Clin. Cardiol. 25, 28–32 (2002)

Sarpogrelate, a Specific 5HT2-Receptor Antagonist, Improves the Coronary Microcirculation in Coronary Artery Disease

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Summary

Background: Serotonin (5-hydroxytryptamine: 5-HT) reduces the coronary blood flow (CBF) as a product of aggregating platelets. Sarpogrelate, a specific 5HT2-receptor antagonist, has been reported to increase the coronary collateral flow in humans; however, its effect on the microcirculation is still not fully understood.

Hypothesis: This study was undertaken to determine whether sarpogrelate might improve the microcirculation in coronary artery disease (CAD).

Methods: To investigate the effect of sarpogrelate on the microcirculation in CAD, we measured CBF in 15 patients with CAD but no significant stenosis in the left anterior descending artery (LAD). The patients were randomly allocated to two groups, including those receiving oral administration of 200 mg of sarpogrelate (SPG, 8 patients, age 61 ± 6 years) and those receiving no medication (controls, 7 patients, age 57 ± 8 years). Prior to and 1 h after the administration of sarpogrelate, or in controls at 1-h intervals, the average peak velocity (APV) at baseline and hyperemia was measured by an intracoronary Doppler guidewire. Systemic blood pressure (SBP) and cardiac output (CO) were also measured.

Results: In the patients receiving SPG, the medication significantly increased the baseline (18 ± 9 to 19 ± 10 cm/s, $p < 0.05$) and maximal APV (55 ± 9 to 64 ± 31 cm/s, $p < 0.05$). However, no significant changes were observed in SBP and CO after the administration of SPG. In the control group, there were no significant differences in baseline and hyperemic APV.

Conclusion: Sarpogrelate increased both baseline and maximal CBF without changing the systemic hemodynamics. These findings thus support that SPG improves the microcirculation by antagonizing the vasoconstrictive products of the aggregating platelets in CAD.

Key words: coronary microcirculation, 5HT2-receptor antagonist, adenosine, nitric oxide

Introduction

Serotonin (5-hydroxytryptamine: 5-HT) is secreted by activated platelets and plays a role in the platelet aggregatory effect; it has also been reported to have a vasoactive effect on the coronary circulation.[1–3] The intracoronary injection of serotonin can both dilate and constrict the human coronary arteries; namely, dilation occurs in angiographically normal coronary arteries and constriction in coronary atherosclerosis.[2, 3] Serotonin has a dual effect on the coronary vessels: an indirect endothelium-mediated vasodilatory effect and a direct vasoconstrictive effect on vascular smooth muscle.[4]

Serotonin-induced vasoconstriction is mediated by both 5-HT1-like and 5-HT2 receptors and by a predominant mediation of 5-HT2 over 5-HT1-like receptors.[5] This vasoconstriction has been shown to be prevented by ketanserin, an antagonist of 5-HT2.[5] Constriction by intracoronary serotonin infusion has been induced in patients with coronary atherosclerosis, particularly in small epicardial distal and collateral vessels.[2, 3] As a result, there are regional differences in the response to serotonin in the human coronary circulation. A clinical study[6] has shown sarpogrelate, a specific 5-HT2 blocker, to augment the flow reserve of collateral circulation. Under normal conditions, the coronary blood flow is determined by coronary vascular resistance, which is primarily regulated by coronary arteries measuring < 400 μm in diameter.[7] The effect of sarpogrelate on the microcirculation is still not fully understood. The present study was designed to evaluate whether or not the administration of sarpogrelate improves the microcirculation in patients with coronary artery disease (CAD).

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Received: November 22, 2000
Accepted with revision: April 5, 2001

Methods

The study group consisted of 15 consecutive patients (9 men, 6 women; age range 44–68 years; mean 60.3 ± 7.2) with CAD who were referred to our institution and who agreed to participate in this sarpogrelate study. The subjects included six patients with old myocardial infarction, four patients with stable angina pectoris, and five patients with normal coronary arteries and a positive standard exercise test for myocardial ischemia. No patient had myocardial hypertrophy, valvular heart disease, or heart failure. All patients had angiographically insignificant stenosis in the left anterior descending coronary artery (LAD). Written informed consent was obtained from all patients before the start of the study. All medications, including antianginal agents, were discontinued for at least 12 h prior to the start of the study.

This investigation consisted of an open crossover study comparing two groups, with one receiving no medication (control group) and the other the oral administration of 200 mg of sarpogrelate (SPG group). A coronary flow study and coronary angiogram were performed twice at 1-h intervals. Sarpogrelate was administered after performing the first coronary flow study and a coronary arteriogram in the SPG group (Fig. 1).

Both diagnostic routine coronary angiography and left ventriculography were carried out by a right femoral approach. No significant coronary stenosis in the LAD was found by visual inspection. After 5,000 U of heparin was administered by an intravenous bolus injection, a 6.0 Fr coronary angiography catheter was positioned in the left main coronary ostium. A 0.014" Doppler guidewire (FloWire, Cardiometrics, Inc., Irvine, Calif., USA) was advanced into the proximal LAD through a coronary angiography catheter. The position of the Doppler guidewire was confirmed by angiography of the left coronary artery. After an intracoronary injection of 3 mg of isosorbide dinitrate to obtain maximal dilation of the conduit artery, a Doppler flow study was performed. The phasic coronary flow velocity patterns were recorded at baseline and during hyperemia induced by adenosine triphosphate disodium (ATP), the precursor of adenosine, which was injected through the coronary angiography catheter. Adenosine is an endothelium-independent vasodilator that primarily affects the microcirculation. An ATP dosage of 30 μg, which was previously reported to be the optimal dosage to elicit a maximal increase in blood flow,[8] was used. Average peak velocity (APV) was measured from the phasic coronary flow velocity recording. The coronary flow reserve value was obtained from the ratio of maximal hyperemic APV to baseline APV. During the study, heart rate (HR) and systemic arterial blood pressure (SBP) were continuously monitored. The rate-pressure product (RPP) was obtained by multiplying the systolic BP by HR. Angiography of the left coronary artery was performed before and 1 h after administration in the SPG group and at a 1-h interval in the control group. In addition, 8 ml of nonionic contrast agent was injected during coronary angiography. The Doppler flow measurements were repeated after randomization to either the SPG or control group. In the SPG group, right-sided pressures (pulmonary arterial blood pressure [PAP], pulmonary capillary wedge pressure [PCWP]) and cardiac output (CO) were obtained before and 1 h after oral drug administration. Cardiac output was measured by thermodilution method. Coronary angiography was analyzed quantitatively using the videodensitometric method. The diameter of the proximal LAD, where the tip of the Doppler guidewire was placed and the flow velocity was recorded, was measured. The diameters of the selected vessels were measured using a commercially available software package (Kontron Elektronik, Cardio 500, Munich, Germany) containing a digitizing board. An automated edge-detection program was used for these measurements to determine the densities and to identify the inflection point. Using this method, the diameter of the arterial segment was measured at the site of the flow velocity measurements. Venous blood for the plasma sarpogrelate concentration was sampled 1 h after the oral administration of sarpogrelate.

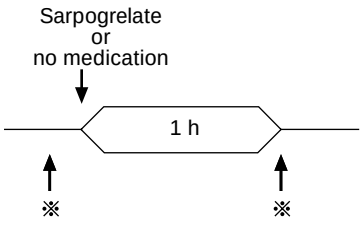

FIG. 1 Time schedule of the study protocol. ※: Doppler flow study, coronary angiogram, systemic hemodynamics.

Statistical Analysis

All data are presented as the mean ± standard deviation. The effect of sarpogrelate was evaluated by an analysis of variance corrected by the paired Student's *t*-test. All categorical variables were analyzed by Fisher's exact test. Correlations of the data between the change of APV and the plasma sarpogrelate concentration were obtained using the Pearson correlation coefficient. Statistical significance was considered if the null hypothesis was rejected at a level of $p < 0.05$.

Results

No significant differences were observed in the SPG group compared with the control group regarding the patient's age, status of CAD, and coronary risk factors (Table I). In the SPG group, after the administration of sarpogrelate, baseline APV significantly increased from 17.9 ± 9.1 to 19.1 ± 9.5 cm/s ($p < 0.05$) (Fig. 2), as did the APV during hyperemia by ATP infusion from 54.6 ± 23.2 to 64.1 ± 30.9 cm/s ($p < 0.05$) (Fig. 3). As a result, the coronary flow reserve remained unchanged (from 3.4 ± 0.8 to 3.5 ± 0.6). No significant differences were observed in either the hemodynamic parameters, SBP (systolic/diastolic) (112.5 ± 12.4/67.4 ± 10.4 vs. 115.0 ± 13.9/70.6 ± 14.1 mmHg), HR (72.5 ± 14.6 vs. 74.1 ± 17.3/min), RPP

TABLE I Clinical characteristics of the study group

	Sarpogrelate n = 8	Controls n = 7
Age, years	60.6 ± 8.0	60.0 ± 6.8
Male sex, n (%)	4 (50)	5 (71)
Status of ischemic heart disease		
OMI, n (%)	4 (50)	2 (29)
AP, n (%)	2 (25)	2 (29)
Microvascular angina, n (%)	2 (25)	3 (43)
Smoking, n (%)	3 (38)	3 (43)
Hypertension, n (%) [a]	4 (50)	3 (43)
Hyperlipidemia, n (%) [b]	5 (63)	5 (71)
Diabetes, n (%) [c]	3 (38)	2 (29)

[a] ≥ 160/95 mmHg.
[b] Total cholesterol ≥ 220 mg/dl.
[c] Fasting blood glucose ≥ 110 mg/dl.
Abbreviations: OMI = old myocardial infarction, AP = angina pectoris.

(82.3 ± 18.7 vs. 84.2 ± 18.1 beats/min × mmHg × 10^2), mean PAP (10.8 ± 3.5 vs. 11.0 ± 2.2 mmHg), PCWP (4.5 ± 2.5 vs. 5.8 ± 3.0 mmHg), and CO (4.6 ± 1.1 vs. 4.2 ± 1.0 l/min) or the LAD diameter before and 1 h after sarpogrelate administration (2.64 ± 0.5 vs. 2.64 ± 0.6 mm) .

In the control group, no differences were seen in the baseline APV (from 16.6 ± 6.3 to 16.3 ± 6.0 cm/s) (Fig. 3) and the APV by ATP infusion (from 52.6 ± 22.5 to 53.1 ± 22.7 cm/s) (Fig. 3) after 1 h. In addition, BP (122.1 ± 17.3/75.7 ± 12.8 vs. 120.1 ± 18.6/76.7 ± 13.5 mmHg), HR (71.6 ± 10.1 vs. 69.6 ± 9.8/min), RPP (86.3 ± 8.0 vs. 82.8 ± 10.8 beats/min × mmHg × 10^2), and LAD diameter (from 2.76 ± 0.6 to 2.77 ± 0.5 mm) also remained unchanged after 1 h.

In the SPG group, the APV changes of the baseline and post-treatment values did not significantly correlate with the plasma levels of sarpogrelate (APV changes of baseline: r = 0.38, NS; APV changes post treatment: r = 0.20, NS).

Discussion

The coronary blood flow is regulated by morphologic stenosis and the vasomotor response of the epicardial large coronary arteries and microcirculation. Since none of the patients in this study had any significant stenosis of the LAD and the epicardial coronary diameter measured by QCA was unchanged, we speculate that the change in APV, which was measured in the LAD using a Doppler guidewire, thus reflected the changes in microcirculation.

Coronary microangiopathy is associated with atherosclerosis of the epicardial coronary arteries and coronary risk factors.[9–11] In addition, in patients with coronary risk factors such as hypertension and angina pectoris, in the absence of relevant coronary stenosis, structural abnormalities of intramyocardial arterial vessels can also contribute to a limitation of vasodilation.[11]

A subgroup of patients with positive exercise test results and normal coronary angiograms is considered to have microvascular angina. Zeiher *et al.*[12] reported impaired endothelium-dependent vasodilation of the coronary microcirculation to be associated with exercise-induced thallium perfusion defects in patients without hemodynamically significant epicardial lesions. A dysfunction of the coronary microcirculation was similar to that in the peripheral conduit arteries in atherosclerotic disease[13] and may thus contribute to ischemic manifestations. Because all the subjects in this study had epicardial atherosclerotic disease, coronary risk factors, and microvascular angina, all were suspected to have an impaired coronary microcirculation. In this study, after the administration of sarpogrelate, both baseline and maximal coronary blood flow during hyperemia by ATP infusion increased significantly, thus suggesting that sarpogrelate improved the microcirculation in CAD.

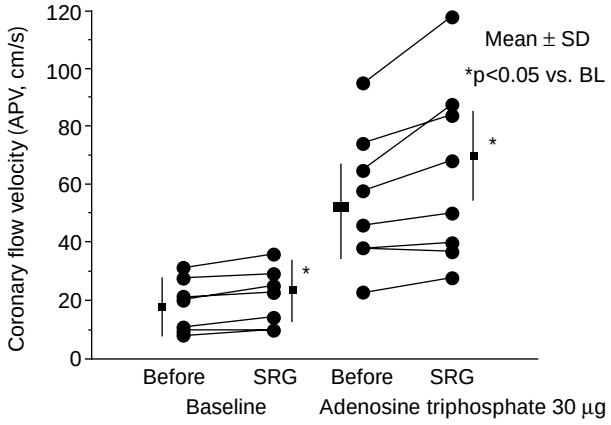

FIG. 2 Effects of sarpogrelate (SRG) medication on average peak velocity (APV) at baseline and during adenosine triphosphate intracoronary infusion in the sarpogrelate group. Each black circle represents the APV measurements for one subject. Black squares represent group mean ± standard deviation (SD). BL = baseline.

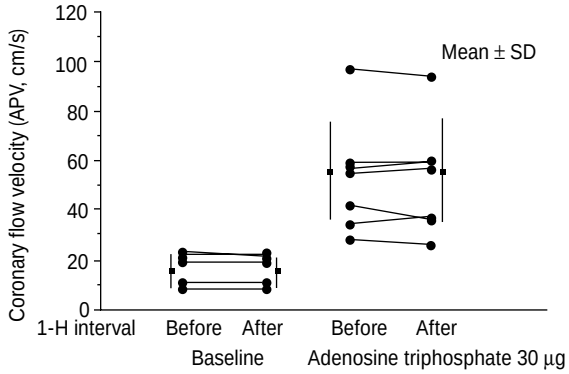

FIG. 3 Average peak velocity (APV) changes at baseline and during adenosine triphosphate intracoronary infusion at 1-h intervals in the control group. Each black circle represents the APV measurements for one subject. Black squares represent group mean ± standard deviation (SD).

At the site of coronary artery obstruction and endothelial injury platelets are activated, and these activated platelets release serotonin which have been reported to play a role in the aggregatory and constrictive effects on the coronary circulation.[1–3] Atherosclerotic vessels are known to have an increased sensitivity to the constrictive effects of serotonin, which is particularly intense in epicardial small distal and collateral vessels.[3] Golino *et al.*[2] demonstrated that the infusion of serotonin at doses that caused only a modest reduction in the epicardial cross-sectional area was associated with a significant reduction in the coronary blood flow, thus suggesting that serotonin may have a particularly potent constrictive effect on vessels too small to be seen angiographically.

In the absence of hemodynamically significant epicardial large coronary artery obstruction, the coronary blood flow is determined by coronary vascular resistance, and most coronary vascular resistance resides in the coronary microvasculature.[14] Many different regulatory factors influence the caliber of coronary arterioles and small arteries in the coronary microcirculation and appear to have a potential to affect total coronary vascular resistance.[14] Adenosine, which is a metabolic vasodilator, can dilate coronary arterioles and small arteries measuring > 100 μm in diameter; however, such arteries have far less sensitivity than arterioles.[15] Nitric oxide (NO), an important endothelium-derived releasing factor,[16] tonically dilates and lessens the resistance of small coronary arteries measuring between 100 and 300 μm in diameter. Nitric oxide may contribute to metabolic vasodilation secondary to an increase in shear stress in the arteries due to downstream arteriolar dilation.[17] In subjects with angiographically normal coronary arteries with risk factors for atherosclerosis, the coronary sinus adenosine levels increased in response to cardiac pacing, thus suggesting that adenosine production may be a compensatory mechanism when NO production is reduced.[18] The inhibition of NO synthesis by intracoronary L-NAME (NO synthesis antagonist) has been reported[19] to result in the constriction of small coronary arteries but the dilation of arterioles. Arteriolar dilation after the inhibition of NO synthesis accounts for a further diminished coronary microvascular dilation in response to adenosine. The constrictive response to serotonin therefore depends on the endothelial function.

It is also possible that hyperconstriction with serotonin in the coronary microcirculature reflects an enhanced reactivity of smooth muscle cells. In pigs,[19] it was shown that chronic administration of an NO synthesis antagonist caused the development of structural changes in small coronary arteries that were similar to those in patients with microvascular angina,[20] and a hyperreactivity of the microvascular smooth muscle to serotonin. A constrictive response to serotonin could be caused by an impairment of the relaxant response mediated by the endothelium to an enhanced production of endothelium-derived constricting factors, to an enhanced reactivity of vascular smooth muscle, or to a combination of these mechanisms.[4]

Serotonin-induced vasoconstriction is mediated by 5-HT1-like and 5-HT2 receptors, and by the predominant activation of 5-HT2 over 5-HT1-like receptors.[5] This vasoconstriction was prevented by ketanserin, an antagonist of 5-HT2.[5] In this study, sarpogrelate, a specific 5-HT2 blocker, increased the coronary flow in patients with CAD with microvascular disease. The precise mechanism underlying the improvement in the microcirculation due to sarpogrelate administration could not be clearly elucidated in our study. However, one explanation may be that the increased coronary blood flow after the administration of sarpogrelate was due to the prevention of the constriction of small coronary arteries caused by a 5-HT2 blocking effect.

Coronary circulation is affected by systemic hemodynamic change. In this study, after the administration of sarpogrelate, no hemodynamic changes were observed. The increased blood flow after sarpogrelate administration may reflect a functional change in the microcirculation. In a clinical study,[6] sarpogrelate augmented the flow reserve of the collateral circulation and improved the exercise capacity in anginal patients with well-developed collaterals. Serotonin was released into the coronary circulation of some patients with CAD.[21] A dysfunction of the coronary microcirculation causes myocardial ischemia, and sarpogrelate may thus have an antianginal effect. One limitation of our study is that the number of patients was small and the patient populations were also a heterogeneous mixture of those with mild to moderate CAD. This study should therefore be duplicated in larger sets of populations.

Conclusion

Sarpogrelate increases both the baseline and maximal coronary blood flow without changing systemic hemodynamics. These findings provide support that in coronary artery disease sarpogrelate improves microcirculation by antagonizing the vasoconstrictor products of aggregating platelets.

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