

Chronotherapy in hypertension

NEWS

Patients taking blood pressure medicines at bedtime had better heart health than those on a morning schedule.^[1]

(RE)VIEWS

Circadian variations in health and disease

Day–night variations in secretion of cortisol, melatonin, growth hormone, body temperature, blood pressure, platelet aggregability, vascular tone, plasma volume, etc. are well-known chronophysiological facts.

The risk and intensity of asthmatic attacks are very high during early morning compared to afternoon, maximal joint pain and stiffness during early morning in rheumatoid arthritis, increased frequency of myocardial infarction in the morning, and increased ischemic stroke in the mid-morning are some of the well-known disease conditions that seem to more or less faithfully obey the circadian pattern.

Chronotherapeutics

Chronotherapeutics (a subdivision of chronopharmacology) deals with enhancing the efficacy and safety of drugs by timing their concentrations during the 24 h to synchronize with biological rhythm determinants of a disease. Well-known examples include the long acting β -adrenergic agonists/slow release theophylline at nighttime to coincide with the early morning maximal narrowing of bronchial diameter in asthma, bedtime administration of H_2 blockers/proton pump inhibitors for maximal efficacy during maintenance therapy, the late evening increase in cholesterol synthesis with nighttime intake of HMG CoA reductase inhibitors, and so on.

Blood pressure

In humans, the blood pressure varies according to the circadian rhythm, being low during night with rapid elevation in the morning between 5 a.m. and 9 a.m. The pattern is similar in hypertensive patients with a morning surge in blood pressure in most cases. An interplay of factors such as, increased sympathetic tone, blood pressure, and heart rate, with an attendant increase in myocardial oxygen demand, and

enhanced coagulability are some of the plausible reasons for an increased occurrence of angina, acute myocardial infarction, sudden cardiac death, and stroke in the morning than at other times.

Chronotherapy may minimize side effects (fatigue and drowsiness), and maximize beneficial effects of antihypertensive medications. Ingestion of antihypertensives can affect circadian patterns of BP, but whether this translates into an effect on clinical outcomes is unknown. In a recent open label study, bedtime dosing demonstrated a significant reduction in risk for a composite outcome of cardiovascular death, myocardial infarction, and stroke. Each 5-mmHg decrease in the mean sleep-time systolic BP was associated with a 14% reduction in the risk for cardiovascular events. Thus, at least one antihypertensive at bedtime reduces the risk for cardiovascular events.^[2]

Chronopharmaceutical drug delivery

Needless to say that research on better drug delivery with a focus on drug kinetics timing (chronopharmacokinetics) is ongoing. A drug delivery system capable of releasing drug after pre-determined time delays has been reported with respect to propranolol. The drug formulation is sealed inside the insoluble capsule body by an erodible tablet (ET) which releases the drug to match the demands of chronotherapy.^[3] A new pulsatile, colonic drug delivery device incorporating trimetazidine for better treatment of angina pectoris has also been reported recently.^[4] The first chronotherapeutic agent for hypertension and angina pectoris involving a special verapamil preparation has been released to cover early morning hours, and a multinational study is in progress to evaluate the effectiveness.^[5]

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