics — The Need to Listen to Nature's Rhythm

Nandini Chatterjee¹

The concept of chronopharmacology is not new¹ but its use in day to day practice is suboptimal even though awareness about the circadian rhythm and its clinical ramifications has gained momentum.

Circadian rhythm is a system of 24 hour oscillations of the bodily functions in conjunction to the solar day. It controls sleep/wake cycles, food intake, body temperature, neurohumoral as well all metabolic processes. Day and night as well as the sleep/wake cycle has profound effect on the physiology of the organ systems of our body by causing fluctuations in hormones and neurotransmitters. Similarly disease symptomatology varies at various times of the day. Diseases, such as hypertension, asthma, coronary syndromes, peptic ulcer, arthritis, etc, follow the body's circadian rhythm.

For example, there is a physiologic fluctuation in BP which peaks at around 21 hours and dips to minimum at night during sleep (SBP by 3-6 mm Hg DBP by 2-3 mmHg).

It has also been observed that acute myocardial infarction, sudden cardiac death and syncopes are more common in early mornings probably due to increased glucocorticoid levels and increased tendency of platelet aggregation in the mornings.

Hypothalamic nuclei maintain a daily rhythmic fluctuation in corticotrophin releasing hormone and AVP which in turn controls ACTH and cortisol levels in the daytime. Cortisol levels peak in the morning to prepare the body for activity and feeding.

Insulin secretion and sensitivity is lowest between 3-5 am leading to early morning hyperglycemia (Dawn Phenomenon). The Somogyi phenomenon is found in diabetics on insulin where there is hypoglycaemia in the late evening/night due to increased sensitivity and early morning hyperglycemia due to counter regulatory hormone action. The solution is to decrease night insulin dose.

Osteoarthritis worsens during the day and is most troublesome in the evenings but for people with rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day progresses.

Observing such rhythmic patterns, the science of

chronopharmacology which includes chronopharmacokinetics and dynamics, has evolved.

Chronopharmacokinetics involves the study of temporal changes in drug absorption, distribution, metabolism and excretion with respect to time of administration. In order to optimise therapeutic outcomes and minimise side effects².

Chronodynamics refers to dosing time, i.e., rhythm-dependent, differences in the effects of medications. Such administration-time differences are due to rhythms in the free-to-bound drug fraction, number and conformation of drug-specific receptors, ion channel dynamics, and rate limiting step(s) in metabolic pathways. Both the beneficial and adverse effects of medications can vary significantly according to their administration time³.

Here are some instances involving different organ systems and their diseases where circadian biology may be used to our advantage

Gastrointestinal System :

Gastric acid secretion is highest at night. Chronotherapy of peptic ulcers with **evening once daily dosing of H2 receptor antagonist is an effective measure⁴**.

Differences in chronopharmacokinetic profiles between Propranolol, a lipophilic β -blocker, and Atenolol, a hydrophilic β -blocker, in patients with hypertension showed that Propranolol, but not Atenolol, is absorbed more rapidly after morning administration compared with evening administration. This confirms that the absorption rate of a lipophilic, but not a hydrophilic, drug is faster after the morning dosage in humans.

Cardiovascular System :

BP is at its nadir during the sleep cycle and rises steeply during early morning awakening period but nightly dip is lost or reversed at times. **ACE inhibitors given at night ensures night time dip and controls early morning rise. Statins are to be given in the evening before bedtime as cholesterol synthesis peaks in the early morning** and this may produce better LDL reduction

Joints :

For **osteo arthritis, painkillers are best given in the noon**. The same drug will be effective when taken after the evening meal for rheumatoid arthritis. In severe **morning**

¹MD, FICP, Professor, Department of Medicine, IPGME&R and SSKM Hospital, Kolkata 700020

symptoms of Rheumatoid arthritis, steroid works better as a night time release formulation.

Lungs :

A normal lung function undergoes circadian changes and reaches a low point in the early morning hours. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during early morning hours. Ex: **Theophylline preparation taken once a day in the evening so that blood level reaches peak in early morning**⁵.

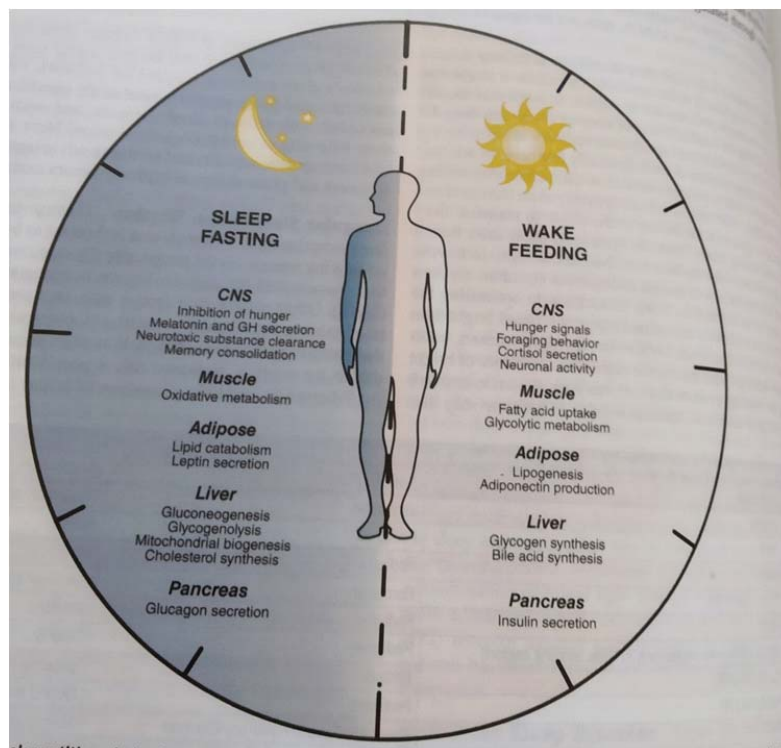
Cancer :

Chronobiological cycles for normal cells and tumour cells may be different. Cancer drugs should be timed to cycles of tumour cells making them more effective against cancer and less toxic to normal tissues. Blood flow to tumours and tumour growth rate are greater during activity phase than rest phase.

5-Fluorouracil works best at night in colon carcinoma as the malignant cells are more susceptible at that time. This displays the phenomenon of Chronoesthesia, which is the circadian change in the susceptibility of any biosystem to a drug (including organ systems, tumors) parasites, etc. **Doxorubicin is less toxic in the early morning as WBC recover faster.**

If symptoms of a disease display circadian variation, drug release should also vary over time. Variations, both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems with adequate dose at appropriate time. Various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices are coming up⁶.

To conclude, chronobiology is a vast subject hitherto untapped to its full potential. Not only medications but the concepts of chronoexercise and chrono diet are catching



up. It is important to sensitize the medical fraternity to the benefits of this branch of medicine by broadening the horizon of our collective consciousness.

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