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Review Article

Chronobiology and chronotherapeutics

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Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure and chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day, and based upon this, chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. Though the biochemical, physiological and pathological variations over a 24hour period in humans has been well known in ancient science of Ayurveda, but the modern science is not much aware of it.

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours[1]. Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle[1]. Most people sleep at night and rise in the morning. In night-shift workers (who typically sleep during the day), most circadian rhythms are shifted to match their sleep-wake cycle [2].

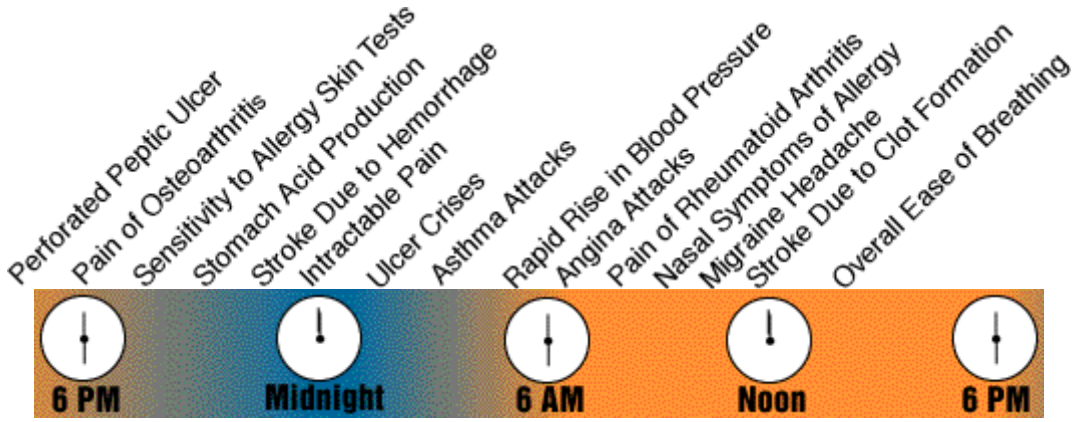
The goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time.

Many drugs display normal, reproducible daily variations in pharmacokinetics and pharmacodynamics. Lemmer [3] identified more than 100 drugs that display significant variation in concentrations or effects, or both, over 24 hours. Perhaps the best example is heparin. Even when it is administered at a constant infusion rate, the activated partial thromboplastin time and the risk of bleeding vary significantly according to the hour of the day and are higher at night [4]. The narrower the therapeutic window (i.e., risk-benefit ratio) for a specific drug, the more important the implication of the circadian variation in plasma levels [3].

There are number of conditions which show a circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Some of the conditions, which may be significantly benefited, are given below:

1. Hypertension
2. Myocardial infarction
3. Cerebrovascular accidents
4. Bronchial asthma
5. Peptic ulcer
6. Arthritis
7. Hypercholesterolemia

CIRCADIAN RHYTHMS OF DISEASES
Peak Time of Event/Variable



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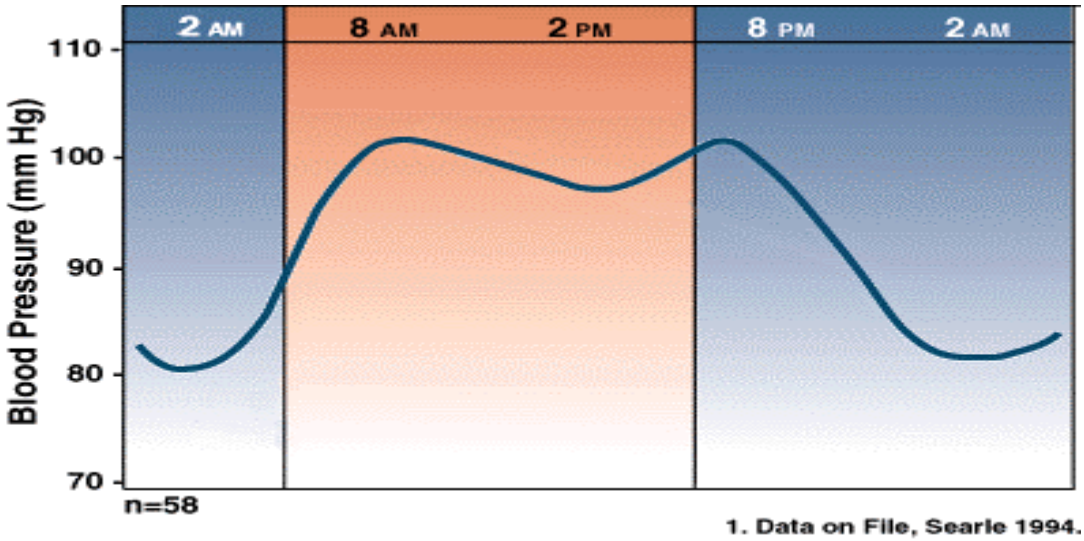
Heart rate and blood pressure are increased in the early morning hours (morning or A.M. surge). The blood pressure declines form mid afternoon and is minimum at midnight[5, 6]. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or "a.m." surge[6, 7].

Systolic blood pressure rises approximately 3 mm Hg/hour for the first 4-6 hours post-awakening, while the rate of rise of diastolic blood pressure is approximately 2 mm Hg/hour[8].

Delivery of the drugs according to the variations is relatively a new practice. The first such agent developed for hypertension and angina is COER(R-Verapamil).

Advantage of this formulation is that delivery of the active drug tailored to the typical circadian rhythms and heart rate, and the patients are better covered in the early morning when cardiovascular need appears to be greatest, and the effects of traditional medications seems to wane the timings of various antihypertensives and can be adjusted according to their onset of action, half life and duration of action.



1. Data on File, Searle 1994. Study LAV 01.

Myocardial Infarction

Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 A.M. and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone[9, 10].

Cerebrovascular accidents

The cerebrovascular accidents have been shown to occur on the first hours of morning between 10 A.M. and 12 noons, and the incidence declines steadily during the evening and the midnight.

A major objective of chronotherapy for cardiovascular disease is to deliver the drug in higher concentration during time of greatest need and in lesser concentrations when the need is less. ACE inhibitors are more effective when administered during night. Atenolol, Nifedipine and amolodipine are more effective when administered at night.

The first chronotherapeutic therapy for hypertension and angina pectoris has recently been developed which matches drug delivery to the circadian pattern of blood pressure and rhythm of myocardial ischemia. Verapamil has been employed in this system where release is observed after 4-5 hours and continues for 18hours. Taken at bedtime, this provides optimal blood concentration between 4A.M. and 12 noons [11,12,13].

Data from recent studies demonstrate that antihypertensives and antianginal therapy can be designed to mimic the circadian rhythms. Future research will evaluate whether timings of drug delivery has an effect on the outcomes like control of hypertension, silent ischemia, myocardial infarction and quality of life.

Bronchial asthma

Asthma may be the most common disease with the largest circadian variation. Because asthma has such a striking circadian variation, several types of chronotherapy have been tried. In one study[14], use of a timed-release formulation of theophylline (Theo-24) achieved therapeutic drug concentrations during

the night and avoided toxic levels during the day when the dose was ingested at 3 pm. Another study [15] showed that a single daily dose of inhaled corticosteroids, when administered at 5:30 pm rather than 8 am, was nearly as effective as four doses a day. In addition, oral prednisone has been shown to be much more effective in improving several features of nocturnal asthma (i.e., overnight fall in forced expiratory volume in 1 second [FEV_1], 4 am FEV_1, and response to a standard dose of inhaled $beta_2$ agonist) when administered at 3 pm rather than 8 am [16].

Arthritis

The new cyclooxygenase-2 inhibitors effectively relieve osteoarthritis symptoms when taken in the morning; better results are obtained in rheumatoid arthritis when part of the dose is taken in the evening[17].

Peptic ulcer disease

In the past, $histamine_2$ antagonists were administered at regular intervals around the clock, on the basis of pharmacokinetic properties. However, because maximal acid secretion, peptic ulcer disease pain, and perforation of gastric and duodenal ulcers are more common at night, administration of these drugs at bedtime is more effective. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer recurrence [18].

Hypercholesterolemia

When the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors were first introduced, morning dosing was recommended. This strategy was re-evaluated after the discovery of the circadian rhythm of cholesterol biosynthesis [19], in which higher rates of cholesterol intake and hepatic cholesterogenesis occur during the evening hours, even in the fasting state.

One clinical study [20] showed that evening administration of an HMG-CoA reductase inhibitor was more effective at lowering serum cholesterol levels than the same dose given in the morning. Initially, studies involving morning dosing of HMG-CoA reductase inhibitors failed to show a reduction in cardiovascular morbidity and mortality. However, the first primary prevention trial that studied evening dosing [21] revealed a significant reduction in serum cholesterol levels as well as rates of such cardiovascular end-points as myocardial infarction, unstable angina, and stroke. On the basis of these findings, it now is recommended that five of the six currently approved HMG-CoA reductase inhibitors be administered between the evening meal and bedtime; atorvastatin calcium (Lipitor) may be an exception because of its long elimination half-life [21].

Table 1. Circadian Rhythms and the Severity or Manifestation of Clinical Disease

Disease or Syndrome	**Circadian Rhythmicity**
Allergic rhinitis	Worse in early a.m./upon arising
Bronchial asthma	Exacerbations more common during sleep
Rheumatoid arthritis	Symptoms are most intense on awakening
Osteoarthritis	Symptoms worse in the middle/latter portion of the day
Angina pectoris	Chest pain and ECG changes more common during the early a.m.
Myocardial infarction	Incidence greatest in the early a.m.
Sudden cardiac death and	Incidence highest in ventricular tachycardia morning after awakening
Peptic ulcer disease	Symptoms worse in the early (sleep) a.m.
Allergic rhinitis	Worse in early a.m./upon arising
Peptic ulcer disease	Symptoms worse in the early (sleep) a.m.
Stroke	Incidence greatest in the early a.m.

Table 2. Drugs with different onset of action and duration of action

Drugs	Onset of action	Duration of action
Calcium Channel Blockers		
Amolodipine	2-6 hrs.	2-4days
Nifidipine	30-60mins.	3-12hrs.
ACE Inhibitors		
Enalapril	1hr.	24hrs.
Beta-blockers		
Atenolol	20-30mins..	2-4hrs
Beta-agonist Salbutamol	Oral-within 30mins Inhalation-within 5mins.	Oral 4-8hrs Inhalation-3-8hrs.
NSAIDs		
Naproxen	1hr.	Up to 12hrs.
Ketoprofen	30mins.	6-8hrs.
Piroxicam	3-4hrs.	Up to 2 days.
Peptic ulcer		
Ranitidine	Within 1hr.	12hrs.
Famotidine	30-60mins.	6-8hrs.
Angina		
Nitrates (GTN)	Sublingual-within a minute.	Sublingual- 20-30mins.
	Tablet- 1-3hrs.	Oral-3-5hrs.
		Sustained release tablet (SR) 8-12hrs.

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