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Effect of a Platelet-Activating Factor Receptor Antagonist, E5880, on Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

—Open Clinical Trial to Investigate Efficacy and Safety—

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Abstract

The efficacy and safety of a new platelet-activating factor receptor antagonist, E5880, were investigated for preventing cerebral vasospasm after subarachnoid hemorrhage (SAH) in 71 patients with SAH who underwent surgery for ruptured aneurysms within 3 days. Intravenous E5880 administration (300 μg or 1200 μg twice daily) was begun within 4 days and continued for 14 days. The incidence of symptomatic vasospasm, low-density area on computed tomography, and angiographic vasospasm was lower than in placebo groups in previous studies. Clinical outcome was favorable compared with previous studies. No clinically important adverse events were observed. These results suggest that E5880 is safe and effective in the treatment of patients with cerebral vasospasm due to SAH.

Key words: cerebral vasospasm, subarachnoid hemorrhage, platelet-activating factor receptor antagonist

Introduction

Delayed neurological deficits due to cerebral vasospasm are still the leading cause of death and disability following subarachnoid hemorrhage (SAH).[15,16] The etiology and pathogenesis of vasospasm after SAH are not completely understood, preventing the development of effective treatment. Arterial luminal narrowing does not always correlate with ischemic symptoms or with decreased cerebral blood flow in patients with cerebral vasospasm.[18,22,31] Thus, factors other than arterial narrowing may contribute to ischemia during cerebral vasospasm, such as platelet aggregation on the damaged endothelium of the artery undergoing vasospasm,[4,25] increased procoagulant activity in the circulating blood,[12,17] microthrombi in peripheral vessels,[26] and release of vasoactive substances from the platelets.[2,6]

Intraluminal platelets are consumed in patients with vasospasm.[11] We previously reported that platelet-activating factor (PAF) concentrations in cerebrospinal fluid (CSF)[9] and plasma[12] increase during the period when cerebral vasospasm typically occurs. Furthermore, PAF concentrations in the CSF and plasma of patients with cerebral infarctions caused by cerebral vasospasm were higher than those in patients without cerebral infarction.[9,12] In addition, intrathecal injection of PAF aggravated vasospasm, and intrathecal or intravenous administration of PAF receptor antagonists prevented cerebral vasospasm in a rabbit model of basilar artery constriction and neurological deterioration.[8,10] These results strongly suggest that PAF contributes to the pathogenesis of vasospasm following SAH and that PAF receptor antagonists possibly may prevent or reduce the development of cerebral vasospasm.

E5880 (1-ethyl-2-[*N*-(2-methoxy)benzoyl-*N*-[(2R)-2-methoxy-3-(4-octadecylcarbamoyloxy)piperidinocarbonyloxypropyloxy]carbonyl]aminomethyl-pyridinium chloride) is a new PAF receptor antagonist which inhibits both the platelet aggregation and

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decrease in blood pressure induced by PAF.[19] Intravenous E5880 dilates spastic arteries, prevents neurological deterioration, reduces ischemic brain lesions, and lowers increased plasma thromboxane B_2 concentrations in the rabbit SAH model.[8] We therefore conducted a phase IIa clinical trial to investigate the clinical efficacy and safety of E5880 in patients with SAH.

Materials and Methods

I. Selection of patients

The trial was conducted in 11 Japanese neurosurgical units and included 71 patients with SAH treated between October 1996 and December 1997. All patients were classified as World Federation of Neurosurgical Societies (WFNS) grades I to IV[30] and Hunt and Kosnik (H & K) grades I to IV,[13] and underwent surgery for ruptured aneurysms within 3 days (Table 1). Exclusion criteria included the following: pregnancy; age of less than 20 or more than 75 years; absence of a subarachnoid clot on computed tomography (CT) at admission; massive intraventricular and/or intracerebral hematoma on CT at admission; obvious low-density areas on CT at admission; arterial stenosis due to cerebral vasospasm on angiography at admission; severe complications, such as cardiopulmonary, hepatorenal, or metabolic diseases; and administration of ticlopidine hydrochloride, sodium ozagrel, fasudil hydrochloride, nizofenone fumarate, aspirin, dipyridamole, trapidil, or calcium antagonists except for treatment of hypertension immediately prior to the onset of SAH. Other treatments for vasospasm, such as hypertensive-hypervolemic therapy, low-molecular weight dextran, glycerol, and mannitol, were allowed. The prohibition of the following drugs was recommended: thrombolytic drugs, such as urokinase or tissue plasminogen activator administered via ventricular or cisternal drainage; intraarterial administration of papaverine hydrochloride; antiplatelet drugs, such as cilostazol, alprostadil, sarpogrelate hydrochloride, limaprost alfadex, beraprost sodium, and ethyl icosapentate; and barbiturates for coma therapy.

Table 1A Demographic data of 71 patients treated for cerebral vasospasm following aneurysmal subarachnoid hemorrhage

Parameter	L group (n = 34)	H group (n = 37)	p Value
Sex			0.637
male	15 (44.1)	19 (51.4)	
female	19 (55.9)	18 (48.6)	
Age			0.185
≤59	23 (67.6)	17 (45.9)	
60–69	9 (26.5)	16 (43.2)	
≥70	2 (5.90)	4 (10.8)	
mean ± SD	53.1 ± 12.6	56.6 ± 12.1	0.239
Location of aneurysm			0.251
AcoA	13 (38.2)	9 (24.3)	
ACA	0	2 (5.4)	
MCA	12 (35.3)	13 (35.1)	
ICA	6 (17.6)	12 (32.4)	
VBA	3 (8.8)	1 (2.7)	
WFNS			0.826
grade I	17 (50.0)	15 (40.5)	
grade II	7 (20.6)	11 (29.7)	
grade III	5 (14.7)	5 (13.5)	
grade IV	5 (14.7)	6 (16.2)	
H & K			0.638
grade I	5 (14.7)	3 (8.1)	
grade Ia	1 (2.9)	2 (5.4)	
grade II	18 (52.9)	15 (40.5)	
grade III	8 (23.5)	13 (35.1)	
grade IV	2 (5.90)	4 (10.8)	
Hijdra score			0.632
0–20	14 (41.2)	13 (35.1)	
21–30	20 (58.8)	24 (64.9)	
mean ± SD	20.4 ± 7.24	21.5 ± 5.45	0.479
Fisher grade			0.164
group 2	11 (32.4)	6 (16.2)	
group 3	23 (67.6)	31 (83.8)	
Surgery			0.771
day 0	17 (50.0)	18 (48.6)	
day 1	13 (38.2)	17 (45.9)	
day 2	3 (8.80)	1 (2.70)	
day 3	1 (2.90)	1 (2.70)	
mean ± SD	0.600 ± 0.770	0.600 ± 0.770	0.763
Initiation of drug			0.720
day 1	2 (5.90)	1 (2.70)	
day 2	7 (20.6)	10 (27.0)	
day 3	14 (41.2)	17 (45.9)	
day 4	11 (32.4)	8 (21.6)	
day 5	0	1 (2.70)	
mean ± SD	3.00 ± 0.890	2.90 ± 0.850	0.794

II. Drug administration

Informed consent was obtained either from the patients or from their closest relative before drug administration. Eisai Co., Ltd. (Tokyo) supplied the pharmacy in each participating center with a box containing six packs of 28 ampules. Three packs contained 300 μg E5880 ampules (low dose), whereas the other three packs included 1200 μg E5880 ampules (high dose). The six packs were numbered at random and assigned to eligible patients in numerical order. One box was supplied per six patients. The dose of E5880 was dissolved in 5 ml saline and administered intravenously over 5 minutes twice a day. Treatment was started within 4 days after onset and routinely continued for 14 days. Thirty-four patients were treated with low-dose E5880 (L group) and 37 patients with high-dose E5880 (H group) (Table 1A).

III. Clinical, radiological, and laboratory assessments

On admission the patient's clinical grade was classified according to the WFNS[30] and H & K[13] scales. SAH severity was graded on CT according to the

Table 1B Demographic data of patients included in analyses of symptomatic vasospasm, low-density area (LDA) on computed tomography, and angiographic vasospasm

Parameter	Symptomatic vasospasm or LDA			Angiographic vasospasm		
	L group (n = 32)	H group (n = 36)	p Value	L group (n = 23)	H group (n = 26)	p Value
Sex			0.635			1.00
male	14 (43.8)	18 (50.0)		11 (47.8)	12 (46.2)	
female	18 (56.3)	18 (50.0)		12 (52.2)	14 (53.8)	
Age			0.208			0.267
≤59	21 (65.6)	16 (44.4)		15 (65.2)	11 (42.3)	
60–69	9 (28.1)	16 (44.4)		6 (26.1)	12 (46.2)	
≥70	2 (6.3)	4 (11.1)		2 (8.7)	3 (11.5)	
mean ± SD	53.6 ± 12.5	57.3 ± 11.5	0.204	53.9 ± 12.0	58.0 ± 11.6	0.228
Location of aneurysm			0.287			0.542
AcoA	13 (40.6)	9 (25.0)		10 (43.5)	8 (30.8)	
ACA	0	2 (5.6)		0	1 (3.80)	
MCA	10 (31.3)	13 (36.1)		8 (34.8)	9 (34.6)	
ICA	6 (18.8)	11 (30.6)		4 (17.4)	8 (30.8)	
VBA	3 (9.4)	1 (2.8)		1 (4.3)	0	
WFNS			0.734			0.882
grade I	16 (50.0)	14 (38.9)		12 (52.2)	11 (42.3)	
grade II	6 (18.8)	11 (30.6)		5 (21.7)	7 (26.9)	
grade III	5 (15.6)	5 (13.9)		2 (8.7)	4 (15.4)	
grade IV	5 (15.6)	6 (16.7)		4 (17.4)	4 (15.4)	
H & K			0.661			0.611
grade I	5 (15.6)	3 (8.3)		4 (17.4)	3 (11.5)	
grade Ia	1 (3.1)	2 (5.6)		1 (4.3)	2 (7.70)	
grade II	16 (50.0)	14 (38.9)		12 (52.2)	9 (34.6)	
grade III	8 (25.0)	13 (36.1)		4 (17.4)	9 (34.6)	
grade IV	2 (6.3)	4 (11.1)		2 (8.7)	3 (11.5)	
Hijdra score			1.00			0.151
0–20	12 (37.5)	13 (36.1)		11 (47.8)	7 (26.9)	
21–30	20 (62.5)	23 (63.9)		12 (52.2)	19 (73.1)	
mean ± SD	20.7 ± 7.35	21.3 ± 5.47	0.680	19.9 ± 6.87	22.1 ± 5.04	0.211
Fisher grade			0.380			0.157
group 2	9 (28.1)	6 (16.7)		7 (30.4)	3 (11.5)	
group 3	23 (71.9)	30 (83.3)		16 (69.6)	23 (88.5)	
Surgery			0.723			0.328
day 0	16 (50.0)	17 (47.2)		9 (39.1)	12 (46.2)	
day 1	12 (37.5)	17 (47.2)		10 (43.5)	13 (50.0)	
day 2	3 (9.4)	1 (2.8)		3 (13.0)	0	
day 3	1 (3.1)	1 (2.8)		1 (4.30)	1 (3.8)	
mean ± SD	0.700 ± 0.790	0.600 ± 0.690	0.802	0.800 ± 0.830	0.600 ± 0.700	0.341
Initiation of drug			0.664			0.642
day 1	2 (6.30)	1 (2.80)		1 (4.3)	0	
day 2	7 (21.9)	10 (27.8)		5 (21.7)	9 (34.6)	
day 3	13 (40.6)	17 (47.2)		12 (52.2)	12 (46.2)	
day 4	10 (31.3)	7 (19.4)		5 (21.7)	5 (19.2)	
day 5	0	1 (2.8)		0	0	
mean ± SD	3.00 ± 0.900	2.90 ± 0.840	0.806	2.90 ± 0.790	2.80 ± 0.730	0.760

Fisher scale[5] and Hijdra score.[7] Neurological observations, including consciousness levels as indicated by the Glasgow Coma Scale[29] and the Japan Coma Scale,[21] as well as motor and speech functions as determined by an objective scale,[27] were performed prior to drug administration, daily during drug treatment, and at 1 month after SAH. Deterioration of neurological findings from termination of drug treatment to 1-month follow up was also recorded. Angiography was performed on admission and as often as possible between day 5 and the last day of drug treatment. CT was usually performed four times: on admission, prior to initiation of drug administration, between day 7 and the last day of drug administration, and at 1 month after the SAH. The angiography and CT findings were initially assessed by the participating neurosurgeons. Subsequently, the findings were independently assessed by a neuroradiologist. If the conclusion of the two evaluations differed, the neurosurgeons were asked for a reassessment. Clinical outcome was assessed at 1 month after SAH according to the Glasgow Out-

Table 1C Demographic data of patients included in analyses of clinical outcome and drug safety

Parameter	Clinical outcome			Drug safety		
	L group (n = 29)	H group (n = 36)	p Value	L group (n = 33)	H group (n = 36)	p Value
Sex			0.804			0.706
male	13 (44.8)	18 (50.0)		15 (45.5)	18 (50.0)	
female	16 (55.2)	18 (50.0)		18 (54.5)	18 (50.0)	
Age			0.144*			0.178
≤59	20 (69.0)	16 (44.4)		22 (66.7)	16 (44.4)	
60–69	8 (27.6)	16 (44.4)		9 (27.3)	16 (44.4)	
≥70	1 (3.40)	4 (11.1)		2 (6.06)	4 (11.1)	
mean ± SD	53.4 ± 12.1	57.3 ± 11.5	0.190	53.6 ± 12.4	56.8 ± 12.0	0.240
Location of aneurysm			0.373			0.263
AcoA	11 (37.9)	9 (25.0)		13 (39.4)	9 (25.0)	
ACA	0	2 (5.60)		0	2 (5.56)	
MCA	9 (31.0)	13 (36.1)		11 (33.3)	13 (36.1)	
ICA	6 (20.7)	11 (30.6)		6 (18.2)	11 (30.6)	
VBA	3 (10.3)	1 (2.80)		3 (9.10)	1 (2.78)	
WFNS			0.444			0.805
grade I	15 (51.7)	14 (38.9)		16 (48.5)	14 (38.9)	
grade II	4 (13.8)	11 (30.6)		7 (21.2)	11 (30.6)	
grade III	5 (17.2)	5 (13.9)		5 (15.2)	5 (13.9)	
grade IV	5 (17.2)	6 (16.7)		5 (15.2)	6 (16.7)	
H & K			0.778			0.582
grade I	5 (17.2)	3 (8.30)		5 (15.2)	3 (8.33)	
grade Ia	1 (3.4)	2 (5.60)		1 (3.03)	2 (5.56)	
grade II	13 (44.8)	14 (38.9)		17 (51.5)	14 (38.9)	
grade III	8 (27.6)	13 (36.1)		8 (24.2)	13 (36.1)	
grade IV	2 (6.90)	4 (11.1)		2 (6.06)	4 (11.1)	
Hijdra score			1.00			0.779
0–20	11 (37.9)	13 (36.1)		13 (39.4)	13 (36.1)	
21–30	18 (62.1)	23 (63.9)		20 (60.6)	23 (63.9)	
mean ± SD	20.6 ± 7.24	21.3 ± 5.47	0.637	20.5 ± 7.21	21.4 ± 5.51	0.481
Fisher grade			0.238			0.180
group 2	9 (31.0)	6 (16.7)		10 (30.3)	6 (16.7)	
group 3	20 (69.0)	30 (83.3)		23 (69.7)	30 (83.3)	
Surgery			0.848			0.697
day 0	14 (48.3)	17 (47.2)		16 (48.5)	17 (47.2)	
day 1	12 (41.4)	17 (47.2)		13 (39.4)	17 (47.2)	
day 2	2 (6.90)	1 (2.80)		3 (9.10)	1 (2.78)	
day 3	1 (3.40)	1 (2.80)		1 (3.03)	1 (2.78)	
mean ± SD	0.700 ± 0.770	0.600 ± 0.670	0.808	0.602 ± 0.780	0.603 ± 0.772	0.764
Initiation of drug			0.521			0.531
day 1	2 (6.9)	1 (2.80)		2 (6.06)	1 (2.78)	
day 2	6 (20.7)	10 (27.8)		7 (21.2)	10 (27.8)	
day 3	11 (37.9)	17 (47.2)		13 (39.4)	17 (47.2)	
day 4	10 (34.5)	7 (19.4)		11 (33.3)	7 (19.4)	
day 5	0	1 (2.80)		0	1 (2.78)	
mean ± SD	3.00 ± 0.930	2.90 ± 0.840	0.706	3.00 ± 0.889	2.86 ± 0.851	0.790

Numbers in parentheses indicate percentages of the total within each group. Comparison of the data was performed using Fisher's exact test and Wilcoxon's U test (*$p<0.15$). ACA: anterior cerebral artery, AcoA: anterior communicating artery, H & K: Hunt and Kosnik, ICA: internal carotid artery, MCA: middle cerebral artery, VBA: vertebrobasilar artery, WFNS: World Federation of Neurosurgical Societies.

come Scale (GOS).[14]

Blood pressure, pulse, and body temperature were measured and recorded on the morning prior to the first drug administration as well as on the 7th and 14th days after initiation of drug administration. The following laboratory parameters were also measured on the 7th and 14th days: erythrocyte, leukocyte, and platelet counts; hemoglobin; hematocrit; leukogram; prothrombin time; fibrinogen; total bilirubin; glutamate oxaloacetate transaminase (GOT); glutamate pyruvate transaminase (GPT); alkaline phosphate; lactate dehydrogenase; γ-glutamyl transpeptidase; total protein; albumin; albumin-globulin index; total cholesterol; blood urea nitro-

Table 2 Incidence of symptomatic vasospasm in 68 patients with subarachnoid hemorrhage treated with E5880 300 μg twice daily (L group) or 1200 μg twice daily (H group)

	Absent	Present		Fisher's exact test	
		Transient	Permanent*	Present	p Value
L group (n = 32)	27 (84.4)	2 (6.30)	3 (9.40)	5 (15.6)	1.00
H group (n = 36)	31 (86.1)	4 (11.1)	1 (2.8)	5 (13.9)	

Numbers in parentheses indicate percentages of the total within each group. *Permanent symptomatic vasospasm is defined as prolonged symptoms due to cerebral vasospasm for 1 month after subarachnoid hemorrhage.

gen; creatinine; creatine phosphokinase; uric acid; Na^+; K^+; Cl^-; urine protein, glucose, and urobilinogen; and urine occult blood test. Normal or abnormal data were recorded, and the clinical significance of changes was estimated.

The following endpoints were defined to determine treatment efficacy: reduction of the incidence of symptomatic vasospasm in the H group compared with the L group; reduction of the incidence and size of low-density areas due to vasospasm on the postoperative CT in the H group compared with the L group; reduction of the incidence or severity of angiographic vasospasm in the H group compared with the L group; and increase in positive outcome (good recovery: GR and moderate disability: MD) at 1 month after SAH in the H group compared with the L group. The safety ratio was assessed for both groups.

IV. Statistical analysis

Demographic data, clinical variation, and radiological and clinical assessments between the L group and the H group were compared using Fisher's exact test and Wilcoxon's rank sum test. Significance was established at $p = 0.15$ for demographic data, and $p = 0.05$ for others.

Results

I. Demographic and clinical data

Two of the 71 patients were excluded from the analysis because one patient did not undergo surgery for ruptured aneurysms within 3 days and the other patient received E5880 before giving consent. Furthermore, treatment was discontinued during the trial in four patients because of a request from the family for the patient's withdrawal, repeated vomiting, reoperation for aneurysm clipping, and intracerebral hemorrhage. The drug-efficacy analysis included 68 patients for the occurrence of symptomatic vasospasm (32 in the L group and 36 in the H group), 68 for the degree of low-density area on CT (32 in the L group and 36 in the H group), 49 for the degree of angiographic vasospasm (23 in the L group and 26 in the H group), and 65 for functional outcome at 1 month after SAH (29 in the L group and 36 in the H group) (Table 1B, C). Drug-safety analysis was performed based on data from 69 patients (Table 1C). The demographic and clinical data of the patients, including sex, age, location of aneurysm, neurological grades on admission, severity of SAH, timing of surgery, and timing of drug administration, were compared between the L group and the H group. The H group tended to include more patients with H & K grades III and IV, WFNS grades III and IV, and Fisher group 3, although the difference was not statistically significant. There was a difference in the age distribution between the L group and the H group that reached statistical significance in the analysis of functional outcome at 1 month after SAH ($p = 0.1443$).

II. Incidence of symptomatic vasospasm

Symptomatic vasospasm was defined as the presence of either temporary or permanent neurological deterioration, including consciousness disturbance, motor paresis, or aphasia in the absence of other potential causes, such as surgery, hydrocephalus, intracranial bleeding, seizure, and metabolic disturbances in the postoperative period. No significant difference in the incidence of symptomatic vasospasm during E5880 treatment was found between the two experimental groups (Table 2).The H group tended to include more patients with severe H & K grades, so we compared the incidence of symptomatic vasospasm in patients with H & K grades III and IV. Symptomatic vasospasm occurred in four of 10 patients with H & K grades III and IV from the L group and three of 17 patients from the H group ($p = 0.365$) (Table 3). Although symptomatic vasospasm tended to occur less frequently in H group patients than in L group patients with severe SAH, the difference was not statistically significant. None of the patients with H & K grades I and Ia (6 patients in the L group and 5 patients in the H group) experienced symptomatic vasospasm. The occur-

Table 3 Effect of treatment of E5880 300 μg twice daily (L group) or 1200 μg twice daily (H group) on the clinical and radiological assessments and outcome in patients with subarachnoid hemorrhage in Hunt and Kosnik grades III and IV

	Symptomatic vasospasm		Low-density area		Angiographic vasospasm		Outcome	
	Present	p Value	More than mild	p Value	More than mild	p Value	GR + MD	p Value
L group	4/10 (40.0)	0.365	3/10 (30.0)	0.638	4/6 (66.7)	0.620	7/10 (70.0)	1.00
H group	3/17 (17.6)		3/17 (17.6)		5/12 (41.7)		13/17 (76.5)	

Values are numbers of patients and percentages (in parentheses) of the total within each group.

Table 4 Incidence of low-density areas on postoperative computed tomography in 68 patients with subarachnoid hemorrhage treated with E5880 300 μg twice daily (L group) or 1200 μg twice daily (H group)

	None	Mild	Moderate	High	Severe	Fisher's exact test	
						More than mild	p Value
L group (n = 32)	28 (87.5)	1 (3.13)	2 (6.30)	1 (3.13)	0	3 (9.40)	1.00
H group (n = 36)	31 (86.1)	2 (5.60)	2 (5.60)	0	1 (2.80)	3 (8.33)	

Numbers in parentheses indicate percentages of the total within each group.

rence of permanent symptomatic vasospasm, defined as neurological deterioration persisting until day 30 after SAH, also tended to be less in the H group than in the L group (Table 2). Thus, three of five patients with symptomatic vasospasm in the L group showed permanent symptoms, compared with only one of five patients in the H group.

III. Extent of low-density areas on CT

Low-density areas on postoperative CT (between days 7 and 30) were considered to be due to vasospasm and all other causes, such as brain retraction and occlusion of arteries or veins during surgery, periventricular lucency in hydrocephalus, and edema around the hematoma, could be excluded. The extent of low-density areas was classified into five grades: grade 1 none; grade 2 (mild) small, lacuna-like low-density areas; grade 3 (moderate) low-density areas limited to areas around the branches of the middle and anterior cerebral arteries; grade 4 (high) intermediate between grades 3 and 5; and grade 5 (severe) low-density areas extending to the entire region of middle cerebral artery and/or anterior cerebral artery and beyond. The causes of three cases of grade 2 low-density areas were unknown. At least grade 3 low-density areas were present in three of 32 patients in the L group and three of 36 patients in the H group (Table 4). No significant differences in the distribution of low-density area grades were found between the two groups. Low-density areas of more than grade 2 were detected in three of 10 patients with H & K grades III and IV from the L group and three of 17 patients from the H group ($p = 0.638$) (Table 3). Although low-density areas were observed less frequently in H group patients than in L group patients with severe SAH, the difference was not statistically significant.

IV. Degree of angiographic vasospasm

Postoperative angiography was performed between day 5 and the last day of E5880 administration in 23 of 33 patients in the L group and 26 of 36 patients in the H group. The degree of angiographic vasospasm was classified into five grades: grade 1 none; grade 2 (mild) vasospasm occurring around the aneurysm; grade 3 (moderate) multiple segmental vasospasms; grade 4 (high) diffuse, not string-like vasospasm; and grade 5 (severe) diffuse, string-like vasospasm. The proportion of patients with grade 3 or higher angiographic vasospasm was 14 of 23 patients in the L group and nine of 26 patients in the H group (Table 5). The number of patients with at least moderate angiographic vasospasm was lower in the H group, but the difference between the two groups was not statistically significant ($p = 0.0888$). Multivariate analysis of the incidence of angiographic vasospasm based on Hijdra score prior to surgery and the day of treatment initiation demonstrated that the H group had a significantly lower in-

Table 5 Incidence of angiographically detected vasospasm in 49 patients with subarachnoid hemorrhage treated with E5880 300 μg twice daily (L group) or 1200 μg twice daily (H group)

	None	Mild	Moderate	High	Severe	Fisher's exact test	
						More than mild	p Value
L group (n = 23)	2 (8.70)	7 (30.4)	11 (47.8)	3 (13.0)	0	14 (60.9)	0.0888
H group (n = 26)	4 (15.4)	13 (50.0)	7 (26.9)	1 (3.85)	1 (3.85)	9 (34.6)	

Numbers in parentheses indicate percentages of the total within each group.

Table 6 Clinical outcome at 1 month after subarachnoid hemorrhage (SAH) according to the Glasgow Outcome Scale in 65 patients with SAH treated with E5880 300 μg twice daily (L group) or 1200 μg twice daily (H group)

	GR	MD	SD	VS	D	Fisher's exact test	
						GR + MD	p Value
L group (n = 29)	22 (75.9)	4 (13.8)	3 (10.3)	0	0	26 (89.7)	0.492
H group (n = 36)	23 (63.9)	6 (16.7)	6 (16.7)	1 (2.80)	0	29 (80.6)	

Numbers in parentheses indicate percentages of the total within each group. GR, MD, SD, VS, and D indicate good recovery, moderate disability, severe disability, vegetative state, and death, respectively.

cidence of angiographic vasospasm than the L group in patients with Hijdra scores of 0 to 20 and in patients in whom treatment was initiated on day 3 ($p < 0.05$). Angiographic vasospasm of more than mild grade was observed in four of six patients with H & K grades III and IV from the L group and five of 12 patients from the H group ($p = 0.620$) (Table 3).

V. Clinical outcome

Clinical outcome was classified according to the GOS into GR, MD, severe disability, vegetative state, and death. GR or MD was achieved in 26 of 29 patients in the L group and 29 of 36 patients in the H group (Table 6). Overall, there was no difference in outcome between the two groups ($p = 0.492$). There was an imbalance in age distribution between the L group and the H group in the analysis of outcome. However, even after a statistical correction was performed using the Cochran-Mantel-Haenszel method, there was no difference in clinical outcome between the two groups ($p = 0.768$). GR or MD was found in seven of 10 patients with H & K grades III and IV in the L group and 13 of 17 patients in the H group ($p = 1.00$) (Table 3). The number of patients with GR or MD was higher in H group patients than in L group patients with severe SAH, but the difference was not statistically significant.

VI. Interaction of calcium antagonists, corticosteroids, and urokinase with E5880

Calcium antagonists and corticosteroids were used in some patients to treat hypertension or reduce brain edema. Furthermore, some patients received urokinase, although the study protocol recommended that this drug should not be used during cisternal irrigation. However, no statistically significant interactions of any of these drugs with E5880 were detected for any of the variables analyzed (Breslow-Day test) (data not shown).

VII. Analysis of drug safety

The mean treatment duration with E5880 was 13.4 ± 2.18 days (mean ± SD, n = 33) in the L group and 13.9 ± 0.77 days (n = 36) in the H group. Adverse events were defined as undesirable symptoms that occurred during E5880 treatment or as marked abnormal changes of laboratory parameters. Adverse events that could be causally related to E5880 therapy were considered complications, whereas events that were not related to E5880 therapy were considered accidents. Adverse events were recorded by the participating neurosurgeons and classified as a complication or an accident. Based on the presence of complications as well as on the presence and degree of clinically significant changes in laboratory parameters, the general safety of E5880 at the end of treatment was classified into five categories: safe, almost safe, fairly questionable, questionable, and impossible to judge (the reason needed to be record-

ed). The drug's general safety was indicated by the proportion of patients in whom E5880 was considered safe or almost safe.

Sixteen adverse events were recorded in 12 patients in the L group and 21 adverse events were recorded in 17 patients in the H group, including abnormal laboratory parameters of liver function, intracranial hemorrhage, and hyponatremia. Intracranial hemorrhage included four mild hemorrhagic infarction, one mild epidural hematoma, and one hypertensive intracerebral hematoma. Nine events in eight patients of the L group and 11 events in 11 patients of the H group were classified as complications. The main complications were abnormal laboratory parameters of liver function, hemorrhagic infarction, skin eruption, and vomiting in the L group and abnormal laboratory data of liver function, hemorrhagic infarction, epidural hematoma, and fever in the H group. None of the patients died within 1 month of SAH. Three patients died later, but the causes of death were not considered to be related to E5880. Serious adverse events, such as intracerebral hemorrhage and rupture of another cerebral aneurysm, occurred in three patients during E5880 treatment (2 patients in the L group and 1 patient in the H group). However, these events did not appear to be related to E5880 treatment. There were 124 clinically significant abnormal laboratory values affecting 28 patients in the L group as well as 163 abnormal laboratory values affecting 33 patients in the H group. Forty-six abnormal values in 16 patients in the L group and 78 abnormal values in 25 patients in the H group appeared to be related to E5880 treatment. Overall, E5880 was found to be safe or almost safe in all 33 patients in the L group and 34 of 36 patients in the H group. There was no significant difference in E5880 safety between the two groups ($p = 0.494$).

Discussion

The present study investigated the efficacy and safety of the PAF antagonist E5880 in the treatment of 71 patients with SAH treated with two different doses of E5880. The lower dose administered to the L group was shown to be effective by a non-clinical study.[8] The dose administered to the H group may be more effective than the low dose, based on inhibitory data regarding its effect on platelet aggregation.[19] However, the present study found no difference in protective effect against symptomatic vasospasm. Overall, the incidence of symptomatic vasospasm was lower in the present study than in previous studies of anti-vasospastic drugs.[1,23,24,28] The difference in distribution of H & K or Hunt and Hess grade in drug-treated groups was estimated between the present study and previous studies.[1,23,24,28] The neurological grade distribution of patients in the present study was not different from the SG-75 and AVS trials, whereas the AT877 and ebselen studies included patients with more severe neurological grades (AT877, $p = 0.0499$; SG-75, $p = 0.185$; AVS, $p = 0.395$; ebselen, $p < 0.0001$; chi-square test). Other treatments used for vasospasm together with the trial drugs are also important for the results. The restrictions on treatments and drugs in the present study were the most severe among the five studies.[1,23,24,28] Patients with H & K grades III and IV in the H group tended to show a lower incidence of symptomatic vasospasm compared with those in the L group, although the difference was not statistically significant. No patients with H & K grades I and Ia experienced symptomatic vasospasm. The results of clinical trials that include a relatively high proportion of mild cases tend to be somewhat distorted regarding the drug's efficacy, because mild cases may show improvement even after receiving placebo or lower drug doses. Future clinical trials of the efficacy of E5880 should exclude patients with H & K grades I and Ia. Previous studies found that the incidences of symptomatic vasospasm in placebo-treated patients were 50%, 47.1%, 54.2%, and 41% in trials of AT-877,[24] SG-75,[28] AVS,[1] and ebselen,[23] respectively. We compared neurological severity between the present drug-treated group and the placebo group in previous studies and found no difference except for the ebselen study (AT877, $p = 0.308$; SG-75, $p = 0.175$; AVS, $p = 0.106$; ebselen, $p < 0.0001$; chi-square test). The results achieved in the present study with respect to symptomatic vasospasm appear to be substantially improved compared with those in the placebo-treated groups.[1,23,24,28] Furthermore, a review of 296 publications found an average incidence of symptomatic vasospasm of 32.4% (10,472 of 32,284 SAH patients),[3] which also is higher than in the present study. An international cooperative study demonstrated that vasospasm was a cause of death and disability in 13.5% of SAH patients.[16] In the present study, permanent symptomatic vasospasm occurred only in 9.4% and 2.8% of the L group and H group patients, respectively. These results suggest that E5880 may reduce the occurrence of vasospasm enough to affect functional outcome. Our findings are supported by experimental results demonstrating that intravenous E5880 administration reduced arterial constriction in a rabbit SAH model.[8] This reduction of vascular constriction may contribute to the decrease of symptomatic vasospasm after E5880 treatment.

We also investigated the incidence and extent of low-density areas on postoperative CT. Previous studies reported moderate or severe low-density area due to vasospasm in approximately 20% to 60% of placebo-treated patients.[1,23,24,28] Some of these differences in the incidences may result from differences in the criteria used for classifying low-density areas used in each study, but the results in the present study appear to be more favorable. The beneficial effect of E5880 on low-density areas is further supported by our previous findings that intravenous E5880 administration significantly reduced ischemic lesions, including cerebral infarction, and selective neuronal death in the CA1 region in a rabbit SAH model.[8] We also previously demonstrated that E5880 significantly reduced glutamate neurotoxicity in cultured neurons.[20]

Previous studies had indicated that angiographic vasospasm of moderate or greater severity occurred in approximately 50% to 60% of placebo-treated patients.[1,23,24,28] Similarly, a literature review determined an incidence of angiographic vasospasm of 67.3%.[3] In the present study, the incidence of angiographic vasospasm in the L group (60.9%) was comparable to these data. The H group showed a relatively lower incidence (34.6%), suggesting that this effect was dose dependent.

A positive clinical outcome (GR or MD) was observed in a large proportion of patients in the present study (89.7% in the L group and 80.6% in the H group). These results compare favorably to percentages of 70%, 64.0%, 43.9%, and 71% among placebo-treated patients in the AT-877,[24] SG-75,[28] AVS,[1] and ebselen studies,[23] respectively. The AT-877 study found an outcome worse than MD due to vasospasm in 9% of treated patients and 21% of untreated (placebo) subjects.[24] However, the clinical outcome at 1 month after SAH was worse than MD in patients with permanent symptomatic vasospasm. Thus, the present data suggest that E5880 is more effective than placebo in improving functional outcome in patients with symptomatic vasospasm. In the present study, outcomes worse than MD resulted mainly from direct injury associated with SAH and hydrocephalus, but not from vasospasm (data not shown). The H group included a greater proportion of patients with such factors, which may account for the lower proportion of patients with GR or MD outcomes in that group. Future studies of E5880 should exclude patients with risk factors for poor outcome due to non-cerebral vasospasm and focus on patients at high risk for cerebral vasospasm to determine the drug's efficacy more accurately.

E5880 was found to be safe or almost safe in almost all patients in the study, and many of the mild adverse events observed may have been a result of the normal clinical course of SAH. The main adverse events observed were intracranial hemorrhagic lesions, including intracerebral hematoma, hemorrhagic infarction, and epidural hematoma, as well as abnormal liver function values. Some of these adverse events were thought to be related to E5880 treatment. The inhibitory effect of E5880 on platelet aggregation is specific to PAF-induced platelet aggregation.[19] Accordingly, E5880 should have less effect on bleeding than non-specific inhibitors of platelet aggregation. Consistent with this hypothesis, clinically important changes in laboratory parameters of blood coagulation, fibrinolysis, and bleeding time were detected in a clinical phase I study of E5880. A placebo-controlled double blind study of AT-877 found the incidence of intracerebral hematoma was 5.7% (8 of 140 patients) in the placebo group.[24] The incidence of intracranial hemorrhagic lesions in the present study was 8.7%, comparable to the incidence in placebo-treated subjects in a study of AT-877.[24] Intracerebral hematoma can occur during the natural postoperative course of cerebral aneurysm, so this event was probably not drug-related. Furthermore, hemorrhage can occur as a result of brain contusion induced by the surgical procedure as well as in infarcted brain due to cerebral vasospasm and therefore would also be unrelated to drug administration. Nevertheless, E5880 inhibits platelet aggregation, so careful attention should be paid to hemorrhagic adverse events in future studies.

The laboratory data of this study are difficult to compare with those in other studies, but the incidence of abnormal liver function parameters was not higher in this study than in placebo-treated patients in other studies.[27,28] Surgical invasion, anesthesia, and postoperative administration of antibiotics can all possibly contribute to impaired liver function. However, abnormal levels of GOT and GPT were noted in some toxicity analyses of E5880, and slight increases in GOT and GPT values were detected in both the placebo and the E5880 group. Therefore, E5880 administration may be related to changes in liver function.

This study demonstrated that E5880 is efficacious for preventing cerebral vasospasm and associated ischemic symptoms. The incidences of symptomatic vasospasm and low-density areas on brain CT were lower in this study than in placebo-treated patients in previous studies. E5880-mediated protection against symptomatic vasospasm may be dose dependent. E5880 treatment resulted in a good functional outcome. Clinically relevant adverse events were

not observed. However, E5880 is associated with impaired liver function and intracranial hemorrhagic lesions. These results suggest that E5880 is safe and effective for the treatment of patients with SAH. Further studies focusing on more severe cases as well as placebo-controlled, double-blind studies will help determine the efficacy and safety of E5880 more objectively.

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Commentary

This is a detailed and concisely written description of a recently introduced line of treatment for delayed cerebral vasospasm, the use of a platelet-activating factor receptor antagonist. Possible roles for platelets and PAF in the pathogenesis of vasospasm are noted, along with the effectiveness of E5880 in an animal model of SAH. Patients were randomized to one of two dose levels in a safety and dose-ranging trial of intravenous E5880. The incidence of symptomatic vasospasm, quite tightly defined, was reasonably low at about 15% overall. "Permanent" vasospasm, angiographic spasm, and CT low density areas were all lower in the group receiving the larger dose of E5880, and the proportion of favorable outcomes was slightly higher in this group. None of these differences were significant, as one would expect with this fairly small study. Safety did not seem to be a problem with this drug. The results compared favorably with reports of the natural history and with placebo groups from other trials. As pointed out by the authors, such comparisons are not valid statistically. A placebo-controlled study of E5880, concentrating as suggested on more severely affected patients, would be well worthwhile based on these figures.

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Based on experimental studies in animal models and clinical evidence in subarachnoid hemorrhage, the authors report a phase IIa clinical study that documents the efficacy and safety of the use of platelet-activating factor (PAF) receptor antagonist, E5880, for the prevention of vasospasm after subarachnoid hemorrhage. To date, the management of this devastating complication of subarachnoid hemorrhage usually relies on a multimodality approach using triple H therapy (hypertension, hypervolemia, and

hemodilution), calcium channel blockers, intraarterial papaverine injection, and transluminal angioplasty. There is still no specific way leading to the prevention of this complication, based on a single agent. Some agents have been reported to be effective, as mentioned in this paper. The importance of this study includes the remarkable reduction of vasospasm with this agent as well as the lack of demonstrable adverse effects of this agent in this clinical setting. Concerning the role of PAF in this clinical condition, this agent is thought to be a promising candidate for the appropriate management. As the authors have mentioned, a double-blind placebo-controlled study is recommended to determine the usefulness of this agent in the management of subarachnoid hemorrhage.

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The authors conducted an open clinical trial to investigate the efficacy and safety of a platelet-activating factor receptor antagonist, E5880, for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage, and showed favorable radiographical findings and clinical outcomes in the high dose group compared with the low dose group but without any statistical significance. Failure to prove dose-dependency in efficacy seems to be due to the small numbers of patients, the narrow therapeutic window of dosage, multifactorial aspects of human cerebral vasospasm, etc. They should have monitored at least platelet functions such as aggregation activity in order to clarify the mechanisms of favorable actions of this drug in patients with subarachnoid hemorrhage. Although they insisted in the discussion that E5880 improved radiological findings and clinical outcomes compared with placebo groups in previous clinical studies, a well-designed placebo-controlled study should be performed before determining the impact and efficacy of this drug on cerebral vasospasm.

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