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Chronobiology and chronotherapy of ischemic heart disease ☆

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Abstract

The occurrence of the clinical manifestations of ischemic heart disease (IHD) – myocardial ischemia and angina pectoris, acute myocardial infarction, and sudden cardiac death – is unevenly distributed during the 24 h with greater than expected events during the initial hours of the daily activity span and in the late afternoon or early evening. Such temporal patterns result from circadian rhythms in pathophysiological mechanisms plus cyclic environmental stressors that trigger ischemic events. Both the pharmacokinetics (PK) and pharmacodynamics (PD) of many, though not all, anti-ischemic oral nitrate, calcium channel blocker, and β-adrenoceptor antagonist medications have been shown to be influenced by the circadian time of their administration. The requirement for preventive and therapeutic interventions varies predictably during the 24 h, and thus therapeutic strategies should also be tailored accordingly to optimize outcomes. During the past decade, two first generation calcium channel blocker chronotherapies have been developed, trialed, and marketed in North America for the improved treatment of IHD. Nonetheless, there has been relatively little investigation of the administration-time (circadian rhythm) dependencies of the PK and PD of conventional anti-ischemic medications, and there has been little progress in the development of new generation IHD chronotherapies. Available epidemiologic, pharmacologic, and clinico-therapeutic evidence demonstrates how the chronobiologic approach to IHD can contribute new insight and opportunities to improve drug design and drug delivery to enhance therapeutic outcomes.

Keywords: Coronary heart disease; Anti-ischemic drugs; Circadian rhythm; Chronotherapy; Oral nitrates; β-Adrenoceptor antagonists; Calcium channel blockers

Contents

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1. Introduction

The practice of medicine is properly focused on optimizing treatment in the individual patient rather than applying identical therapeutic schemes to all patients afflicted by the same disease. To achieve optimal results, the clinician is accustomed to adjusting the choice of medications and dosages taking into account the patient's ethnicity, sex, age, body mass, stage and severity of primary disease as well as concomitant diseases, other treatments, drug intolerances and allergies, and even patient preferences, among the multitude of factors that ultimately determine therapeutic success or failure. Many factors are known to influence the pharmacokinetics of medications, and hence drug efficacy in the individual patient, and different pharmaceutical formulations may be used to tailor therapeutic strategies to individual needs. Surprisingly enough, very little consideration has yet to be given to a very important factor which may, by itself, represents a significant and often crucial determinant of therapeutic success: *time*. Since all physiologic functions oscillate rhythmically in time, the activity, toxicity, and kinetics of a medication may depend on its administration time, in relation to the staging of circadian and other biological rhythms. On the other hand, the temporal (biological rhythm) structure of the human body may be altered by disease, leading to significant changes in the response to therapy.

Ischemic heart disease (IHD) constitutes a paradigmatic example of the importance of biological time, in terms of the manifestation of the symptoms of myocardial ischemia, onset of severe ischemic heart disease events, and preventive and treatment strategies. In fact, a temporal variation of mainly (but not solely) 24 h is now very well established not only in the level of activity of almost all cardiovascular functions but also in the pathophysiological mechanisms that trigger morbid and mortal cardiovascular events [1]. Biological rhythms of cardiovascular physiology and function give rise to highly predictable temporal variation in the vulnerability to IHD events and to the requirement for and therapeutic response to medications. Herein, we review the epidemiologic, pharmacologic, and clinico-therapeutic evidence found in the scientific literature that demonstrate the utility of a chronobiologic approach in uncovering new insight into the prognostic assessment of IHD as well as improved drug design and drug-delivery strategies for improved patient management and clinical outcomes. The three classes of medications used to treat cardiac ischemic conditions will be taken into consideration: oral nitrates, calcium channel blockers, and β-adrenoceptor antagonists. Related issues, such as the chronotherapy of coagulation and hypertension, are addressed in great detail in other contributions to this journal issue.

2. Time patterns in the clinical manifestations of IHD

Myocardial ischemia is the underlying pathogenetic mechanism of the cardinal clinical manifestations of IHD. Ischemia of the myocardium may result from either a restricted and insufficient oxygen supply or an increased oxygen requirement. A number of physiologic variables are crucial in determining the discrepancy between the availability and the requirement for oxygen by the myocardium, and predictable temporal changes are exhibited by all of them [2,3]. Quantitatively, circadian (24 h) variations are most prominent, although 7-day, annual, and ultradian (i.e., less than 24 h) periodicities are also well recognized. Such predictable-in-time (biological rhythm) differences in the susceptibility to myocardial ischemia, on the one hand, and in the pathogenetic mechanisms of myocardial ischemia, on the other hand, result in corresponding predictable-in-time differences in the overt expression and manifestations of IHD.

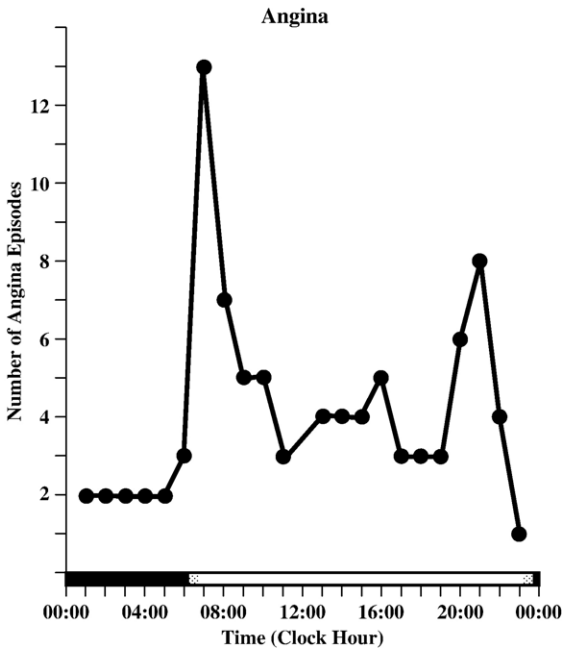

Fig. 1. Twenty-four-hour pattern in ST-segment depression events, i.e., angina pectoris, ascertained by 24-h Holter monitoring of 94 presumably diurnally active IHD subjects. Note the major peak in events ~8 a.m. (08:00) and the somewhat less prominent second peak around bedtime. Shading along the *x*-axis indicates the presumed sleep span of the sample. Clock time along the *x*-axis expressed in military units: e.g., 10:00=10 a.m.; 16:00=4 p.m. Adapted from Deedwania and Nelson [54].