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Effect of the $5HT_{2A}$ Receptor Antagonist, Sarpogrelate Hydrochloride, on the Rate of Restenosis After Percutaneous Old Balloon Angioplasty

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Background: Serotonin receptors, especially $5HT_2$ receptors, are important in vasoconstriction and platelet aggregation and are involved in the chronic progression of endothelial dysfunction after percutaneous transluminal coronary angioplasty (PTCA). Objective: To determine whether the $5HT_{2A}$ receptor antagonist, sarpogrelate hydrochloride, was more effective than aspirin in reducing the rate of restenosis after percutaneous old balloon angioplasty (POBA). Methods: Between March 1996 and June 1997, 45 men and 11 women (average age of 63 years) underwent POBA for acute coronary syndromes. Of these, 26 received the $5HT_{2A}$ receptor antagonist 50 mg three times a day and 30 received aspirin 81 mg daily in a randomized, open trial. Restenosis was defined as a narrowing of the target vessel of at least 50% at follow-up, as measured by quantitative coronary angiography (QCA). Results: The angiographic follow-up rate was 100%. The reference minimal lumen diameter (MLD) before and after POBA did not differ significantly between the two groups (post MLD: 2.67 (0.53) in the $5HT_{2A}$ group and 2.79 (0.56) in the aspirin group; $p=0.42$). The mean (SD) MLD at 6 months was significantly larger in the $5HT_{2A}$ group than in the aspirin group (1.64 (0.69) mm vs 1.06 (0.91) mm; $p=0.03$). Angiographically identified restenosis occurred in 7/26 (27%) of the patients in the $5HT_{2A}$ group and in 13/30 (43%) of those in the aspirin group. In the $5HT_{2A}$ group, restenosis rate was likely to be less frequent in patients with right coronary artery (RCA) stenosis on the initial diagnostic angiogram ($p=0.040$). No complications were observed during the follow-up period. Conclusions: The $5HT_{2A}$ receptor antagonist, sarpogrelate hydrochloride, reduced the rate of restenosis after POBA, especially in patients with RCA stenosis on the initial diagnostic angiogram. No adverse events were reported in this series.

Key words: percutaneous old balloon angioplasty, coronary artery disease, $5HT_{2A}$ receptor antagonists

Introduction

Serotonin, 5-hydroxytryptamine (5HT), is an important vasoconstrictor that is released from aggregating platelets and acts through four 5HT receptor subclasses. It dilates normal coronary arteries but constricts the arteries of patients with coronary artery disease. The constrictor effects are mediated mainly by $5HT_{2A}$ receptors. In addition, 5HT, by activating $5HT_2$ receptors, stimulates the proliferation and migration of endothelial cells, and inhibits the induction of nitric oxide synthase by cytokines in smooth muscle cells. Stimulating the $5HT_2$ receptors on platelets augments platelet aggregation, which favors the formation of thrombi and the release of other vasoconstrictors and mitogens, including 5HT itself. The intimal migration of smooth muscle cells is activated by several platelet-derived factors, which may impair the regeneration of endothelial cells. These findings suggested that 5HT released from aggregating platelets is involved in the progression of chronic endothelial dysfunction[1)～5)].

Ketanserin was the first reported blocker of $5HT_2$

receptors. However, it is not selective, as it also has an affinity for α_1-adrenergic receptors as well. Sarpogrelate hydrochloride (Anplag, Mitsubishi-Tokyo Pharmaceuticals Inc., Tokyo, Japan) is a highly selective $5HT_{2A}$ receptor antagonist without α_1-adrenergic receptor blocking action.

Previous studies reported that the rate of restenosis after percutaneous old balloon angioplasty (POBA) was about 40% with low dose aspirin administration. But, there was no single matched comparison study with low dose aspirin and another antiplatelet agent on the rate of restenosis after POBA.

In this study, we compared the results of quantitative coronary angiography (QCA) performed immediately and 6 months after POBA to investigate the efficacy of sarpogrelate hydrochloride in decreasing the rate of restenosis after POBA and to compare its effects to those of aspirin.

Subjects and Methods

Study population

To qualify for the study, patients had to have at least one coronary vessel with at least 50% stenosis and present to our clinic between March 1996 and June 1997. Exclusion criteria were: ① a left main coronary artery stenosis of more than 50% not protected by collateral vessels or bypass graft; ② contraindication to therapy with antiplatelet agents, such as aspirin and dipyridamole or anticoagulants; ③ a cerebrovascular accident within the previous 6 months; ④ gastrointestinal bleeding or major surgery within the previous 6 weeks; and ⑤ hypertension with a systolic blood pressure above 180 mmHg or a diastolic blood pressure above 100 mmHg.

Patients who declined to take sarpogrelate hydrochloride were also excluded. All patients gave written informed consent. The study protocol was approved by the institutional review board of the Tokyo Metropolitan Fuchu Hospital.

Study protocol

Eligible patients were randomly assigned to receive either sarpogrelate hydrochloride 50 mg three times a day or aspirin 81 mg once a day beginning before POBA. Given the angiographic endpoints, blinding was not employed. Twenty-six out of 56 patients without contraindications received $5HT_{2A}$ receptor antagonist and 30 patients received Aspirin. Eligible patients in the $5HT_{2A}$ group who had single-vessel disease received sarpogrelate alone, whereas those who had multivessel disease received both sarpogrelate and an anti-angina agent, such as isosorbide dinitrate (ISDN), a calcium antagonist, or a β-blocker.

Patients in the aspirin group who had single-vessel disease received aspirin alone; those who had multivessel disease received both aspirin and an anti-angina agent but no other antiplatelet or anticoagulant agents. If POBA was successful, the medication was continued until the follow-up angiographic examination 6 months later. Success was defined as an immediate post-POBA diameter stenosis of no more than 50% and thrombolysis in myocardial infarction (TIMI) grade III flow on the cineangiogram. In case of acute and subacute vessel occlusion, repeat POBA was performed for salvage. (Stent inplantation for bailing out was not performed.)

Coronary angiography and POBA

Cardiac catheterization and PTCA were performed according to standard techniques. Only conventional balloon angioplasty was allowed for this study. The technical aspects of the procedure, including the choice of balloon, inflation time, and pressure, were determined by the five operators. Coronary angiograms were obtained before and after POBA and at follow-up angiography 6 months later, using digital equipment from Toshiba Medical Systems (Tokyo, Japan). Images were obtained in multiple projections after intracoronary injection of 2.5 mg of ISDN. All projections of the initial angiograms were repeated at follow-up. The optimal views of the target lesions from all technically suitable angiograms were analyzed by QCA according to the hand caliper method with the guiding catheter as the reference dimension. The absolute values for the minimal lumen diameter (MLD) as well as the reference vessel diameter were measured. Calcification was assessed by visual estimation on cinÈ angiograms. Intravascular ultrasound was not per-

formed.

Follow-up evaluation

Patients returned for outpatient evaluation every month. The evaluation included blood analysis, cardiac status, and electrocardiographs, as well as an assessment of adherence to drug therapy and any drug-related side effects. Follow-up angiography was performed during the first 6 months if ischemic symptoms recurred and in all patients at 6 months. If a recurrent symptom necessitated repeat POBA at an earlier time, the angiogram obtained before angioplasty was used for the analysis.

Endpoints

Each patient was evaluated for cardiac events (target vessel revascularization [TVR], acute myocardial infarction [AMI], and death) and for clinical events, such as drug-related hemorrhage or gastrointestinal symptoms. The primary endpoint was the restenosis rate at follow-up angiography. Restenosis was defined as recurrent lumen diameter stenosis of 50% or more as determined by QCA. The secondary endpoint was a change in MLD as assessed by QCA. The POBA-related endpoints were residual stenosis of 50% or greater and the occurrence of any major cardiac event. Myocardial infarction was defined as the occurrence of typical symptoms, electrocardiographic changes, and creatine kinase MB isoenzyme elevation to twice the upper limit of normal.

Statistical methods

All data were recorded on standardized forms and were entered in a database. The data are expressed as the mean value ± SD. Differences in categorical variables between the $5HT_{2A}$ and aspirin groups were analyzed using the chi-square test or Fisher's exact test. Continuous variables were analyzed using Student's t-test. We used two-tailed p values for all statistical testing. For multivariate analysis, at first, stepwise logistic regression was used to identify independent predictors of restenosis, second logistic regression was used to determine which factors were independently related to restenosis. Differences with a p value of less than 0.05 were considered statistically significant. All analyses were performed with the Stat view 5.0 statistical software package.

Table 1 Baseline clinical and angiographic characteristics of 56 patients (mean age 63 years) undergoing percutaneous old balloon angioplasty with $5HT_{2A}$ or aspirin to prevent restenosis

Characteristic	n (%)
No. of target vessels	58
No. of patients	56
Unstable angina pectoris (%)	22 (39)
AMI (Q-wave)	31 (53)
AMI (non-Q-wave)	3 (5)
No. of target vessels	
One	31 (55)
Two	16 (29)
Three	9 (16)
LMT	0 (0)
Target vessel	
LAD	25 (43)
LCX	9 (16)
RCA	22 (38)
LMT	0
Diagonal	2 (3)
Infarct-related artery	33 (57)
ACC/AHA classification (%)	
Type A	1 (2)
Type B 1	39 (67)
Type B 2	10 (17)
Type C	8 (14)
Calcification	35 (60)
Thrombus	26 (45)
De novo	47 (81)
Previous PTCA	11 (19)

Results

Between March 1996 and June 1997, 56 patients (58 regions) who underwent elective or urgent POBA for acute coronary syndrome in our hospital qualified for inclusion. Of these, 34 had AMI and 22 had unstable angina pectoris. Their mean (SD) age was 63 (10) years, and 46 patients were men (Table 1). The two groups were similar at baseline (Table 2), although hypertension and non-Q wave infarction were slightly more common in the aspirin group and previous myocardial infarction was more common in the $5HT_{2A}$ group. Also, the number of patients with Canadian Cardiac Society (CCS) grade III disease was higher in the $5HT_{2A}$ group. The lesion characteristics were also similar in the two groups. There were no significant differences in the location of the index lesion, although type B2 lesions (modified American Heart Association/American

Table 2 Clinical background of 56 patients undergoing percutaneous old balloon angioplasty with $5HT_{2A}$ or aspirin to prevent restenosis, by treatment group

	$5HT_{2A}$ Group (n = 26) n (%)	Aspirin Group (n = 30) n (%)
Age (y)	63 ± 11	62 ± 9
Male	23 (88)	23 (77)
Previous MI	8 (31)	4 (13)
Risk factors		
Hypertension	11 (42)	26 (87)
Hyperlipidemia	12 (46)	11 (37)
Diabetes mellitus	6 (23)	14 (47)
Hyperuricemia	1 (4)	3 (10)
Smoking	10 (38)	13 (43)
CCS		
II	9 (35)	8 (27)
III	4 (15)	1 (3)
AMI (Q-wave)	13 (50)	18 (60)
Anterior	5 (38)	8 (44)
Inferior	7 (54)	8 (44)
Lateral	1 (8)	1 (6)
Posterior	0	1 (6)
AMI (non-Q-wave)	0	3 (10)
No. of diseased vessels		
One	16 (62)	15 (50)
Two	6 (23)	10 (33)
Three	4 (15)	5 (17)
Previous PTCA	7 (27)	4 (13)

CCS: Canadian Cardiac Society classification.

Table 3 Baseline characteristics for 58 lesions from 56 patients undergoing percutaneous old balloon angioplasty with $5HT_{2A}$ or aspirin to prevent restenosis, by treatment group

	$5HT_{2A}$ Group (n = 26) n (%)	Aspirin Group (n = 32) n (%)
LAD	11 (42)	14 (44)
LCX	5 (19)	4 (13)
RCA	9 (35)	13 (41)
Side branch	1 (4)	1 (3)
IRA	12 (46)	21 (66)
Modified AHA/ACC lesion type (%)		
A	0	1 (3)
B 1	17 (65)	22 (69)
B 2	8 (31)	2 (6)
C	1 (4)	7 (22)
Calcification	19 (73)	16 (50)
Thrombus	8 (31)	18 (56)
TIMI grade		
0	4 (15)	12 (38)
I	0	3 (9)
II	7 (27)	10 (31)
III	15 (58)	7 (22)
Previous PTCA lesions	7 (27)	4 (13)
De novo	19 (73)	28 (88)
ICT before PTCA	8 (31)	11 (34)

Treatment group vs control group.
IRA: infarct-related artery, TIMI: thrombolysis in myocardial infarction, ICT: intracoronary thrombolysis.
Chronic total occlusion was excluded from type C lesion.

College of Cardiology type[4] were more frequent in the $5HT_{2A}$ group, whereas type C lesions (except for chronic total occlusion) were more common in the aspirin group (Table 3). The POBA was successful in all 56 patients, and all of them underwent follow-up angiography at 6 months. There were no differences in the angiographic results in the two groups, except that postprocedural distal emboli occurred more frequently in the aspirin group (Table 4). The mean reference diameter and MLD before and immediately after POBA were not significantly different (post MLD: 2.67 (0.53) mm in the $5HT_{2A}$ group vs 2.79 (0.56) mm in the aspirin group and 0.34 (0.30) mm vs 0.28 (0.29) mm and 2.18 (0.43) mm vs 2.10 (0.73) mm, respectively). At 6 months, the mean MLD was significantly larger in the $5HT_{2A}$ group than in the aspirin group (1.64 (0.69) mm vs 1.06 (0.91) mm; $p = 0.03$). The percent diameter stenosis at 6 months was significantly smaller in the $5HT_{2A}$ group (37 (24) % vs 57 (36) %; $p = 0.04$). The late loss was not significantly different in the two groups—0.95 (0.75) mm vs 1.25 (0.98) mm ($p = 0.22$) —but was smaller change in the $5HT_{2A}$ group. Angiographically identified restenosis occurred in 27% (7/26) of the $5HT_{2A}$ group and in 43% (13/30) of the aspirin group. In the $5HT_{2A}$ group, restenosis rate was likely to be less frequent in patients with RCA stenosis on the initial diagnostic angiogram ($p = 0.0440$) (Table 5). Target vessel revascularization was required by 7.7% (2/26) and 16.7% (5/30) of the patients in the $5HT_{2A}$ and aspirin groups, respectively (Table 6). Total occlusion was observed in 20% (6/30) of the patients in the aspirin group at 6-month follow-up, but these patients were excluded from TVR. No adverse events were reported in this series.

Discussion

Angiographically identified restenosis occurred in 27% of the $5HT_{2A}$ group and in 43% of the aspirin group. On release from aggregating platelets, 5HT

Table 4 Procedural outcome and early clinical events among 56 patients undergoing percutaneous old balloon angioplasty with $5HT_{2A}$ or aspirin to prevent restenosis, by treatment group

	$5HT_{2A}$ Group (n = 26) n (%)	Aspirin Group (n = 30) n (%)	p value
Angiographic success (%DS ≤50%)	26 (100)	30 (100)	
Procedural success	26 (100)	30 (100)	
Complication (%)			
Death	0	0	
AMI (Q or non-Q)	0	0	
Recoil	0	1 (3)	0.11
Dissection	1 (4)	3 (9)	0.30
Distal emboli	0	5 (16)	0.0006
Local thrombus	0	3 (9)	0.008
Acute/subacute occlusion	0	0	
CVA	0	0	
Transfusion	0	0	

% DS: percent diameter stenosis, CVA: cerebrovascular accident.

Table 5 Related factor to restenosis (multivariate regression)

	$5HT_{2A}$ Group (%)	Aspirin Group (%)	p value
TIMI grade II flow on the initial angiogram	57	23	0.0197
Side branch stenosis on the initial angiogram	14	0	0.0451
RCA stenosis on the initial angiogram	29	62	0.0440

Table 6 Quantitative angiographic and procedural results from 56 patients undergoing percutaneous old balloon angioplasty with $5HT_{2A}$ or aspirin to prevent restenosis, by treatment group

Variable	$5HT_{2A}$ Group (n = 26)	Aspirin Group (n = 30)	p value
Balloon size (mm)	2.93 ± 0.51	2.97 ± 0.62	0.26
Inflation pressure (atm)	7.7 ± 1.2	7.6 ± 1.2	0.76
Inflation time (sec)	170 ± 23	256 ± 191	0.03
Reference (mm)	2.67 ± 0.53	2.79 ± 0.56	0.42
MLD (mm)			
Before POBA	0.34 ± 0.30	0.28 ± 0.29	0.46
After POBA	2.18 ± 0.43	2.10 ± 0.73	0.47
6 month f/u	1.64 ± 0.69	1.06 ± 0.91	0.03
%DS			
Before POBA	88 ± 9	90 ± 10	0.44
After POBA	18 ± 12	24 ± 23	0.26
6 month f/u	37 ± 24	57 ± 36	0.04
Acute gain (mm)	1.69 ± 0.60	1.76 ± 0.73	0.70
Late loss (mm)	0.95 ± 0.75	1.25 ± 0.98	0.22
Restenosis ratio at 6 month f/u (%)	27	43	
Total occlusion at 6 month f/u (%)	0	20	
TVR at 6 month f/u (%)	7.7	16.7	

Data are presented as the mean value ± SD.
MLD: minimal lumen diameter, % DS: percent diameter stenosis, TVR: target vessel revascularization.

activates $5HT_2$ receptors in the vascular smooth muscle of coronary arteries[3)5)6)]. This monoamine also binds to pertussis toxin-sensitive G proteins and mediates the release of nitric oxide[7)8)]. Earlier

studies showed that the endothelial cells regenerated after balloon denudation of the porcine coronary artery selectively lose G protein-coupled responses[9)~11)]. This loss impairs the protective role of the endothelium against the action of vasoconstrictors released by platelets. 5HT dilates normal coronary arteries but constricts the arteries of patients with coronary artery disease[12)~15)]. In addition, 5HT, by activating $5HT_2$ receptors, stimulates the proliferation and migration of endothelial cells. It also inhibits the induction of nitric oxide synthase in smooth muscle cells by cytokines. Stimulating their receptors augments platelet aggregation, which favors the formation of thrombi, the release of other vasoconstrictors, and mitogens. Recent studies have reported that 5HT is released into the coronary circulation during angioplasty[16)] and may contribute to vasoconstriction distal to the dilated site[17)]. This vasoconstrictor effect of 5HT is attenuated by $5HT_2$ antagonists[2)3)]. Ketanserin, a well known $5HT_2$ receptor antagonist, did not reduce restenosis rates after PTCA[18)19)].

Nevertheless, we investigated the effectiveness of sarpogrelate hydrochloride because the target vessel differences for restenosis after POBA was defined and there are some important pharmacological differences between the two agents. First, sarpogrelate has antagonistic effects at $5HT_{2A}$ receptor sites on platelet membranes and vascular smooth muscle cells. Second, the drug is a highly selective $5HT_{2A}$ receptor antagonist without α_1-adrenergic receptor blocking action. Third, it is more effective in inhibiting the proliferation and migration of endothelial cells. Finally, sarpogrelate moderately inhibits collagen-induced, ADP-induced, and arachidonic acid-induced platelet aggregation[20)21)]. All of these properties suggested that sarpogrelate would be more effective than ketanserin in reducing the rate of restenosis in coronary arteries.

Limitations of the study

Our study has some limitations. Only conventional balloon angioplasty was allowed for this study. Our sample was small and the follow-up period was only 6 months. A larger sample size and longer follow-up evaluation will be required. Quantitative coronary angiography was performed by the hand caliper method because an automated QCA system was not available at our hospital. However, hand caliper results are highly consistent with those produced by computer assisted-methods[22)].

Conclusions

Our results suggest that sarpogrelate is useful regimen for reducing the rate of restenosis after POBA, especially in patients with RCA stenosis on the initial diagnostic angiogram. No adverse events were reported in this series. However, longer follow-up and a trial with a larger sample size are required to obtain conclusive results. Moreover, stent investigation will be required.

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経皮的旧バルーン動脈形成術後の再狭窄に関する $5HT_{2A}$ 受容体拮抗薬（塩酸サルポグレラート）の有用性

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〔背景〕セロトニン受容体，特に $5HT_2$ 受容体は血管収縮および血小板凝集に大いに関与し，また，経皮的冠動脈形成術（PTCA）後の血管内皮機能障害の進行にも影響を及ぼしている．

〔目的〕$5HT_{2A}$ 受容体拮抗薬（塩酸サルポグレラート）が経皮的旧バルーン動脈形成術（POBA）後の再狭窄率の減少に有用であるか否かアスピリンと対比し検討する．

〔方法〕1996年3月より1997年6月までに急性冠症候群の診断で入院となりPOBAを施行した56例（男性45例，女性11例；平均年齢63歳）について検討した．56例中無作為に抽出した26例に対し $5HT_{2A}$ 受容体拮抗薬150mg（分3）を投与し，残りの30例に対してはアスピリン81mg（分1）を投与した．また，QCA法により計測し6ヵ月後（follow up時）の冠動脈造影上で標的血管に50%以上の狭窄を認めた場合を再狭窄と定義した．

〔結果〕56例すべてにおいてfollow upを行った．POBA前後での両群間における対照血管最小血管経（MLD）に有意差は認めなかった（$5HT_{2A}$ 群 vs アスピリン群：2.67±0.53mm vs 2.79±0.56mm; p=0.42）．POBA後6ヵ月後（follow up時）のMLDは $5HT_{2A}$ 群の方がアスピリン群より有意に大きい結果であった（$5HT_{2A}$ 群 vs アスピリン群：1.64±0.69mm vs 1.06±0.91mm; p=0.03）．再狭窄率は $5HT_{2A}$ 群 7/26（27%），アスピリン群 13/30（43%）であった．また，$5HT_{2A}$ 群において，診断造影上右冠動脈に有意狭窄を認めた症例でPOBA後の再狭窄が少ない傾向を認めた．全経過中に明らかな合併症は認めなかった．

〔結語〕$5HT_{2A}$ 受容体拮抗薬（塩酸サルポグレラート）はPOBA後の再狭窄率の減少に有用かつ明らかな合併症を認めない安全な薬剤であり，診断造影上右冠動脈に有意狭窄を認めた症例においては特に有用な薬剤であると思われる．