Effects of Nicorandil on Endogenous Fibrinolytic Capacity in Patients With Coronary Artery Disease

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Background Nicorandil is a hybrid-type anti-anginal drug that combines a KATP channel opener and a nitric oxide donor. Recently the IONA study reported that nicorandil improves the prognosis of patients with stable angina pectoris.

Methods and Results To examine the effects of nicorandil on endogenous fibrinolysis, plasma concentrations of tissue-type plasminogen activator (t-PA) antigen, type-1 plasminogen activator inhibitor (PAI-1) antigen and PAI activity were measured in consecutive 11 patients (7 men and 4 women, mean age 63 years, ranges 41-84 years) with coronary artery disease. Nicorandil (15 mg/day) was administered orally to each patient for 2 weeks. Venous blood samples were obtained from each patient before and after the administration of the drug in the early morning before eating. There were no significant changes in the plasma concentrations of t-PA (12.4±1.9 to 9.8±1.5) or PAI-1 (26.3±3.9 to 21.5±4.9) antigens (ng/ml, mean±SEM) before and after nicorandil administration. On the other hand, the plasma activity of PAI (IU/ml, mean±SEM) decreased significantly after the treatment (12.9±3.2 to 5.6±1.9, p=0.039).

Conclusions It is well known that PAI activity determines the whole fibrinolytic capacity and oral administration of nicorandil decreased PAI activity in patients with coronary artery disease. This finding suggests that nicorandil improves the fibrinolytic capacity and may reduce the risk of coronary thrombus formation in such patients. (Circ J 2004; 68: 232–235)

Key Words: Coronary artery disease; Nicorandil; Type-1 plasminogen activator inhibitor

Nicorandil is a hybrid anti-anginal drug that possesses the characteristics of both an ATP-sensitive potassium channel (KATP) opener and a nitric oxide (NO) donor. Those unique pharmacological characteristics enable nicorandil to dilate the small resistant vessels of the coronary arteries as well as the large epicardial ones. Recently the IONA study reported that nicorandil improves the prognosis of patients with stable angina pectoris by reducing the frequency of acute coronary syndrome (ACS)1 which means nicorandil may be able to inhibit intracoronary thrombus formation following the rupture of vulnerable atherosclerotic plaque, the main cause of ACS2. In addition, it was reported that patients undergoing intravenous administration of nicorandil had a better prognosis after reperfusion therapy for acute myocardial infarction (AMI)3 and that intracoronary administration of nicorandil prevented the no-reflow/slow flow phenomenon more effectively than infusion of verapamil in patients undergoing coronary arteryectomy.4 Furthermore, intravenous infusion of nicorandil led to a better recovery of regional left ventricular dysfunction caused by ischemia during balloon angioplasty than that obtained with nitroglycerin.5 Therefore, nicorandil has short- and long-term favorable effects on the clinical course of patients with various types of coronary artery disease (CAD).

The fibrinolytic system plays a major role in the defence mechanism against intracoronary thrombus formation. It is initiated by plasminogen activators, which convert the proenzyme plasminogen into its active form, plasmin. Tissue-type plasminogen activator (t-PA) is one of the plasminogen activators and is secreted from endothelial cells.6 Its activity in blood is regulated by a specific rapid-acting inhibitor, type-1 plasminogen activator inhibitor (PAI-1).7 Thus, the net fibrinolytic activity in plasma reflects the balance between PAI-1 and t-PA8 and PAI-1 is well known as the major controller of the fibrinolytic system.9 In this way, PAI-1 activity is an important variable in the regulation of the pathophysiological conditions in thrombotic disorders. In fact, the patency of the infarct-related coronary artery on coronary angiography is closely related to the plasma activity of PAI-10 and even 3 years after the onset of AMI the plasma concentration of PAI-1 is reportedly still high.11 Because nicorandil inhibits the onset of ACS, it may directly inhibit thrombus formation through modification of the PAI-1 activity. To elucidate this possibility, we examined the effects of nicorandil on the fibrinolytic activity in patients with CAD.

Methods

Study Patients

We studied 11 consecutive patients with ischemic heart disease who were admitted to hospital for coronary angiography (7 men, 4 women; mean age 63 years, range 41–84 years; Table 1). Nine of the patients were diagnosed as unstable angina and 2 of them had coronary spasm...
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mented by provocation test with intracoronary injection of acetylcholine. The 9 patients without coronary spasm were diagnosed as ischemic heart disease with various extents of organic stenosis in their coronary arteries.

Study Protocol

All study patients were treated with nicorandil 15 mg/day for 2 weeks. All other drugs, such as Ca++ channel blockers, ß-blockers, nitrates and aspirin, were unchanged during the study period. Venous blood samples were obtained from the antecubital vein of each study patient before and 14 days after administration of nicorandil. The samples were obtained in the early morning after a 12-h fast because there is significant diurnal variation in t-PA and PAI-1 activity.12 The initial 5 ml of blood was discarded, and the subsequent 4.5 ml of venous blood was collected into a glass tube containing 0.5 ml sodium citrate (0.13 mol/L, pH 7.5). Blood samples were centrifuged at 3,000 rpm for 15 min at 4°C, and aliquots of the samples were immediately stored at –80°C for subsequent assay and analysis. Patients with chest pain syndrome, whose coronary arteries did not have organic lesions or spasm and who were matched the study population in terms of age and sex, were the control subjects. They provided normal values of the fibrinolytic parameters that will be described later. Written informed consent was obtained from each study patient and the study protocol was in agreement with the guidelines of the ethics committee of the institution. The study was approved by the institutional review board of the Kumamoto University Hospital.

Determination of Plasma Concentrations of PAI-1 and t-PA Antigens and PAI Activity

PAI-1 and t-PA antigen concentrations were measured by enzyme-linked immunosorbent assay using commercially available kits (TintElize PAI-1, Biopool Inc, Umeå, Sweden;13 Asserachrome tPA, Diagnostica Stago Inc, Francoville, France14) and the results were expressed in ng/ml. The intraassay and interassay coefficients of variation in the PAI-1 and t-PA antigen assays were, respectively, 4.0% and 8.2% for PAI-1, and 2.4% and 4.7% for t-PA. The normal values for PAI-1 and t-PA antigens in our laboratory (n=35) are 12.3±0.5 and 5.8±0.3 (mean±SEM), respectively.

PAI activity was measured by a commercially available chromogenic single point poly-D-lysine stimulated assay kit produced by Biopool Inc15 and the results were expressed in IU/ml. Intraassay and interassay coefficients of variation in this assay were 9.4 and 11.4%, respectively. The normal value for PAI activity in our laboratory (n=35) is 5.4±0.5 (mean±SEM).

Statistical Analysis

Data are expressed as mean±SEM. Plasma PAI activity and concentrations of PAI-1 and t-PA antigens before and after the treatment were analyzed by paired t-test. Differences between the study patients and control subjects were analyzed by unpaired t-test. P-values less than 0.05 were considered significant.

Results

Plasma Concentrations of PAI-1 and t-PA Antigens

The plasma PAI-1 antigen concentration (ng/ml) at baseline was 26.3±3.9 and it was increased in comparison with that of the control subjects (p<0.01). No significant change was observed after nicorandil treatment (21.5±4.9, Fig 1).

The baseline plasma t-PA antigen concentration (ng/ml) was 12.4±1.9 and it was increased in comparison with that
Plasma PAI Activity

Plasma PAI activity (IU/ml) at baseline was also increased in comparison with that of the control subjects (12.9±3.2 vs 5.4±0.5, p<0.05). Plasma PAI activity was decreased in 10 of the 11 cases. In 1 case with coronary spastic angina that was refractory to medication, the plasma PAI activity was increased. In consequence, the mean plasma PAI activity was significantly decreased from 12.9±3.2 to 5.6±1.9 (p=0.039).

Discussion

In this study plasma PAI activity was decreased by a 14-day treatment regimen with nicorandil, which means the fibrinolytic capacity was improved by the treatment and this effect of nicorandil could be the possible mechanism of the drug observed in the IONA study.

Nicorandil is known to have potential cardioprotective effects other than as an antianginal drug relieving ischemic symptoms. These effects are probably related to its ability to mimic the powerful ischemic preconditioning phenomenon by opening KATP channels. In the IONA study, ischemic symptoms described in the Canadian Cardiovascular Society Functional (CCSF) classification for angina were unchanged by nicorandil treatment. On the other hand, the treatment improved outcome in terms of reducing events related to acute coronary disease and the associated requirement for admission to hospital. In effect, that means nicorandil may have some role in the prevention of intracoronary thrombus formation, probably through its KATP channel opening mechanism.

Some experimental studies have reported that nicorandil can reduce the cytosolic concentration of free calcium, through its inhibition of calcium influx caused in part by the opening of KATP channels. Increasing the intracellular calcium upregulates PAI-1 synthesis in hystiocytes and stabilizes PAI-1 within platelet \( \alpha \)-granules. Based on the results of those studies, we speculate that nicorandil reduces PAI-1 activity through decreasing intracellular calcium concentrations, which explains the reduction of PAI activity observed in the present study. We have previously reported that angina patients with lower PAI activity have a better prognosis than those with higher PAI activity. Therefore, pharmacological interventions that modify PAI activity could improve the prognosis of patients with ischemic heart disease by reducing the risk of intracoronary thrombus formation. We believe this is an explanation for the effects of nicorandil observed in the IONA study.

In the present study, PAI activity changed without changes in the concentrations of PAI-1 and t-PA antigens. There are several kinds of PAI-1 conformation, such as free PAI-1, latent PAI-1 and PAI-1–t-PA complexes, and the total measured PAI-1 antigen represents all these forms of PAI-1 in plasma. Because PAI activity depends on the amount of circulating free PAI-1, a change in PAI activity without an increase or decrease in the concentration of PAI-1 antigen suggests either transformation of latent PAI-1 to active PAI-1 or the presence of circulating plasminogen activators other than t-PA, such as urokinase-type plasminogen activator.

Study Limitations

This is an observational study with a very small number of study patients. We need a trial with a larger study population and with control drugs, such as nitrates, to elucidate the net effects of nicorandil as a KATP channel opener rather than a NO donor. Furthermore, experimental studies that directly demonstrate the effects of nicorandil on PAI-1 production through intracellular calcium reduction are also needed.

In conclusion, we demonstrated for the first time that oral administration of nicorandil decreased PAI activity in patients with CAD, which suggests that nicorandil improves the fibrinolytic capacity and may reduce the risk of coronary thrombus formation in those patients.
References


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