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STUDIES ON THE EFFECT OF ADMINISTRATION OF DDAVP IN PATIENTS WITH CEREBRO-VASCULAR OCCLUSIVE DISEASES FROM THE VIEWPOINT OF BLOOD COAGULATION-FIBRINOLYSIS IN VESSEL WALLS

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ABSTRACT

To clarify the pathogenesis of cerebral thrombosis and to estimate the effectiveness of fibrinolytic treatment by administration of urokinase from the viewpoint of coagulation-fibrinolysis in vessel walls, changes of blood coagulation were investigated by intravenous administration of 1-deamino-8-D-arginine vasopressin (DDAVP) to 10 healthy volunteers and to 14 patients with cerebrovascular occlusive diseases. Results were as follows: 1) After the administration of DDAVP to normal controls, aPTT was shortened, PT was not changed, factor VIII:C and factor VIIIR:Ag were increased, euglobulin lysis time was shortened, plasminogen activator was increased, α_2-plasmin inhibitor was decreased, and no changes of antithrombin III were observed. Increases in factor VIII:C and factor VIIIR:Ag were more prominent in the elder group. Coagulation-fibrinolytic changes were more marked after the administration of 8 μg of DDAVP than those after the administration of 4 μg DDAVP. 2) Activities of coagulation were higher and activities of fibrinolysis and release activity of plasminogen activator were lower in patients with severe cerebral arteriosclerosis than in patients with mild cerebral arterio-

sclerosis. Plasminogen activator was markedly increased in patients with mild cerebral arteriosclerosis, whereas a very slight increase was observed in patients with severe cerebral arteriosclerosis. 3) Plasminogen activator showed higher levels in the patients in whom urokinase therapy had been effective to recanalize the occluded cerebral artery than in those with no recanalization by urokinase therapy. One of the recanalized patients showed a remarkable increase in plasminogen activator after the administration of DDAVP.

INTRODUCTION

It is well recognized that factor VIII complex and tissue activator are released from vessel walls by the administration of 1-deamino-8-D-arginine vasopressin (DDAVP). Because it increases the factor VIII complex through its effects on vessel walls, DDAVP has been administered to mildly affected hemophiliacs and patients with von Willebrand's disease.[2)]

The purpose of this paper is to clarify the pathogenesis of cerebral thrombosis and to estimate the effetiveness of fibrinolytic treatment in respect to coagulation-fibrinolysis in vessel walls. Therefore, we investigated the changes of blood coagulation by intravenous administration of DDAVP to normal volunteers and patients with cerebrovascular occlusive disease.

MATERIALS AND METHODS

Subjects

Fourteen patients with cerebrovascular occlusive diseases, 9 males and 5 females, aged 18 to 75 years (average 57.1 ± 13.2 years) were included in the study (Table 1). In these patients, computed tomography and cerebral angiography were perfomed as soon as possible after admission for exact diagnosis. Severity of cerebral arteriosclerosis was classified into mild and severe cases according to angiographical findings. In these patients urokinase was infused intravenously in a total dose of 180,000 IU per day for 3 to 9 days (average 7 days) in the acute to subacute stages. Among them a total dose of urokinase on the first day was 720,000 IU in case 3, 670,000 IU in case 7 and 640,000 IU in case 8. The occurrence of recanalization of the occluded cerebral artery was examined by cerebral angiography. The effect of DDAVP was investigated during their chronic stages in all the 14 patients.

Fourteen healthy volunteers acted as controls. They were divided into two groups, a younger group and an elder group. The younger group consisted of 5 males and 5 females, aged 21 to 31 years (average 23.6 ± 3.2 years), and the elder group consisted of 2 males and 2 females, aged 52 to 60 years (average 57.0 ± 3.6 years).

Administration of DDAVP

Four μg of DDAVP (Ferring Pharmaceuticals, Sweden) was administered intravenously to the normal controls. After that 4 μg of DDAVP and 8 μg of DDAVP were

Table 1. Clinical findings in 14 patients with cerebrovascular occlusive diseases

Case No.	Sex*	Age (yrs)	Diagnosis**	Recanalization	Cerebral arteriosclerosis	Atrial fibrillation	Diabetes mellitus
1	M	18	BA occlusion	−	severe	−	−
2	M	48	r. IC occlusion	+	mild	+	−
3	M	53	l. IC occlusion r. IC stenosis	− −	severe	−	−
4	M	53	bilat. IC stenosis r. MC stenosis	− +	severe	−	+
5	F	69	r. IC occlusion	−	severe	−	−
6	F	53	r. MC. & AC stenosis	−	severe	+	+
7	M	54	l. MC occlusion	−	severe	−	−
8	M	63	l. MC occlusion	+	mild	−	+
9	M	64	l. MC stenosis	−	severe	−	−
10	F	75	l. MC occlusion	+	mild	+	+
11	F	58	cerebral infarction		mild	−	−
12	M	59	cerebral infarction		mild	−	−
13	F	72	cerebral infarction		severe	−	+
14	M	60	cerebral infarction		mild	−	+

*M=male, F=female. **AC=anterior cerebral artery, BA=basilar artery, IC=internal carotid artery, MC=middle cerebral artery, l. =left, r. =right, bilat. =bilateral.
Cerebral infarction in this table indicates that no occlusion or stenosis of cerebral arteries were revealed by cerebral angiography.

administered intravenously to 2 males (21 and 22 years) and 2 females (21 and 25 years), in order to study how the dosage of DDAVP is related to changes in blood coagulation. Eight μg of DDAVP was administered intravenously to 14 patients with cerebrovascular occlusive diseases.

Assay methods of coagulation, fibrinolysis and inhibitors

Activated partial thromoboplastin time (aPTT), prothrombin time (PT), facter VIII coagulant activity (facter VIII:C), facter VIII-related antigen (factor VIIIR:Ag), fibrinogen, euglobulin lysis time, plasminogen, fibrin-fibrinogen degradation products (FDP), prekallikrein, free kallikrein, plasminogen activator, α_2-plasmin inhibitor, antithrombin III and platelet aggregation by ADP (1μM and 10 μM), collagen (2μg/ml) and epinephrine (10 μM) were assayed at 0, 5, 30, 60, 90, 120 and 300 minutes after the administration of DDAVP. These were assayed at least four times at 0, 30, 60 minutes and 24 hours after the administration of DDAVP in 14 patients.

RESULTS

Changes of coagulation-fibrinolysis were examined in normal controls and in patients after the intravenous administration of DDAVP.

Administration of 4 μg of DDAVP to controls

aPTT was shortened significantly at the time of 5 to 300 minutes after DDAVP administration and was also found to be prolonged in the younger group, as compared with the elder group, before and after the administration. PT was not changed significantly. Factor VIII:C was increased significantly at the time of 5 to 300 minutes (Fig. 1). Factor VIIIR: Ag was increased significantly at the time of 30 to 120 minutes (Fig. 2). Levels of factor VIII:C and factor VIIIR:Ag were higher in the elder group than in the younger group before and after the administration of DDAVP (Figs. 1 and 2).

Euglobulin lysis time was shortened significantly at the time of 5 to 300 minutes. Its shortest time was at 5 minutes after the administration in the younger group, whereas in the elder group it was at 60 minutes (Fig. 3). Plasminogen activator was increased significantly at the times of 60 and 120 minutes in the younger group (Fig. 4). Levels of fibrinogen, plasminogen, FDP, prekallikrein and free kallikrein were not changed significantly.

α_2-Plasmin inhibitor was decreased slightly at the times of 90 and 120 minutes in the younger group. Antithrombin III was not changed significantly, nor were platelet aggregation and platelet counts.

Administration of 4 μg and 8 μg of DDAVP to controls

Changes in coagulation-fibrinolysis were more prominent after the administration of 8 μg DDAVP than after that of 4 μg DDAVP (Figs. 5 and 6).

Administration of 8 μg of DDAVP to patients

Changes in blood coagulation in patients with cerebrovascular occlusive diseases after DDAVP administration were almost the same as those found in the normal controls. Among the patients, however, there were some differences in levels of factor VIII and plasminogen activator depending on the disease severity.

Patients with mild cases of cerebral arteriosclerosis were compared with patients with severe cases. Levels of factor VIII:C and factor VIIIR:Ag were lower, and euglobulin lysis time was shorter before and after the administration of DDAVP in patients with mild cerebral arteriosclerosis than in patients with severe cerebral arteriosclerosis (Figs. 7 to 9). Plasminogen activator showed a definite increase in patients with mild cerebral arteriosclerosis, whereas only a slight increase was observed in patients with severe cases of the disease (Fig. 10).

Also compared were differences between patients in whom the occluded cerebral artery had recanalized following the administration of urokinase and patients with no recanalization of the occluded artery in spite of the administration of urokinase. Levels of factor VIII:C were found to be obviously higher in patients with no recanalization than in patients who underwent recanalization (Fig. 11).

Levels of plasminogen activator were higher before and after the administration of DDAVP in most of the patients who underwent recanalization (Fig. 12). One (Case 8) of these patients showed a remarkable increase in plasminogen activator after the admini-

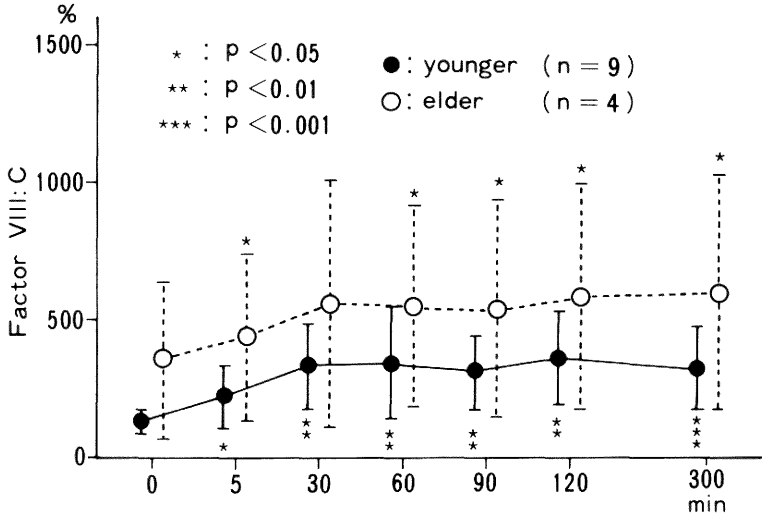

Fig. 1. Changes of factor VIII:C after the intravenous administration of 4 μg of DDAVP in normal controls. Nine out of 10 were examined in the younger group.

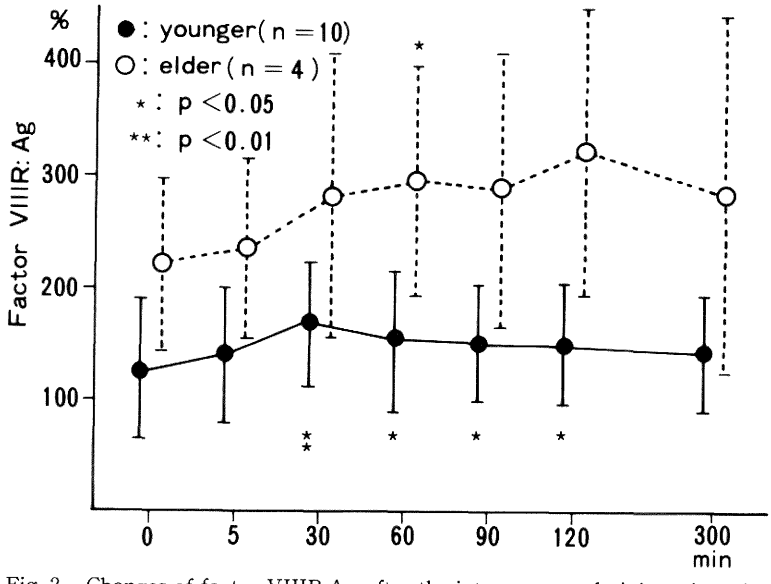

Fig. 2. Changes of factor VIIIR:Ag after the intravenous administration of 4 μg of DDAVP in normal controls.

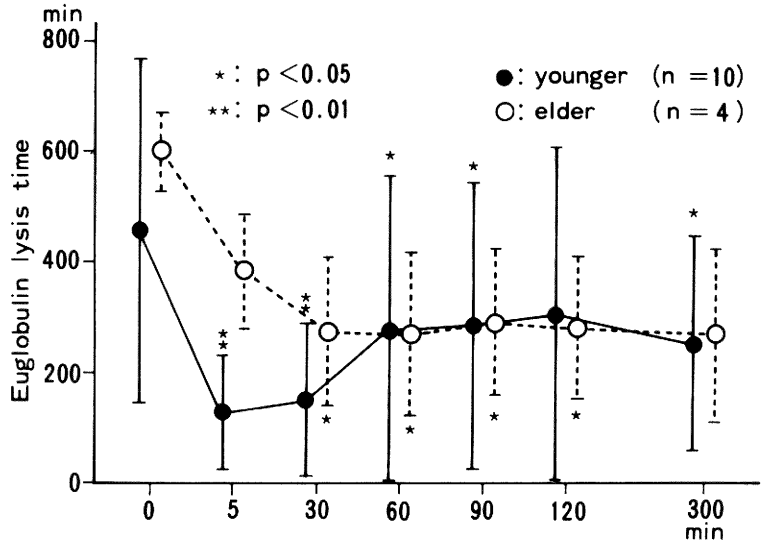

Fig. 3. Changes of euglobulin lysis time after the intravenous administration of 4 μg of DDAVP in normal controls.

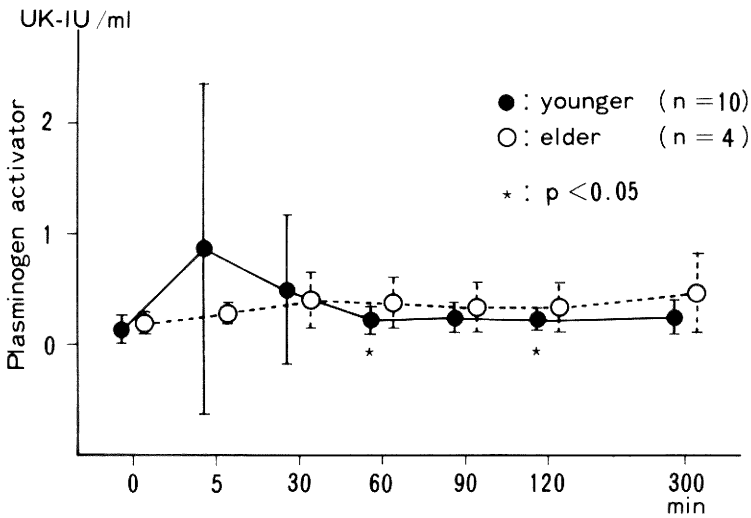

Fig. 4. Changes of plasminogen activator after the intravenous administration of 4 μg of DDAVP in normal controls. UK−IU=international unit of urokinase.

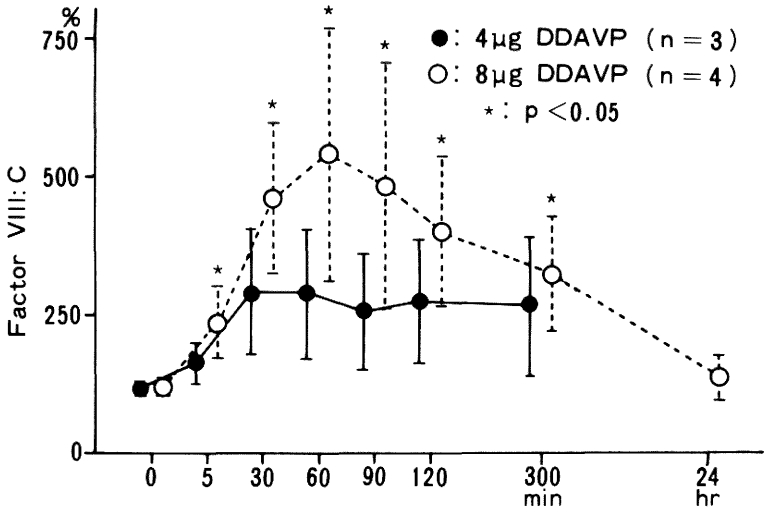

Fig. 5. Changes of factor VIII:C after the intravenous administration of 4 μg of DDAVP and 8 μg of DDAVP in normal controls. Three out of 4 were examined in cases of 4 μg DDAVP administration.

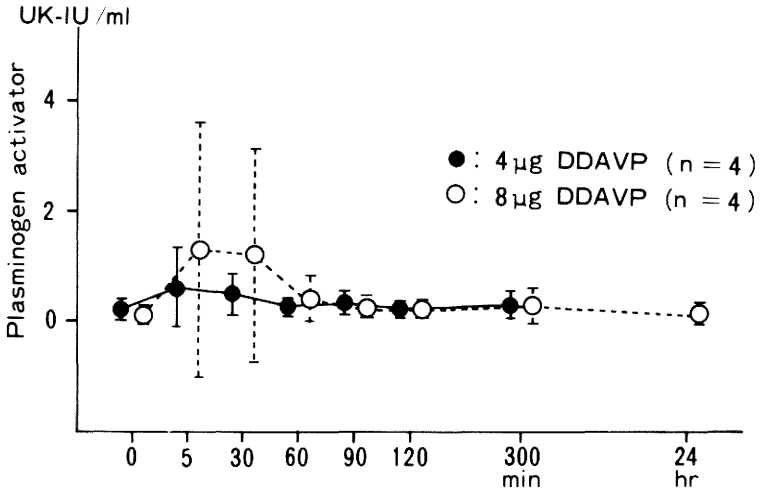

Fig. 6. Changes of plasminogen activator after the intravenous administration of 4 μg of DDAVP and 8 μg of DDAVP in normal controls.

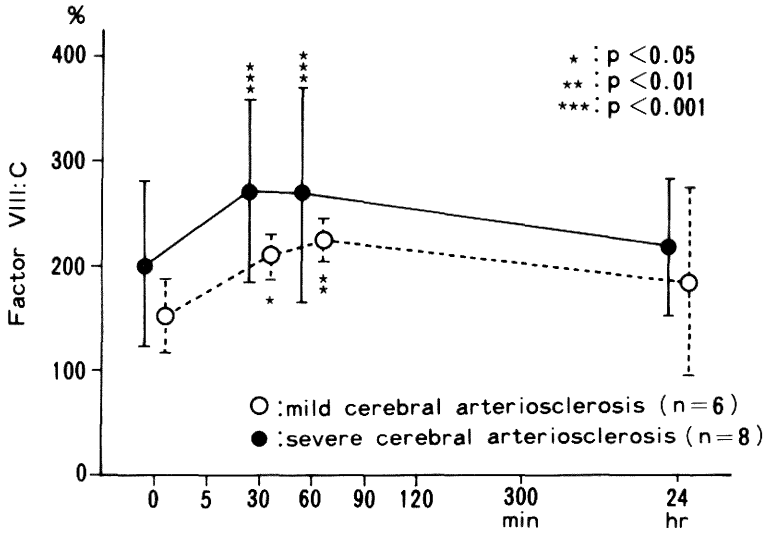

Fig. 7. Differences in changes of factor VIII:C between patients with severe cases of cerebral arteriosclerosis and patients with mild cases after the intravenous administration of 8 μg of DDAVP.

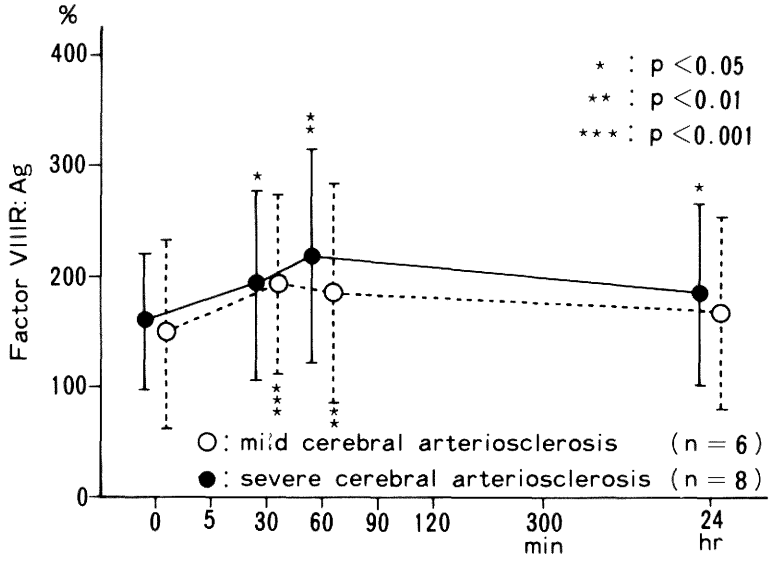

Fig. 8. Differences in changes of factor VIIIR:Ag between patients with severe cases of cerebral arteriosclerosis and patients with mild cases after the intravenous administration of 8 μg of DDAVP.

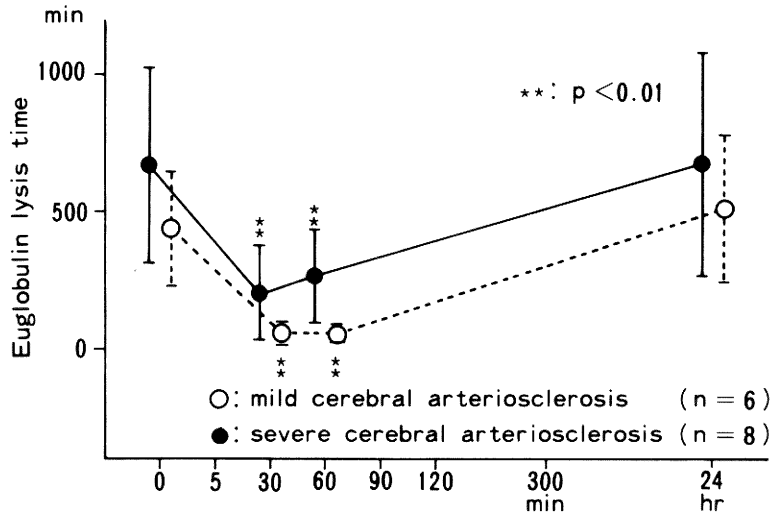

Fig. 9. Differences in changes of euglobulin lysis time between patients with severe cases of cerebral arteriosclerosis and patients with mild cases after the intravenous administration of 8 μg of DDAVP.

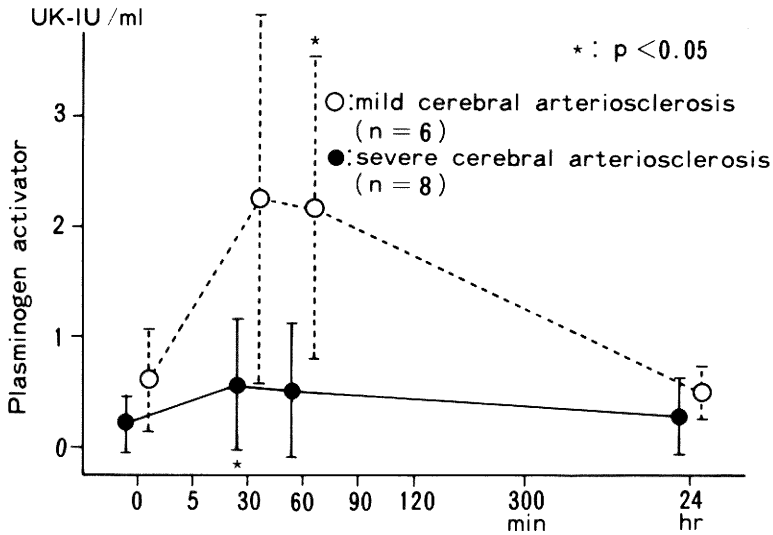

Fig. 10. Differences in changes of plasminogen activator between patients with severe cases of cerebral arteriosclerosis and patients with mild cases after the intravenous administration of 8 μg of DDAVP.

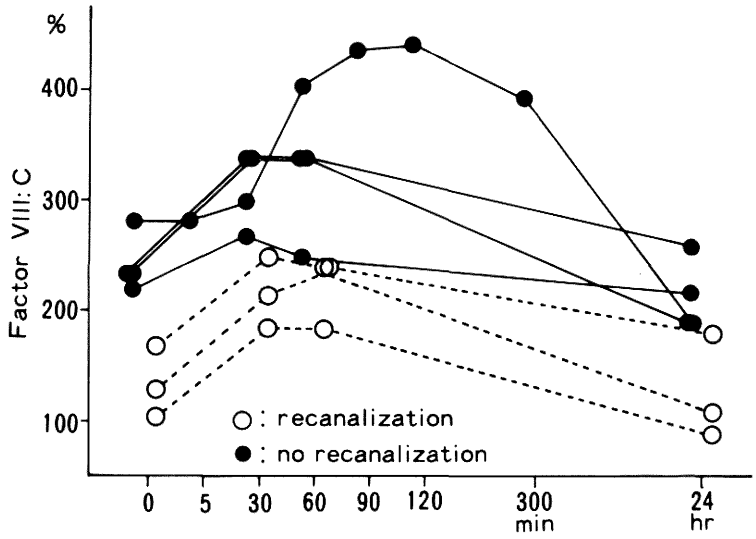

Fig. 11. Changes of factor VIII: C after the intravenous administration of 8 μg DDAVP in patients with occlusion of the cerebral artery.

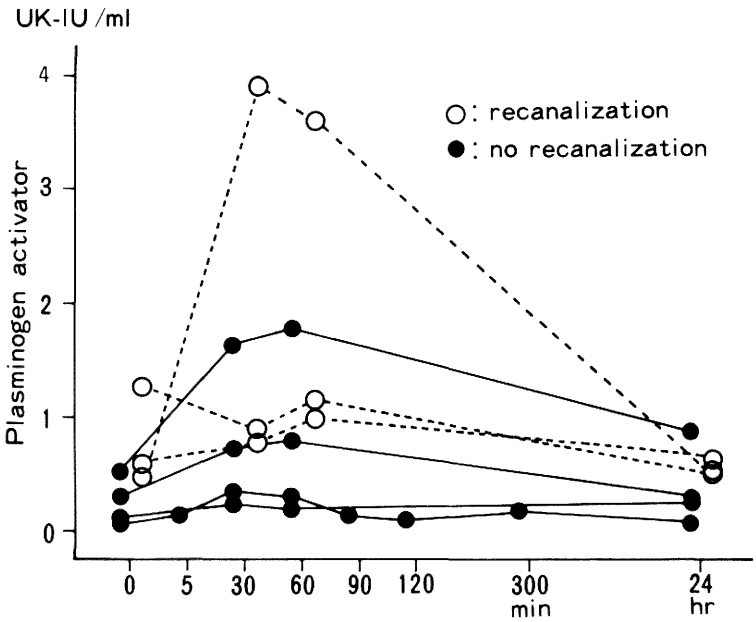

Fig. 12. Changes of plasminogen activator after the intravenous administration of 8 μg of DDAVP in patients with occlusion of the cerebral artery.

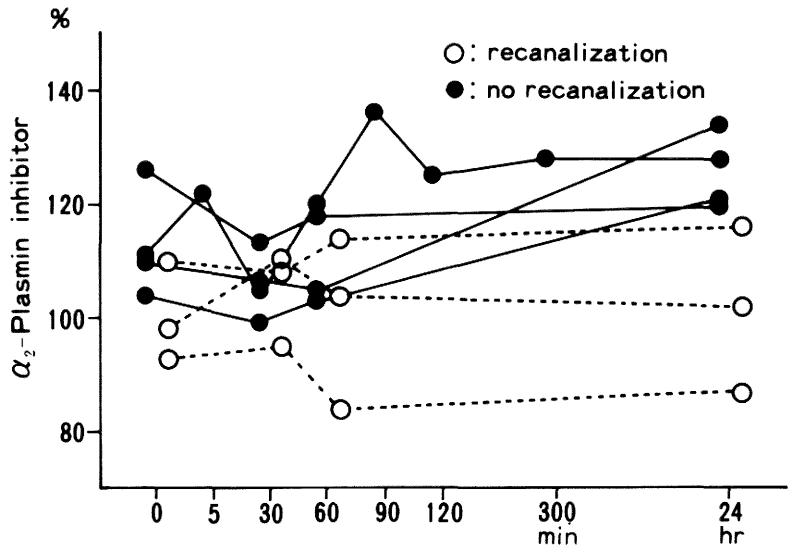

Fig. 13. Changes of the levels of α_2-plasmin inhibitor in patients with occlusion of the cerebral artrey.

stration of DDAVP (Fig. 12).

Levels of α_2-plasmin inhibitor before and after the administration of DDAVP were lower in most of the patients who underwent recanalization than in those patients who did not (Fig. 13).

Discussion

DDAVP, a synthetic derivative of vasopressin, increases factor VIII complex and also stimulates the release of plasminogen activator by its effects on vessel walls.[1,3,4]

In the normal controls of our study, activities of coagulation were higher in the elder group than in the younger group before and after DDAVP administration as confirmed by aPTT, factor VIII:C and factor VIIIR:Ag. Fibrinolysis activities were found to be lower in the elder group in terms of euglobulin lysis time and plasminogen activator. Levels of α_2-plasmin inhibitor were higher in the elder group.

In the study on patients with cerebral arteriosclerosis, coagulation activities were revealed to be higher, while fibrnolysis activities and the release activity of plasminogen activator were found to be lower in patients with severe cases of cerebral arteriosclerosis than in patients with mild cases. Therefore, higher activities of coagulation, lower activities of fibrinolysis and low release activity of plasminogen activator in vessel walls may play important roles in developing cerebral arteriosclerosis followed by cerebral thrombosis. Moreover, the severity of cerebral arteriosclerosis may be evaluated by examining the activities of coagulation-fibrinolysis in vessel walls by the administration of DDAVP.

As for the patients with occlusion of the cerebral artery, coagulation activities were remarkably higher in patients with no recanalization. On the other hand, release activity of plasminogen activator was higher, and levels of α_2-plasmin inhibitor were lower in patients with recanalization. These findings suggest that the recanalization of the occluded artery may be caused by an increase of plasmin in the circulatory blood as well as by an increase of release activity of plasminogen activator in vessel walls.

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