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Long-term treatment with the NO-donor molsidomine reduces circulating ICAM-1 levels in patients with stable angina

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Abstract

Recent clinical evidence has indicated that the severity of atherosclerosis is correlated with the level of soluble ICAM-1 (sICAM-1). Nitric oxide (NO) donors are used to treat patients with stable angina pectoris, and the aim of this study was to investigate the short- and long-term effect of molsidomine on the level of this circulating biochemical marker of endothelial function. We included 172 patients and examined the effect of the NO donor treatment on angina related parameters and on sICAM-1 levels after a 4-week- and a 1-year treatment period. After 4 weeks, angina attacks and sublingual (s.l.) isosorbide dinitrate tablet (ISDN) consumption frequency was significantly ($p < 0.0001$) reduced without altering sICAM-1 levels when compared to the baseline values. The anti-anginal effect of molsidomine 16 mg once a day (o.a.d.) was sustained (s.l. ISDN consumption) or improved (angina attacks frequency; $p < 0.002$) during the following year and a significant decrease in sICAM-1 levels ($p < 0.0001$) was observed. When the sICAM-1 changes during the 1-year treatment period were distributed in four categories (quartiles of the distribution), it was demonstrated that the decrease in s.l. ISDN consumption between the start and the end, was most pronounced in the group with the largest sICAM-1 decrease (fourth quartile of distribution; $p = 0.038$). In conclusion, the reduction in the pro-inflammatory marker sICAM-1 after 1-year daily treatment with molsidomine may indicate that this NO donor besides its anti-anginal function, promotes a less activated state of the endothelium in patients with stable angina.

Keywords: Coronary heart disease; Atherosclerosis; Molsidomine; NO donor; Adhesion molecules

1. Introduction

Angina pectoris is mainly characterised by the presence of atherosclerotic lesions in the coronary artery. In atherosclerosis, the activity of the nitric oxide (NO) pathway in blood vessels decreases and endothelium dilatation is lost progressively, as atherogenesis continues to evolve [1,2]. Organic nitrates are widely used to relief acute symptoms of ischemia in patients with coronary artery disease and atherosclerosis. Molsidomine, a direct NO donor belonging to the group of the sydnonimines, is effective in the chronic treatment of stable angina pectoris [3]. Contrary to organic nitrates, it does not require intermediate thiol groups to release NO and therefore is less prone to induce tolerance [4]. However, studies of the effect of chronic NO administration on the progression of atherosclerosis are very limited, and most of the information is derived from animal experiments. Plaque formation in rabbits was either not affected or reduced [5,6] or increased [7] during chronic NO treatment. Recently, De Meyer et al. reported that chronic administration of the NO donor molsidomine in combination with lowering plasma levels of cholesterol decreased signs of oxidative stress and increased features of stable atherosclerotic plaques [8].

Activation of the endothelial cells and interaction with leucocytes are important steps in the initiation and progression of atherosclerosis. Among several adhesion molecules, intercellular adhesion molecule-1 (ICAM-1) is thought to be

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a key molecule, when circulating monocytes adhere to the endothelium and subsequently transmigrate into the intima. ICAM-1 is strongly upregulated on the endothelium overlying atheromatous plaques in human coronary and carotid arteries [9]. Not only in apoE-knockout mice [10], but also in clinical studies [11], the level of soluble ICAM-1 (sICAM-1) correlates with the degree of atherosclerosis and is suggested to be an appropriate biomarker that reflects the natural history of the development of atherosclerosis [12]. Furthermore, sICAM-1 is related to endothelial vasodilatory function [13] and could be a predictor for further cardiovascular events [14]. Therefore, low sICAM-1 levels may reflect decreased atherosclerotic activity, since in atherosclerotic mice models, ICAM-1 deficiency was shown to substantially protect against the progression of atherosclerosis [15].

The aim of the present study was to investigate whether the slow releasing nitric oxide donor molsidomine used for the chronic treatment of stable angina would influence the level of circulating ICAM-1 after a short- (4-week) and a long (1-year) treatment period.

2. Material and methods

2.1. Study population and experimental design

The patients included in this investigation were enrolled from 28 different hospitals in Hungary and Poland and initially participated in a large double-blind double-dummy randomised 2-week cross-over study aiming to compare the efficacy and safety of once a day (o.a.d.) molsidomine 16 mg to that of twice a day (b.i.d.) molsidomine 8 mg in the treatment of stable angina pectoris. The study design is shown on Fig. 1. Concomitant use of other anti-anginal drugs was forbidden except for sublingual (s.l.) isosorbide dinitrate (ISDN) 5 mg tablets that could be consumed ad libitum to relieve anginal pain symptoms. Of the above-mentioned cohort, 172 patients were then included in a long-term (1-year) open-label study to evaluate the long-term anti-ischemic efficacy and safety of molsidomine 16 mg o.a.d. During that part of the study, concomitant use of beta-blockers and/or calcium antagonists as well as ACE inhibitors and statins was authorized. However, the chronic use of oral nitrates and sildenafil was still not allowed. Molsidomine 16 mg o.a.d. had to be taken orally at the morning time every day during 1 year.

Weekly anginal crises frequency, weekly s.l. ISDN 5 mg tablet consumption frequency and sICAM-1 concentrations were measured at three time points i.e. after the run-in 7-day period under placebo (baseline), and at the end of, respectively, the short- and the long-term study.

Blood samples (5 ml) were collected in non-heparinized tubes for the determination of sICAM-1 concentrations. After having been left at room temperature, they were centrifuged. The serum samples were stored at $\leq 20\,^{\circ}C$ in the different hospitals; within 6 weeks, the samples were transported on dry ice to the laboratory. On arrival, they were stored at $-70\,^{\circ}C$ until analysis. Circulating ICAM-1 was measured using a commercially available ELISA from R&D Systems, Europe. A reference sample was divided in aliquots and included in 10 separate assays. This resulted in a mean of 249.2 ng/ml with a standard deviation of 13.7 ng/ml and a CV of 5.5%.

The study was conducted in accordance with the Guidelines for Clinical Investigation of anti-anginal drugs provided by the CPMP, Good Clinical Practices (step 4) as implemented in the European Community and Ethical Principles defined in the recently revised Declaration of Helsinki. All patients gave their written informed consent for the investigation.

2.2. Statistical analyses

Descriptive statistics (means, S.D., and %) were used to characterize the demographics and other features of the population.

Analyses of variance for repeated measures with the time as *within factor*, followed by post hoc Bonferroni's tests when

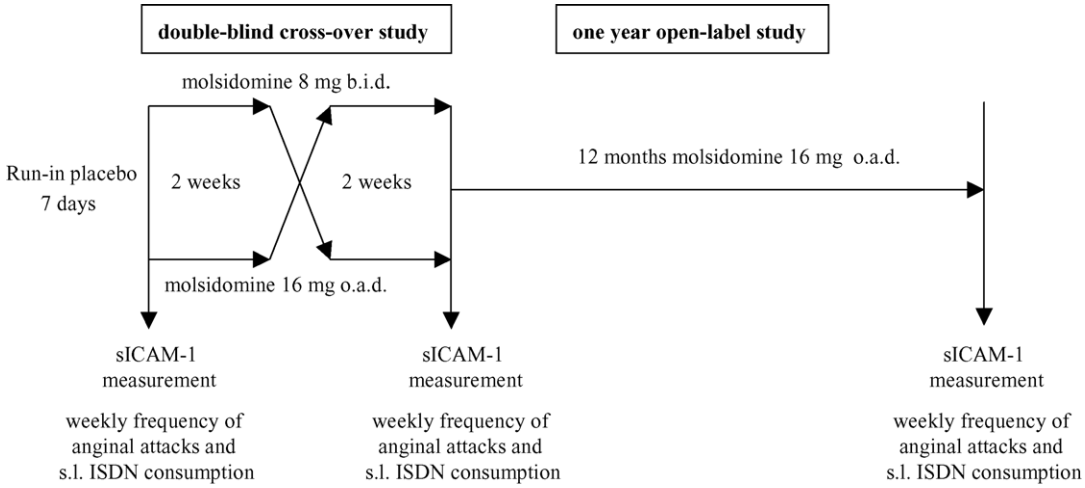

Fig. 1. Design of the study.