

Medical chronobiology

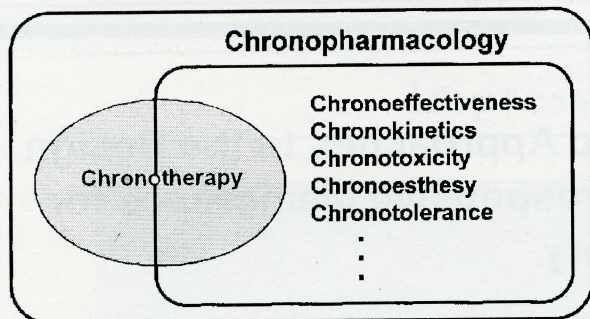


Fig. 1. The concept of medical chronobiology.⁶

wide range of disorders. Chronokinetic parameters such as absorption, distribution, metabolism, and elimination are influenced by different physiological functions of the body, which may vary with time of day. These time-dependent changes in kinetics may proceed from circadian variations. In other words, body functions do not remain constant over the 24 h of a day.¹¹⁻¹³ Thus, circadian variations in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow, drug protein binding, liver enzyme activity and/or hepatic blood flow, glomerular filtration, renal blood flow, urinary pH and tubular reabsorption may play a role in changing the pharmacokinetics and pharmacodynamics of drugs (Fig. 2).

Chronotherapy refers to the utilization of a chronopharmacological approach to clinical therapy for enhancing both the effectiveness of and tolerance to a drug by adjusting the regimens of drug administration.⁴ The periodic alterations give rise to day-night

differences in the susceptibility or resistance of individuals to the manifestation or expression of many diseases.¹⁴ Because of changes due to circadian rhythms, the timing of drug administration seems to be important for improving rational drug therapy, and increasing drug efficacy and safety. The morning daily or alternate-day timing of methylprednisolone was considered during the 1960s to be the first chronotherapy introduced into clinical medicine.¹⁵ Recently, rhythmic changes in plasma hydrocortisone (cortisol) concentrations are well accepted and are reflected in the current regimens of corticosteroid therapy.

Controlled-release Systems and Chronopharmacology

Controlled drug delivery systems (DDSs) have offered several advantages over conventional dosage forms of the same drug, including (a) a more constant drug level in the blood with limited fluctuation, (b) more efficient utilization of a drug, (c) closer site of action deliveries and (d) better patient compliance due to by less-frequent administration.¹⁶ This is consistent with the concept of medical homeostasis, a principle of pharmacotherapy which calls for constancy of blood and tissue concentrations of medications. This concept still prevails in clinical therapy.⁴ According to this concept, many controlled-release dosage forms or devices have been designed to control the release rate of drugs and to maintain constant drug concentrations in blood or tissues. However, certain drugs, such as non-steroid anti-inflammatory drugs and anticancer drugs, even when being delivered at a constant rate in

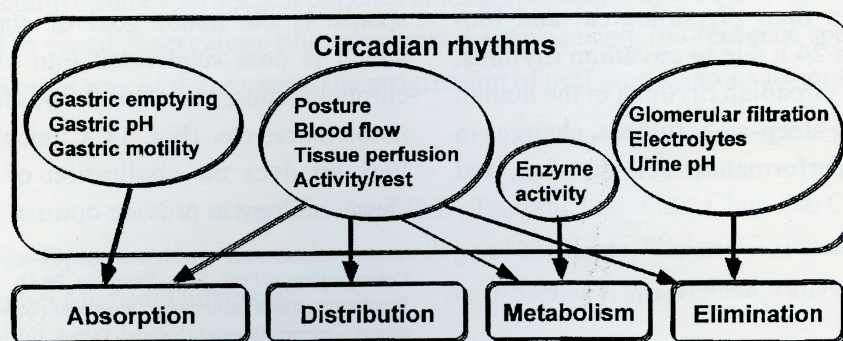


Fig. 2. Effects of circadian rhythms on the chronokinetics of drugs.¹³