Beneficial effects of Vastarel MR in protecting patients with stable coronary artery disease against early morning ischemic burden

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Abstract

Many biological and physiological functions are ruled by cyclical rhythms. The rates of manifestation of cardiovascular conditions such as angina pectoris, myocardial infarction, sudden cardiac death, and stroke also present a cyclical rhythm. Awareness of these circadian variations in biologic functions and in the occurrence of cardiovascular events makes it essential to develop pharmaceutical formulations that are capable of achieving optimal results by providing adequate blood concentrations at the time of maximum risk. Trimetazidine (Vastarel) MR is an example of a pharmaceutical product that has pharmacokinetic and 24-h anti-ischemic efficacy profiles that are adapted to match circadian rhythms in coronary artery disease.

■ *Heart Metab.* 2009;44:25–28.

Keywords: Circadian variation, coronary artery disease, trimetazidine MR

Introduction

Many biological and physiological functions are ruled by cyclical rhythms, and it has long been established that annual and lunar cycles have an impact on numerous metabolic pathways, endocrine and neuroendocrine systems, immunological responses, and many other physiological functions. Furthermore, beyond these annual and lunar variations, each and every day, many systems also undergo daily variations. In accordance with these cyclical daily variations in human functions, a number of diseases such as allergic rhinitis, asthma, rheumatoid and osteoarthritis, and peptic ulcer show circadian differences in terms of their severity. The rates of manifestation of many cardiovascular conditions such as angina pectoris, myocardial infarction, sudden cardiac death, and stroke also present with cyclical rhythms: in terms of circa-annual variation they are more frequent in autumn and winter, and in terms of circadian rhythm they are more frequent in the early morning hours. It has been shown that 30–40% of cases of sudden death [1], acute coronary syndromes, and strokes [2] occur between 06.00 AM and noon. More precisely, the figures indicate that, during this period there is a 40% greater risk of heart attack, a 29% increased risk of cardiac death, and a 49% increased risk of stroke compared with what would be expected if these events happened at random and were evenly distributed throughout the day [3].

In view of this knowledge of circadian variation in biologic functions and in the occurrence of

cardiovascular events, it is essential to develop pharmaceutical formulations that are capable of achieving optimal results by providing adequate blood concentrations at the time of maximum risk. The development of trimetazidine (Vastarel) MR, a modified release formulation of trimetazidine, is an example of a pharmaceutical product that has pharmacokinetic and 24-h anti-ischemic efficacy profiles that are specifically adapted to match circadian rhythms in coronary artery disease.

Circadian variations in myocardial ischemia

Many hemodynamic, environmental, and hematological changes are associated with awaking. Blood pressure and heart rate, for instance, have clearly established circadian rhythms, with a typical peak in the early morning and maximum daily values during the first 4–6 h after waking. Both blood pressure and heart rate decline from mid afternoon onwards, reaching their lowest values between midnight and 03.00 AM. These changes are mostly dependent on sympathetic nervous system activity, through the excretion of catecholamines and neuroendocrine activation: catecholamine and neurohormone concentrations, which diminish during sleeping hours and increase on awakening, are largely responsible for the variations in blood pressure, heart rate, and coagulability. Beyond the direct effect of increased catecholamine concentrations, it has been suggested that there is also increased end-organ responsiveness to catecholamines during the early morning hours, probably related to circadian variation in the autonomic control of the cardiovascular system [4,5].

The amplitude of the cardiovascular circadian rhythm in healthy people is of little clinical significance. However, in cardiovascular diseases, the amplitude of circadian changes is usually increased, and this has important consequences. Patients with stable coronary disease present with a clear early morning peak in the occurrence of symptomatic and silent ischemic episodes [6] (*Figure 1*). Beyond the time of awakening, it seems that the fact of getting up itself, and becoming active, also play major roles [7].

The available data clearly indicate that the vast majority of ischemic episodes occur within 2 h of in individual's getting up [8] (*Figure 2*). Indeed, getting up is linked with a significant imbalance between myocardial oxygen supply and demand. Oxygen supply is mainly restricted by a morning constriction of the coronary arteries that is possibly linked to several mechanisms, including sympathetic nervous system hyperactivity [9], a morning increase in plasma concentrations of cortisol and angiotensin II [10], an increase in blood viscosity [8], and an

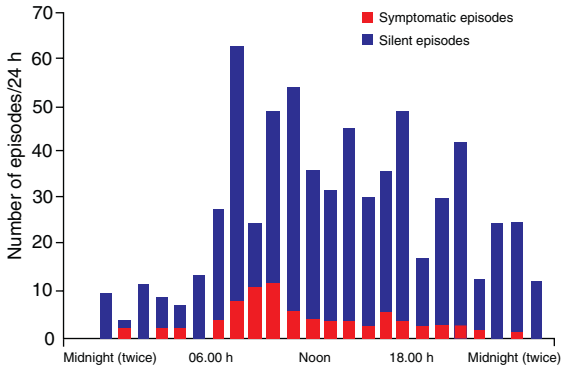

Figure 1. Circadian distribution of the occurrence of symptomatic and silent ischemic episodes.

increased heart rate (shortening of diastole). The morning increase in sympathetic nervous activity itself leads to increases in several parameters that directly influence myocardial oxygen consumption, such as heart rate and myocardial contractility.

Finally, early morning is also the period of the day during which patients are the least well treated. This period corresponds to minimal plasma concentrations of medications, as (depending on the product's dosing regimen), the last intake of drug will have taken place 12–24 h previously.

The significant rate of morning ischemic events is therefore a very strong argument in favor of driving the development of therapeutic treatments by focusing on this specific problem through a ''chronotherapeutic'' approach.

Improvement of the 24-h anti-ischemic efficacy of trimetazidine with a modified release formulation

This specific issue of a chronotherapeutic approach is precisely the reason why a modified release formulation of trimetazidine was developed. Trimetazidine is a metabolic antianginal drug that ensures an increase in myocardial energy production during

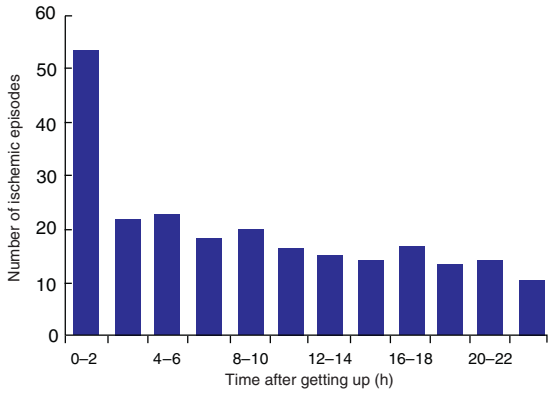

Figure 2. Rate of ischemic episodes with respect to time after getting up.

ischemia. By selectively inhibiting 3-keto acyl coenzyme A thiolase (3-KAT), it partially inhibits free fatty acid oxidation during myocardial ischemia, consequently favoring glucose oxidation. This results in an increase in the amount of ATP available to ensure correct cardiac function [11].

Many trials in patients with stable angina had already demonstrated the clinical efficacy of trimetazidine 20 mg, either in monotherapy [12] or in combination with other drugs [13], compared with placebo [14] or other molecules [15]. Various data also provided clear-cut evidence of the benefits of prescribing trimetazidine in specific patient populations, such as those with diabetes [16,17] or ischemic cardiomyopathy [18–21]. However, even if it provides very satisfactory clinical results, trimetazidine 20 mg was not specifically designed to answer the problem of early morning ischemic events. This is the reason why a modified release formulation of the drug was developed.

The modified release formulation of trimetazidine, trimetazidine (Vastarel) MR, relies on a specific hydrophilic matrix that enables the progressive release of the active ingredient, trimetazidine, over time. It ensures a sustained effect with an increase in the minimum plasma concentrations of trimetazidine 12 h after the last intake of the drug.

In a cross-over design study that involved administration of trimetazidine MR twice a day or trimetazidine 20 mg three times a day and the measurement of plasma and urine concentrations of the drug over 4 days, trimetazidine MR provided better 24-h coverage than did trimetazidine 20 mg three times daily, with fewer fluctuations in concentrations of the drug. Moreover, at steady state, the minimum concentration at the end of the dosing interval (C_{min}) of trimetazidine MR was increased by 31% compared with that of trimetazidine 20 mg three times daily, and peak–trough concentration fluctuations were reduced from 121% to 86% (*Figure 3*) [22].

Beyond these pharmacokinetic features, the modified release formulation of trimetazidine also seems to bring a particularly well adapted answer to the clinical

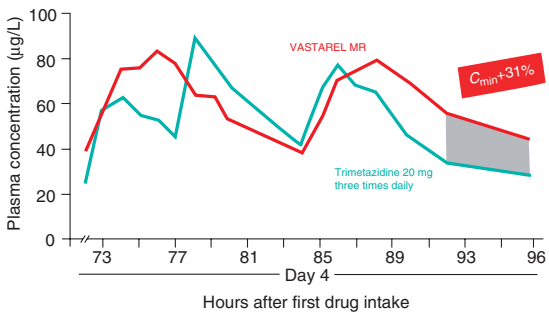

Figure 3. Mean plasma concentration–time curves after several doses of trimetazidine 20 mg three times daily or Vastarel MR twice daily.

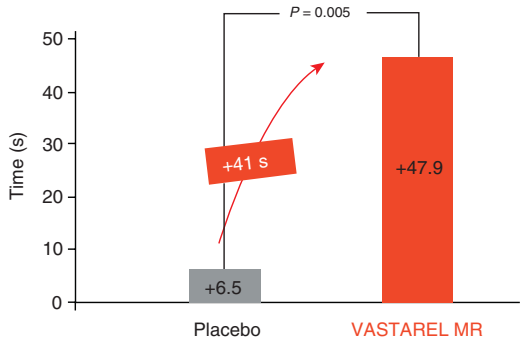

Figure 4. Change in time to 1-mm ST-segment depression at trough plasma concentrations (12 h after last intake of study medication) after 2 months of treatment, in 223 patients with stable angina.

issue of circadian increases in ischemic events. In a pivotal study that assessed the antianginal and anti-ischemic efficacy of trimetazidine MR at trough plasma concentrations in 223 patients with stable angina, trimetazidine MR improved the time to 1-mm ST-segment depression ($P = 0.005$) and delayed the time to onset of angina ($P = 0.049$) after 2 months of treatment [23]. Six months after the beginning of treatment, patients receiving trimetazidine MR also showed a trend towards a greater decrease in the number of angina attacks per week than those receiving placebo (*Figure 4*).

This study confirmed that, thanks to its sustained anti-ischemic and antianginal efficacy, trimetazidine MR is able to protect the patients 12 h after the last dose was given (ie, during the early morning hours), at times when they are at increased risk of cardiovascular events.

Conclusion

The aim of chronotherapy is to deliver drugs at adequate concentrations during the time of greatest need. In the case of coronary artery disease, this represents the early morning post-waking period. With a twice daily dosing regimen and proven efficacy at trough plasma concentrations, trimetazidine MR is an antianginal treatment that is particularly well adapted for use in patients with stable coronary disease, preserving contractile energy over a cycle of 24 h. ■

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