

Hepatic Function and Fibrinolysis in Patients with Hereditary Angioedema Undergoing Long-Term Treatment with Tranexamic Acid

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Prophylactic treatment with antifibrinolytic agents, epsilon-aminocaproic and tranexamic acid, reduces the incidence and severity of attacks in patients with hereditary angioedema. Long-term effectiveness or risk of antifibrinolytic agents has not been established. Sixteen patients needing continuous prophylaxis because of frequency and severity of attacks were treated with tranexamic acid. In four patients this treatment was ineffective and the drug was withdrawn after 2 months. A remission or reduction in the frequency or severity of attacks was observed in 12 patients treated for a period ranging from 8 to 34 months. Hepatic tests and blood fibrinolytic activity were not influenced by long-term oral treatment with tranexamic acid.

Key words: Hereditary angioedema; tranexamic acid

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Until recent years the prognosis of hereditary angioedema (HAE) was extremely poor. In fact, 15 years ago mortality was reported as high as 30% and most deaths were due to laryngeal edema. In recent years, with better diagnosis and therapy, the mortality rate is decreasing. Therapy for attacks of HAE can be divided into three stages: (1) acute treatment of severe attacks, (2) short-term prophylaxis (3) long-term prophylaxis (10). (1) Severe attacks can be treated with fresh-frozen plasma (4, 22) or infusion of purified preparations of the lacking protein (the C1 inhibitor) (18, 30). A kallikrein inhibitor (aprotinin) can also be used (16, 18). However, in the case of major airway obstruction an elective tracheostomy must be done. (2) Short-term preventive therapy (for the patient who is undergoing traumatic procedures, particularly dental surgery, which can precipitate attacks) may be successfully

achieved with antifibrinolytic agents (10, 21), fresh-frozen plasma (8, 15), attenuated androgen (9) and infusion of a purified preparation of the C1 inhibitor. (3) Patients with frequent and severe attacks require long-term prophylaxis. Two classes of drugs can be used for this purpose: androgens and antifibrinolytic agents. Good results have been obtained with methyltestosterone: an increase of C4 and sometimes of C1 inhibitor levels was demonstrated in four patients undergoing this treatment (31). A significant reduction in attacks has been obtained with long-term therapy using less masculinizing androgens, such as fluoximesterone and oxymetholone (6, 28). It has recently been shown that danazol, a derivative of ethinyltestosterone with markedly attenuated androgenic potential, effectively prevents attacks in hereditary angioedema by increasing the serum levels of C1 inhibitor (15). We

have also treated seven patients with excellent results (unpublished observations). However, this drug produces amenorrhoea in women, is hazardous during pregnancy and may interfere with the normal sexual maturation of children (26). Success with antifibrinolytic agents was first obtained with epsilonaminocaproic acid (EACA) (11, 19) and later with tranexamic acid (a cyclized EACA derivative) (3, 20, 30). This latter drug is more potent than EACA and more convenient to use (21). Our own experience with tranexamic acid in patients with HAE is also positive (18). However, the long-term effects of this drug in humans is unknown. The potential thrombotic effect of tranexamic acid (5, 29) and the report of liver tumors in animals treated for long periods with extremely high doses (10) prompted us to study fibrinolytic activity and hepatic parameters in patients treated for long periods with this drug.

MATERIAL AND METHODS

Twelve patients suffering from frequent (one or more per month) and severe attacks

of HAE prophylactically treated with tranexamic acid were studied. The age of the patients (four males and eight females) ranged from 10 to 48 years. The diagnosis was established on the basis of clinical history, low serum levels of the fourth component of complement (C4) and C1 inhibitor as assayed immunochemically, and low enzymatic activity of C1 inhibitor ("A" variant of HAE). One patient had low C4 serum levels, and normal concentration of C1 inhibitor with no functional activity ("B" variant of HAE) (27).

Nine patients were given tranexamic acid orally, 2 g/day. One patient (S.T.) received 3 g/day. Two children, aged 10 and 13 were given 1.5 g/day. The period of observation ranged from 8 to 34 months and several of these patients are still under treatment. A complete remission or reduction in the frequency and severity of attacks was observed in all patients (Table 1). Tranexamic acid appeared ineffective in four other patients so the drug was withdrawn after 2 months. These patients, as well as 45 patients with rare and mild attacks of HAE occasionally treated with this drug, were not included in this study.

Table 1

Clinical characteristics of 12 HAE patients undergoing treatment with tranexamic acid

Patient	Sex	Age (years)	Type of HAE	Dose (g/day)	Duration of therapy (months)	Side effects
F.B.	F	45	A	2	34	None
F.F.	M	42	A	2	20	None
S.T.	F	44	A	3	16	Dyspepsia
S.A.	F	38	A	2	15	Dysmenorrhea
S.G.	F	42	A	2	16	None
D.G.	F	10	A	1.5	8	None
V.G.	M	24	A	2	13	Anal pruritus
D.F.	F	13	A	1.5	11	None
M.A.	F	25	B	2	11	None
F.G.	F	48	A	2	13	Superficial venous thrombosis
P.G.	M	27	A	2	14	None
Z.G.	M	35	A	2	9	None

C1 inhibitor and C4 levels were determined by single radial immunodiffusion on cellulose acetate strips (1) and C1 inhibitor activity was measured according to Lachmann et al. (17). All values were expressed as percentage of normal mean value. Serum glutamic-oxalacetic transaminase (SGOT) (25), glutamicpyruvic transaminase (SGPT) (25), alkaline phosphatase (AP) (14), and gamma-glutamyl transpeptidase (γ GT) (32), were determined with the reagent kits of Boehringer, Mannheim. Bilirubin was assayed with Roche-kit, according to Jendrassik's method. Alpha-feto protein was measured by the method of Pietrogrande et al., which can detect as little as 40 μ g/l (23). Whole blood fibrinolytic activity was assayed using dilute clot lysis time with sodium acetate buffer (12). The patients' clotting function was screened by prothrombin time (2), partial thrombo-plastin time (24), and platelets count provided by optical mean. Electrophoresis was performed on cellogel with Veronal buffer pH 8.6.

RESULTS

The serum levels of C1 inhibitor and C4, and the functional activity of C1 inhibitor were not modified by long-term treatment with tranexamic acid (Table 2). SGOT, SGPT, AP, γ GT and bilirubin, determined after long-term treatment with tranexamic acid, were always within the normal range. Serum protein electrophoretic patterns (not reported in Tables) were normal. Measurable amounts of serum alpha-feto protein were detected in two patients, both before and after treatment with tranexamic acid. The pretreatment clotting tests gave values within the normal range for all patients. Dilute clot lysis time remained in the normal range (60–500 min) (Table 2).

Three patients complained of negligible side effects: dyspepsia, dysmenorrhoea and anal pruritus. One patient had a superficial thrombophlebitis of one leg, which subsided

spontaneously after 2 days of bed rest (Table 1).

DISCUSSION

Long-term treatment with tranexamic acid in patients with HAE was restricted in this study to severely affected patients who had previously experienced laryngeal edema and to those in whom frequency and severity of attacks resulted in chronic unemployment. In four patients, with no clinical and biochemical differences, the treatment with tranexamic acid appeared ineffective and was stopped after 2 months. Twelve patients had a remission or a reduction in the rate or severity of attacks during long-term treatment with this drug. It is not clear, however, how tranexamic acid works. Since C1 inhibitor activity and C4 levels are not influenced by this drug, it has been suggested that the antifibrinolytic therapy may be acting not on the activation of C1 but on some other step inhibiting the continuation of the sequence of reaction that leads to angioedema, mainly reducing the rate of propagation of the attack (10). Moreover, it has been recently published that a fibrinolytic enzyme may have to do with the release of a vasoactive kinin from the human second component of complement, once it has been cleaved by C1 esterase preparations (7). Thus, the action mechanism of tranexamic acid seems different from that of androgens, which are able to augment C1 inhibitor synthesis (13, 31).

Our study indicates that long-term treatment with tranexamic acid does not influence hepatic tests. High values of alpha-feto protein were detected in one patient (Z.G.) who also had ulcerative colitis. Another patient (V.G.) had 40 ng/ml of alpha-feto protein before and after treatment with tranexamic acid. Blood fibrinolytic activity did not appear to be modified by tranexamic acid. Side effects were negligible (one patient with superficial thrombophlebitis recovered in 2 days) and did not necessitate stopping treatment. In

Table 2

Patient	C1 INH enz. %		C1 INH imm. %		C4 %		SGOT mU/ml	SGPT mU/ml	AP mU/ml	γ -GT mU/ml	Bilirubin Tot. Conjug. mg%	α -Feto ng/ml	Fibrinol. activity (mm)	
	Before	After	Before	After	Before	After							Before	After
F.B.	nd	20	14	21	29	16	16	18	24	7	0.4	0.1	180	220
F.F.	nd	8	16	10	18	12	29	21	37	15	0.6	0.1	nd	230
S.T.	nd	18	14	14	10	15	19	29	48	25	0.8	0.2	nd	175
S.A.	nd	6	24	0	0	0	18	18	20	14	0.5	0.1	nd	230
S.G.	nd	6	14	0	0	0	18	24	20	16	0.6	0.1	nd	500
D.G.	nd	18	10	15	19	20	18	18	104*	19	0.7	0.2	nd	200
V.G.	10	5	16	15	18	10	14	12	24	7	0.7	0.2	280	315
D.F.	35	20	13	36	27	30	21	14	128*	6	0.6	0.1	nd	nd
M.A.	10	15	67	47	18	0	14	18	20	3	0.8	0.3	300	340
F.G.	10	5	30	34	50	0	12	20	20	16	0.5	0.1	260	280
P.G.	10	5	12	20	20	35	24	21	25	10	0.9	0.4	275	200
Z.G.	25	30	30	15	29	20	16	19	30	6	0.4	0.1	nd	280
n.v.	100 $\pm$ 10		100 $\pm$ 16		100 $\pm$ 14		<27	<33	<48	<28	<1	<0.3	<500	

C1 esterase inhibitor activity, C1 esterase inhibitor and C4 concentration (expressed as percentage of the normal mean value $\pm$ s.d.) and blood fibrinolytic activity were investigated before and after long-term treatment. Serum glutamic oxalacetic, glutamic pyruvic transaminase, alkaline phosphatase, gamma-glutamyltranspeptidase and bilirubin were assayed after therapy.

Alpha-1-feto protein was measured in sera of patients after treatment; in two cases where the protein was found, the assays were also performed in serum samples obtained before starting therapy.

nd=not done.

* Children (n.v. <148).

conclusion, the present investigation indicates that long-term therapy with tranexamic acid in the dose range utilized is well tolerated.

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