

# Chronobiology, chronotherapy and timing of aspirin ingestion

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## Chronobiology and Chronopharmacokinetics

A circadian pattern in activity has been demonstrated for a multitude of physiologic factors affecting cardiovascular function. For example, upon awakening, adrenergic tone is augmented. This heightened sympathetic tone, together with elevations in cortisol release leads to increased vasomotor tone, increased blood pressure, and increases in platelet adhesiveness and aggregation. Activity of thromboxane A2 also follows a circadian pattern of occurrence, with peak activity in early morning hours, or upon awakening. Superimposable upon this circadian activity pattern of physiologic factors is the circadian occurrence of acute ischemic events, arrhythmia, and sudden cardiac death. There is a direct correlation between early morning peak activity of physiologic stressors and acute coronary events.

Chronopharmacokinetic studies have indicated that factors affecting drug disposition also follow a circadian activity pattern. For example Gastric pH is lowest in early morning hours from 2am to 6am, promoting drug absorption and dispersion. Gastric emptying time is delayed during the hours of sleep, and also with ingestion of food. Pharmacological agents competitively inhibiting the renin-angiotensin-aldosterone system are more effective in reducing blood pressure at night, when peak renin-angiotensin-aldosterone activity has been documented to occur. Agents acting to competitively inhibit the adrenergic system are more effective during early morning and daytime hours when heightened sympathetic tone is present.

## Chronotherapy

Chronotherapy refers to the investigation and application of optimal timing of medication, which is based in chronobiology, or time dependent changes. The Physician's Health Study (PHS) was a randomized, double blind placebo controlled 2x2 factorial trial of aspirin in the primary prevention of cardiovascular disease (CVD) and beta-carotene in the primary prevention of CVD and cancer. The beta carotene component continued to its scheduled termination after 12 years of treatment and follow up and showed no significant evidence of benefit or harm [1]. In contrast, the aspirin component was terminated early based on the unanimous recommendation of the external and multidisciplinary Data and Safety Monitoring Board (DSMB) [2] due primarily to the emergence of a statistically extreme benefit of aspirin of 44% on the development of a first myocardial infarction (MI) [3]. Subsequently it was shown that about 40% of first MIs in the PHS occurred between 7am and 10am, which was significantly higher than

the 12.5% expected under the null hypothesis of no variation by time [4].

## Early morning and evening administration of aspirin

On the basis of chronobiology and chronotherapy clinicians were advised to instruct their patients to take aspirin for long term treatment or primary prevention in the early morning [5]. For patients who are not inclined to take their morning medication upon awakening, however, evening administration may be preferable to late morning or afternoon in order to achieve optimal coverage for the early morning hours. Further, the evening administration of aspirin may, in fact, be optimal in "non-dippers", defined individuals who do not exhibit the normal J-curve of blood pressure. Non-dippers tend to include subpopulations of patients such as diabetics, patients with congestive heart disease, and those with chronic kidney disease. These patients may benefit from evening administration of aspirin [6,7].

The choice of timing as well as whether to prescribe aspirin should be an individual clinical judgement and, thus, left to the discretion of the well informed clinician. The timing should be chosen to promote patient compliance, and to provide protection during the well characterized vulnerable early morning period.

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on patents for inflammatory markers and CV disease that are held by Brigham and Women's Hospital; and has an investment management relationship with the West-Bacon Group within SunTrust Investment Services, which has discretionary investment authority and does not own any common or preferred stock in any pharmaceutical or medical device company.

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