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Effect of Oren-gedoku-to on Platelet Aggregation

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Summary. **A traditional Chinese herbal medicine "Oren-gedoku-to" (黄連解毒湯) was administered to 21 patients with cerebrovascular disease. In 17 cases (81%) symptomatic improvement was observed. Abnormally increased platelet aggregation in three cases returned to normal levels after administration. Oren-gedoku-to may be useful for patients with cerebrovascular disease who present vague complaints.**

INTRODUCTION

Essential hypertension, diabetes mellitus and hyperlipidemia are known risk factors for myocardial infarction and cerebral infarction. Increased platelet aggregation has more recently been recognized as another risk factor. Controlling these factors may delay the onset or evolution of myocardial infarction or cerebral infarction.

Oren-gedoku-to (黄連解毒湯) containing wogonin (scutellariae radix) and gardeniae fructus (fruit of gardenia jasminoides ellis) is prescribed in hypertension or cerebral infarction. The drug has been shown to inhibit platelet aggregation and blood coagulation.[1,2] Gardeniae fructus can be turned into a fibrinolytic drug when mixed with other crude drugs, such as worenine (coptidis rhizoma), wogonin, and/or palmatine (phellodendri cortex).[1]

We here report the changes in clinical symptoms, biochemistry, and the effect on platelet aggregation observed during this study.

SUBJECTS AND METHODS

A total of 21 patients were studied: 8 patients with cerebral infarction and 13 patients with transient ischemic attack (TIA). The complications were hypertension in 8 patients, and myocardial infarction in 4 patients. The population consisted of 3 males and 18 females aged 45 to 82 (70 ± 8, mean$\pm$1SD) years. At least six months had elapsed after the first TIA, myocardial infarction, or cerebral infarction. No platelet aggregation inhibitors nor anti-coagulant drugs had been administered (particularly, ticlopidine, dipyridamole, trapidil, dilazep, cilostazol, halidor, or warfarin). Other medicines were given continually during the examination period. The prescriptions and dosages were maintained as consistently with the original as possible.

A daily dosage of 5.0-7.5 grams of oren-gedoku-to was orally administered. Before and 14 days after the initial administration, the following examinations were conducted early in the morning:

(1) Hematology and biochemistry

Red blood cells (RBC), hemoglobin (Hb), hematocrit (Ht), white blood cells (WBC), platelets, glutamate oxaloacetate (GOT), glutamate pyrurate transaminase (GPT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), cholinesterase (Ch-E), total bilirubin (TB), total protein (TP), albumin (Alb), triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL), blood urea nitrogen (BUN), creatinine (Cre), Na, K, Cl, urea acid (UA) and amylase were examined using standard methods.

(2) Coagulation and fibrinolysis

Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fbg), fibrin degradation product (FDP), thrombo test (TTO), HTP, antithrombin III (AT III), plasminogen, α_2-plasmin inhibitor (α_2-PI), thrombin-antithrombin III complex (TAT) and protein C were examined using standard methods.

(3) Platelet aggregation

A Hematracer VI (Nikoh Bioscience, Japan) was used in a transmission mode. Whole blood was mixed with a 3.8% sodium citrate solution in a 1:9 ratio, and centrifuged at 800 rpm at room temperature for nine min to obtain platelet rich plasma (PRP). The resultant platelet suspension was prepared to $300\times10^3/\mu l$ from which 0.2 ml was separated. To this amount, 22 μl of platelet aggregation accelerator was added and prepared so as to ultimately obtain the following final concentrations: 2.0 and 0.5 μl/ml for collagen (Horm Co.), 1.0 and 0.1 μl/ml for epinephrine (Sigma Co.), and 10, 3, 1 μM for ADP (Sigma Co.). The maximum aggregation ratio (%) was then determined, and spontaneous aggregation (SPA) was also measured.

(4) Symptom

Clinical symptoms were evaluated four weeks after initial administration to determine the level of improvement.

All values are presented as mean±1SD. The data were analyzed using Student's t-test.

RESULTS

(1) Improvement of symptoms (Fig. 1)

The overall improvement level four weeks after initial administration was as follows: 1 with marked improvement, 3 with intermediate improvement, 13 with slight improvement, 2 with no improvement. Two patients withdrew from the study. Thus, some degree of improvement was reported in 17 patients (81%).

Two patients withdrew due to abdominal pain and constipation which disappeared following discontinuation of administration. No other side effects were observed.

(2) Hematological and biochemical data (Table 1)

No change in values in hematology or biochemistry were detected.

(3) Coagulation and fibrinolysis (Table 2)

No change in coagulation or fibrinolytic examinations were detected before and after administration, except in 2 cases where an abnormally high TAT (16.3 and 28.7 μg/l) observed before treatment decreased to a normal level (4.6 and 3.1 μg/l, respectively).

(4) Platelet aggregation (Table 3)

The maximum platelet aggregation ratios before and after oren-gedoku-to administration are as shown in Table 3. In brief, no inhibition was observed for collagen, epinephrine, or ADP.

(5) Cases

Increased platelet aggregation, observed in 3 cases before administration, decreased to a normal level after treatment. The three cases are described below.

Case 1

A female aged 69. Blood pressure 140/90 mmHg, RBC $402\times10^4/\mu l$, Hb 11.9 g/dl, Ht 37.5%, and

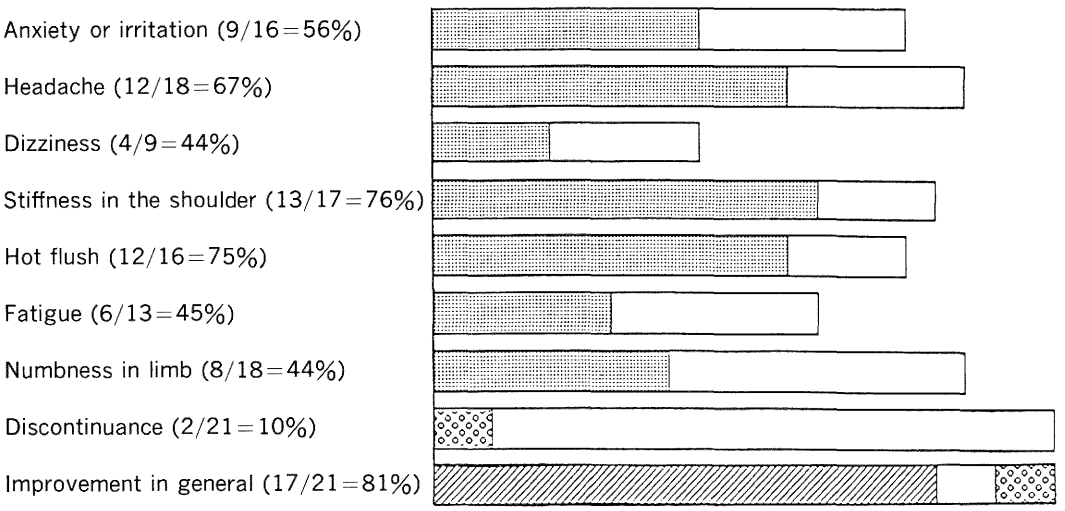

Fig. 1. Improvement of symptoms after Oren-gedoku-to administration. 17 cases (17/21=81%) improved in general.

platelet $230\times10^3/\mu l$. No polycythemia assigned. The patient had hypertension and TIA, for which nifedipine and delapril were prescribed. The patient complained of irritation, headache and stiffness in the shoulder. The initial platelet aggregation test recorded a maximum aggregation with epinephrine 0.1 μg/ml 63%, and ADP 1 μM 72% (Fig. 2A). The symptoms disappeared four weeks after administration of oren-gedoku-to (7.5 g/day). The platelet aggregation test two weeks after initial administration recorded a normal epinephrine which was 0.1 μg/ml 10%, ADP 1 μM 37% (Fig. 2B).

Case 2

A female aged 78 complaining of depression, hot flush, malaise and limb numbness was diagnosed as having cerebral infarction. She also had gastric ulcer. The initial platelet aggregation test recorded an accelerated maximum aggregation with epinephrine 0.1 μg/ml 77%, and ADP 1 μM 74% (Fig. 3A). Her symptoms improved after administration of oren-gedoku-to (5.0 g/day). The platelet aggregation two weeks and four weeks after initial administration recorded a decrease (epinephrine 0.1 μg/ml 1%, ADP 1 μM 13% (Fig. 3B), and epinephrine 0.1 μg/ml 4%, ADP 1 μM 21%, respectively (Fig. 3C)).

Case 3

A male aged 74. Blood pressure was mildly elevated (154/100 mmHg). The platelet aggregation test recorded an accelerated maximum aggregation with collagen 0.5 μg/ml 62% (Fig. 4A). Two weeks after administration of oren-gedoku-to (7.5 g/day), the platelet aggregation recorded a decreased response to collagen which was 0.5 μg/ml 3% (Fig. 4B). His symptoms (hot flush and limb numbness) improved after administration of oren-gedoku-to.

DISCUSSION

When measuring platelet aggregation, the aggregation rate is an important factor as well as the maximum agglutination ratio. The present study employed only the maximum agglutination ratio.

Patients with cerebral infarction or Gaisbäck disease in terms of Western medicine, in whom coagulation is increased are usually given an antiplatelet

Table 1. Hematological and biochemical data before and after oren-gedoku-to administration (n=21).

	RBC($\times10^4$)	Hb(g/dl)	Ht(%)	WBC	platelet ($\times10^3$)	GOT (IU/I)	GPT (IU/I)
Before	391±37	12.1±1.1	37.3±2.8	5689±1437	253±91	22±9	14±5
After	388±41	12.1±1.2	37.0±3.4	5668±1159	239±84	19±4	15±6

	ALP (IU/I)	γ-GTP (IU/I)	LDH (IU/I)	CPK (IU/I)	Ch-E (IU/I)	TG (mg/dl)	TB (mg/dl)	Alb (g/dl)	TG (mg/dl)
Before	73±25	22±17	293±77	78±49	430±97	0.52±0.20	6.9±0.5	4.3±0.3	130±91
After	76±28	22±17	299±70	69±35	426±86	0.45±0.16	6.9±0.6	4.2±0.4	137±94

	TC (mg/dl)	HDL (mg/dl)	BUN (mg/dl)	Cre (mg/dl)	Na (mEq/I)	K (mEq/I)	Cl (mEq/I)	UA (mg/dl)	Amylase (IU/I)
Before	194±41	55±20	17±5	0.9±0.2	143±2	3.9±0.4	105±3	4.7±1.4	144±48
After	186±37	54±20	15±4	0.9±0.2	143±2	4.0±0.3	105±4	4.7±1.4	143±42

Table 2. Coagulation and fibrinolysis data before and after oren-gedoku-to administration (n=21).

	PT(%)	APTT(sec)	Fbg(mg/dl)	FDP(μg/ml)	TTO(%)	HPT(%)
Before	107±18	27.1±2.9	314±89	3.8±1.9	88±19	106±15
After	110±17	25.7±6.1	297±68	3.0±1.0	100±27	109±15

	AT III(%)	plasminogen (%)	α2-PI(%)	TAT(μg/l)	protein C(%)
Before	103±12	100±19	97±11	5.4±6.4	108±21
After	101±16	95±16	95±16	3.8±1.4	112±18

Table 3. Platelet aggregation, blood pressure and heart rate before and after oren-gedoku-to administration (n=21).

	Collagen 2.0 μg/ml (%)	Collagen 0.5 μg/ml (%)	Epinephrine 1.0 μg/ml (%)	Epinephrine 0.1 μg/ml (%)	ADP 10 μM (%)	ADP 3 μM (%)	ADP 1 μM (%)
Before	66±18	20±20	57±25	11±21	71±9	62±14	27±16
After	64±13	19±17	58±23	5±3	71±5	64±13	27±11

	SPA (%)	platelet $\times 10^3/\mu l$	blood pressure (mmHg)	heart rate (/min)
Before	2±1	253±91	132±15/79±11	72±9
After	3±2	239±84	122±13/72±9	73±8

SPA=spontaneous aggregation

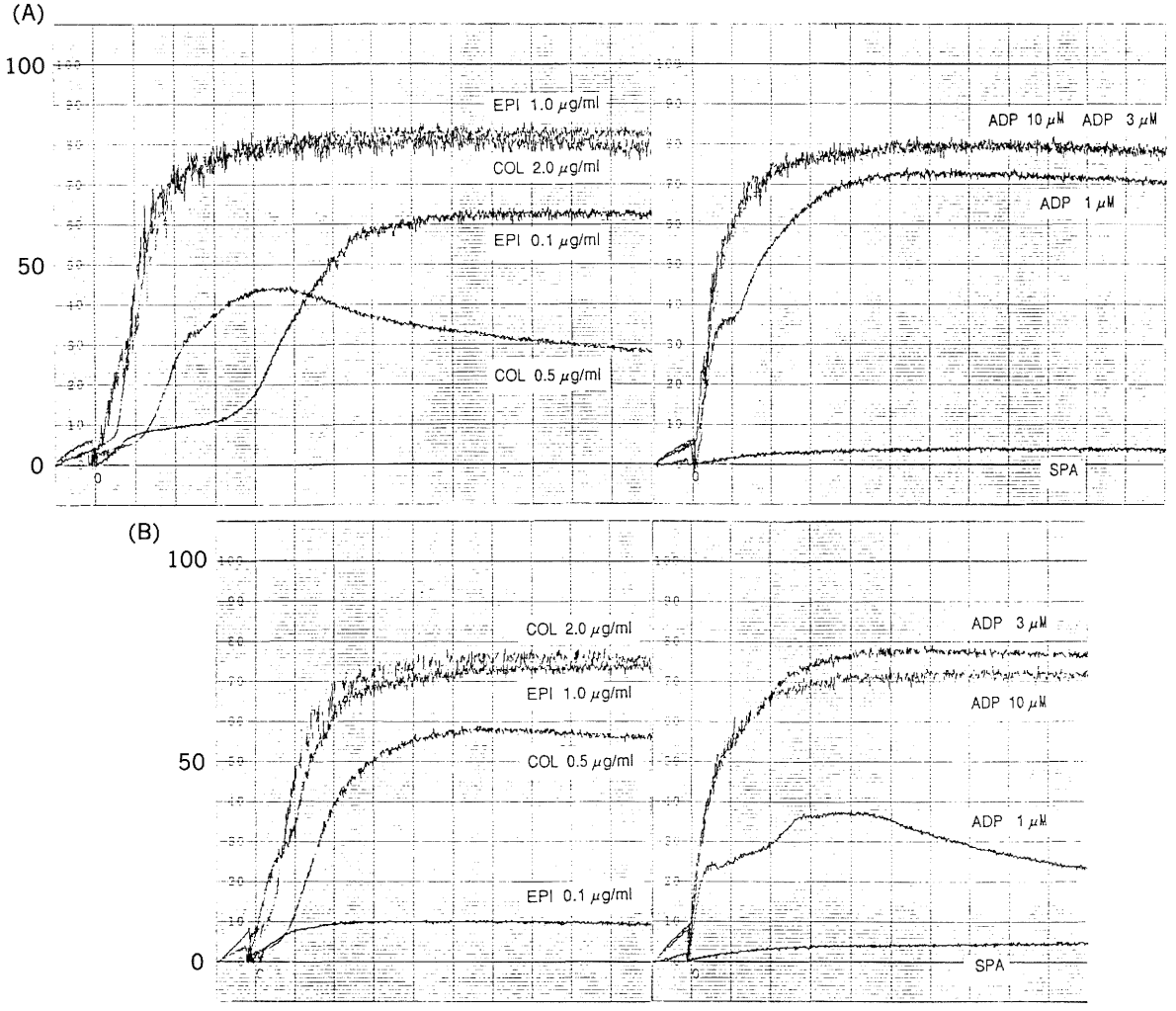

Fig. 2. Platelet aggregation test in Case 1. The maximum aggregation ratio was accelerated as in epinephrine 0.1 μg/ml 63%, and ADP 1 μM 72% before oren-gedoku-to administration (A). At two weeks after administration, the maximum aggregation ratios in epinephrine 0.1 μg/ml and ADP 1 μM decreased to normal levels (10% and 37%, respectively) (B). COL=collagen, EPI=epinephrine, SPA=spontaneous aggregation

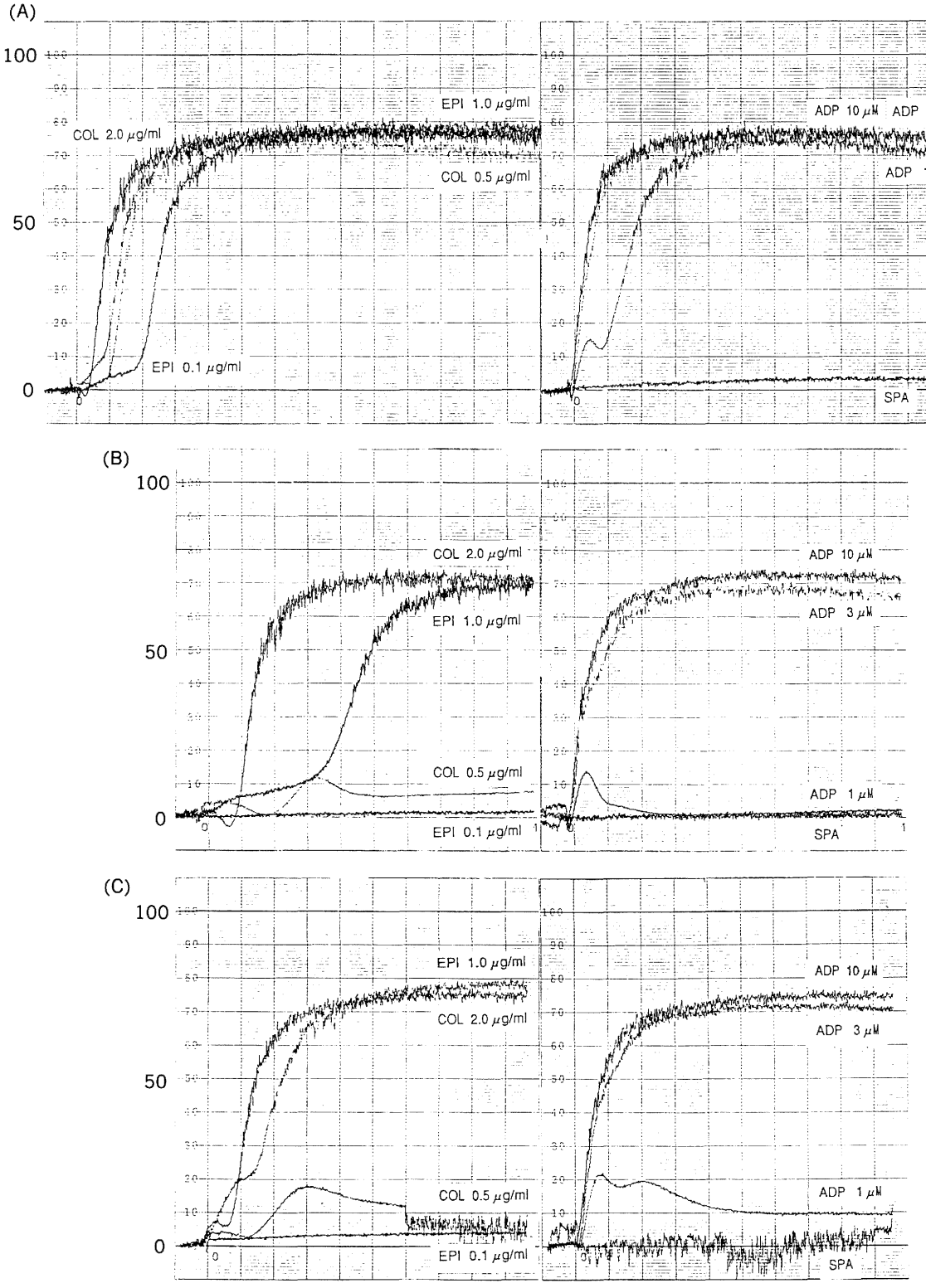

Fig. 3. Platelet aggregation test in Case 2. Increased maximum aggregation ratio (A) improved two weeks (B) and four weeks (C) respectively after administration of oren-gedoku-to.

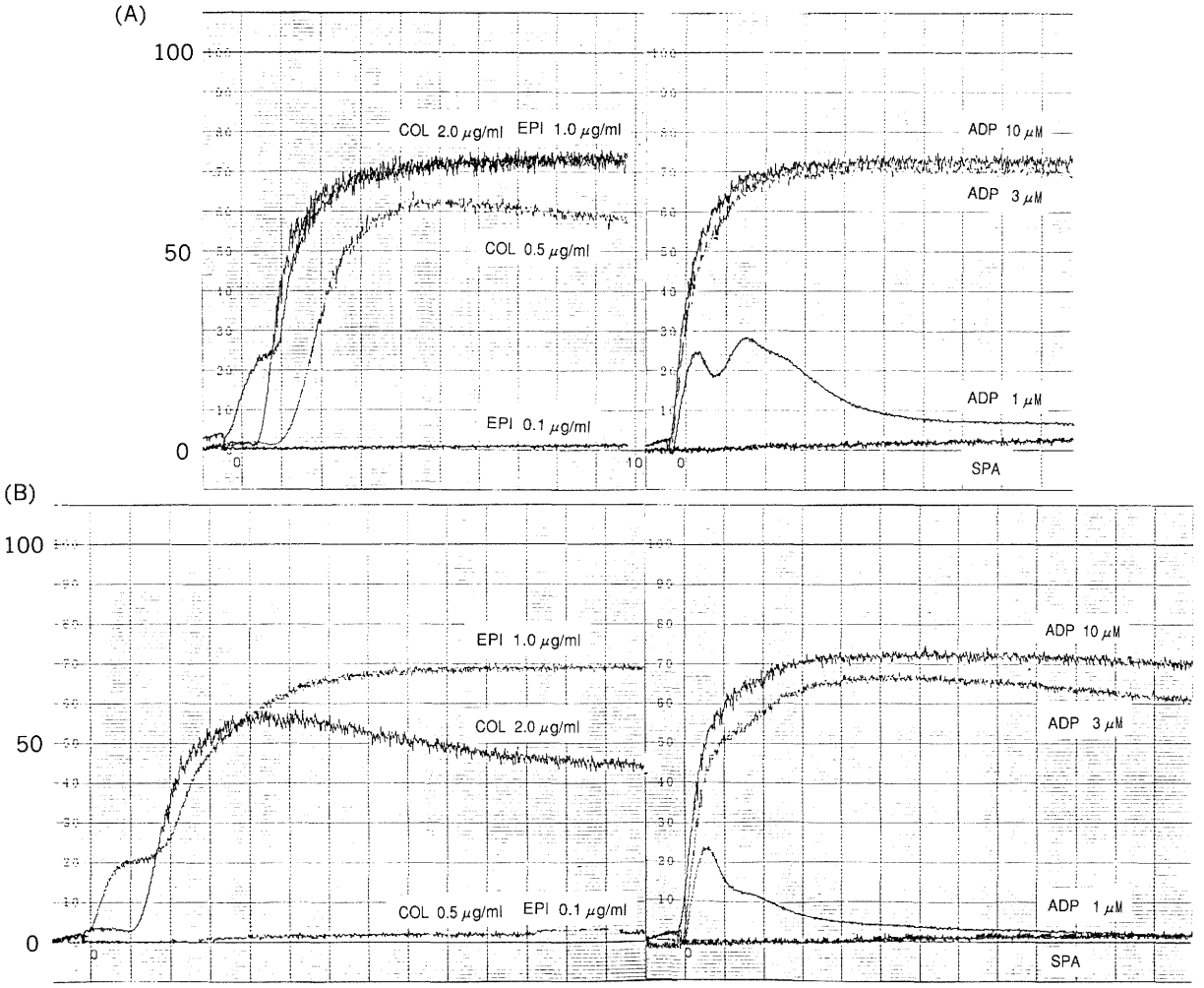

Fig. 4. Platelet aggregation test in Case 3. Increased maximum aggregation ratio (collagen 0.5 μg/ml, 62%, A) improved two weeks after administration of oren-gedoku-to (collagen 0.5 μg/ml, 3%, B).

drug such as aspirin, ticlopidine or dipyridamole to decrease platelet aggregation.[3] Because these patients express vague complaints, such as irritation, depression or limb numbness, Kanpo (prescriptions used in traditional Japanese medicine) are also used.[4,5] Oren-gedoku-to has been used in patients with hypertension who complain of insomnia, irritation, or other disruptions.

Oren-gedoku-to is comprised of four different herbs; worenine (coptidis rhizoma), wogonin (scutellariae radix), palmatine (phellodendri cortex), and gardeniae fructus (fruit of gardenia jasminoides ellis); it has been used from ancient times in patients with hypertension and/or cerebrovascular disease complaining of headaches, hot flushes, and/or depression. Worenine has been reported to be effective for anticoagulation, sedation, and normalization of blood pressure, wogonin for coagulation and allergies, palmatine for sedation and normalization of blood pressure, gardeniae fructus for sedation and acceleration of fibrinolysis. Phellodendri cortex, which contains these four substances, has been reported to be effective in various aspects, including normalizing blood pressure, repressing cerebral arteriosclerosis, and improving cerebral bloodflow.[6,7]

We confirmed an improvement in 17 of 21 patients (81%) after oren-gedoku-to was administered. Although the mean values of hematology, biochemistry, and blood pressure showed no change after administration, elevated blood pressure decreased.

Also, mean values of platelet aggregation and fibrinolysis showed no change before and after admi-

nistration, but values in patients with abnormal platelet aggregation or fibrinolysis returned to their normal levels respectively. This implies that oren-gedoku-to is able to improve abnormal platelet aggregation and fibrinolysis, two important considerations in cerebrovascular disease.

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