Clinical Research

Anti-inflammatory and profibrinolytic effect of
tetramethylpyrazine in acute coronary syndromes

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Background and Objectives Tetramethylpyrazine (TMP) is a herb used widely in Traditional Chinese Medicine (TCM) as an antianginal drug. The exact mechanism whereby TMP treat ischemic heart disease is still not fully understood. The purpose of this study is to examine the anti-inflammatory effect of TMP in patients with acute coronary syndromes (ACS). Methods Thirty-two patients with acute myocardial infarction or unstable angina were randomly assigned to TMP group or control group. All patients received the same standard treatment. Patients in TMP group received TMP 3mg/kg every 12 hours for 5 days. Plasma concentrations of high-sensitivity C-reactive protein (CRP), serum amyloid A (SAA) and plasminogen activator inhibitor-1 (PAI-1) were measured at baseline and after 5 days of therapy. Results Both CRP and SAA concentrations increased significantly in control group (P<0.05) whilst in TMP group, only SAA had a significant increase (P<0.05); the absolute increase of CRP, SAA, and PAI-1 were significantly less in TMP group than in control group (P<0.05). Conclusion TMP has an anti-inflammatory and profibrinolytic effect in patients with ACS. These effects may contribute to the clinical benefits of TMP in ischemic heart disease. (J Geriatr Cardiol 2005; 2(4):233-235)

Key Words acute coronary syndromes; inflammation; tetramethylpyrazine

Materials and methods

Patients

Patients admitted to the General Hospital of Chinese PLA from October 2002 to December 2003 with a diagnosis of acute myocardial infarction or unstable angina were recruited. Patients were included if they presented within 48 hours after the onset of ischemic discomfort and met one or more of the following criteria: electrocardiography changes (ST-segment depression or elevation of at least 0.5 mm, T-wave inversion of at least 3 mm in at least three leads), elevated levels of cardiac markers, a history of coronary disease, or an age of at least 65 years in patients with diabetes or vascular disease. Patients with glucocorticoid treatment, primary PCI, systemic infection, congestive heart failure and hemoglobin<10g/L were excluded. A total of thirty-two patients were enrolled and randomly assigned to control or TMP groups. There was no significant difference in the baseline characteristics between the two groups (Table 1).

Treatment

All patients received aspirin (100-150 mg/day), unfractionated or low-molecular-weight heparin, β-blockers, ACEIs, nitrates or other concomitant medications such as statins at the discretion of the treating physician; patients with ST-segment-elevation MI (STEMI) received urokinase (1000, 000-1500,000 units intravenously over 30 minutes) unless contraindicated. Patients in TMP group received TMP 3mg/kg every 12 hours, administrated within 24 hours of hospital admission and prepared in 100ml of 10% dextrose with regular insulin 4 U and KCl 1 g at 20-30ml/h intravenously for 5 days; patients in the control group received the same infusion, but without TMP.

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Blood sampling and biochemical analyses

Blood samples were collected before the administration (baseline) and at 6th day of admission in the hospital. High-sensitivity C-reactive protein (CRP) and serum amyloid A (SAA) were measured by commercially available ELISA kits (CRP, from Diagnostic systems Laboratories, USA; SAA, from Biosource International ). Plasminogen activator inhibitor-1 (PAI-1) was determined by Sandwich ELISA using a rabbit anti-human PAI-1 monoclonal antibody (Technoclone, Austria).

Statistical analysis

Data were expressed as mean ± SEM for continuous variables and as absolute frequencies for categorical variables. Because values of CRP, SAA, and PAI-1 were skewed, medians were used to express levels of these parameters and non-parametric tests (Wilcoxon’s signed rank test) were applied. Other variables were compared using Student’s t test or $\chi^2$ test. Statistical significance was set as $P<0.05$, analyzed using Stat 7.0 software.

Results

High-sensitivity CRP

CRP concentration increased significantly ($P<0.05$) in control group, but had no significant change in TMP group. The absolute increases from baseline to the 6th day in CRP concentrations were significantly less ($P<0.05$) in TMP group than in control group. (Table 2).

SAA

SAA concentrations increased significantly both in con-
Discusson

Tetramethylpyrazine is the biologically active ingredient isolated from a popular Chinese medicinal plant, Ligusticum wallichii franchet, which has been widely used and effectively since the 1970s to treat ischemic heart disease, cerebrovascular and thrombotic vascular diseases. The mechanism underlying its therapeutic action in the treatment of coronary heart disease has been investigated extensively. Previous studies showed TMP could relax coronary artery, possibly by blocking calcium channel and suppressing endothelium-1 expression, inhibit platelet thrombus formation, possibly by enhancing NO synthase, and alleviate reperfusion injury, possibly by scavenging of oxygen free radicals. However, it has also been reported that TMP has an anti-inflammatory effect. Previous studies have showed that TMP has effects on a variety of proinflammatory factors, such as NO, ET-1, thromboxane A2, making it possible to regulate inflammatory response.

The role of inflammation in the initiation and progression of atherosclerosis as well as ACS has been the focus of intense investigation, especially the predictiveness of CRP and SAA as markers of inflammation. Patients presenting with ACS usually showed elevated blood levels of biochemical inflammation markers, and elevated plasma CRP or SAA is associated with a higher risk for early mortality in patients with ACS.

In this study, our data confirm that after ACS, plasma CRP and SAA concentrations increase, reflecting an enhanced degree of systemic inflammation. More importantly, our data demonstrate that TMP significantly reduces the magnitude of this increase of both CRP and SAA despite the anti-inflammatory effect of background treatment medicines such as aspirin and statins. We believe that this might be one of the mechanisms of the therapeutic effect of TMP in the treatment of ischemic heart disease.

An increase in PAI-1 has also been reported to be associated with higher 30-day mortality in acute STEMI, and a reduction in the rise of PAI-1 correlates with thrombolytic efficacy. Song and colleagues showed that Ligustrazini inhibit both basal and LPS-induced PAI-1 protein and mRNA expression in endothelial cells. In our study, TMP treatment in patients with ACS associated with a moderate reduction of plasma PAI-1 level, implicating TMP may promote fibrinolysis by inhibiting PAI-1 expression in vascular endothelial cells, which may also account for its beneficial effect.

The major limitation of this study is the relatively sample, so it was not power enough for us to assess the possible selection bias, which might happen because this study was not a blind study.

In summary, our study showed that in patients with ACS, treatment with TMP markedly reduces the magnitude of increase in inflammation and suppresses the antifibrinolytic factor. We hypothesize that these effects, along with its known vasodilatory and platelet antiaggregatory action, provide a novel explanation for the mechanism of the beneficial clinical effect of TMP in the treatment of cardiovascular and cerebrovascular disease.

References