Hypertension and Chronotherapy: Shifting the Treatment Paradigm

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The treatment of diseases has been based on the concept of homeostasis and has not incorporated an understanding of biologic rhythms and their underlying mechanisms. Biologic rhythms are implicated in cardiovascular events. Failure to recognize the circadian decline in blood pressure may result in iatrogenic chronopathological events, including anterior ischemic optic neuropathy and cerebrovascular accidents. Chronotherapeutics is the purposeful alteration of drug level to match rhythms to optimize therapeutic outcomes and minimize size effects. For the treatment of hypertension, this idea has the potential for a therapeutic paradigm shift. Am J Hypertens 2001;14:277S–279S © 2001 American Journal of Hypertension, Ltd.

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The treatment of diseases has been based on the concept of homeostasis and has not incorporated an understanding of biologic rhythms and their underlying mechanisms.1 Medical chronobiology is concerned with the mechanisms of bioperiodic influences on health and diseases.2 The well documented circadian variations in blood pressure (BP),3 heart rate,4 hormone secretion, and platelet aggregation5 are examples of the impact of chronobiology. In this issue of the Journal, a primer of this important area provides clinicians with terminology and applications for patient care.6

Chronopathology is the study of biological rhythms in disease processes and in morbid and mortal events. Most medical conditions are affected by circadian rhythms. Cardiovascular diseases, which account for the greatest morbidity and mortality, are greatly affected by body rhythms.7 It is now generally recognized that myocardial infarctions, sudden cardiac death, transient ischemic attacks, and cerebrovascular accidents occur at a higher frequency in the early morning hours. In this issue, new information is provided in this evolving area of research.8

Most cardiovascular medicines are designed to achieve a constant or near-constant effect throughout the 24-hour dosing interval.9 In many cases, however, the requirement for medication is not the same at nighttime as it is during the day.9 Moreover, treatment outcomes may be affected by body rhythms. Failure to recognize these points may possibly account for chronopathological events, including anterior ischemic optic neuropathy10 (Fig. 1) and cerebrovascular accidents among persons with hypertension whose pressure falls markedly during the night (“extreme dippers”).11

The focus of this symposium is the chronotherapy of hypertension. Chronotherapeutics is the purposeful alteration of drug level to match rhythms to optimize therapeutic outcomes and minimize size effects.12 One should not assume that a drug dosed in the morning will have the same antihypertensive effect as a drug dosed in the evening.13 Novel drug delivery systems have the potential to provide antihypertensive medication at the time when the need is greatest.14,15 For the treatment of hypertension, this idea has the potential for a therapeutic paradigm shift (Fig. 2).

There are few data for the application of this concept to hypertension.16–19 The pharmacology of chronotherapeutic agents is described in this issue.20 Controlled-Onset Extended-Release (COER-24) verapamil HS (Covera-HS, G.D. Searle Co., Chicago, IL) has an osmotic pump drug delivery system like nifedipine-GITS consisting of a semipermeable membrane surrounding a drug layer and a push layer that swells, pushing the active drug through two precision laser-drilled micropores.21 Chronotherapeutic Oral Drug Absorption System (CODAS) verapamil PM (Verelan PM, Schwarz Pharma, Inc., Mequon, WI) is designed to provide a drug-release profile that complements the circadian pattern of BP.21 The technology incorporates a 4- to 5-hour delay in the beginning of drug delivery, followed by extended release of verapamil.22 This is accomplished by a combination of water-soluble and water-insoluble polymers applied to small drug-
loaded beads that are contained in a capsule. The rate of release is essentially independent of pH, posture, and food. Multiparticulate systems such as used in the CODAS system have been shown to be independent of gastrointestinal motility. This neglected area of medicine should receive high priority because of its potential to positively influence treatment outcomes.23

References


FIG. 1. Anterior ischemic optic neuropathy in a patient. The optic disk margin is blurred and more vascular compared with the optic disk of the normal retina. (Photographed by Michael S. Stanley, Ophthalmic Photographer.)

FIG. 2. Flowchart depicting a transition in therapeutics.