

TREATMENT OF HEREDITARY ANGIONEUROTIC EDEMA WITH TRANEXAMIC ACID AND CINNARIZINE

Kyllikki Ohela

From the South Saimaa Central Hospital, Lappeenranta, Finland

Abstract. Six out of 7 Finnish patients suffering from hereditary angioneurotic edema were helped during attacks, by treatment with tranexamic acid (AMCA, Cyklokapron®, Kabi) in doses of 1.5 g 3 times daily, follow-up time 3-25 months. 3 of these patients also had continuous AMCA treatment, in the course of which 2 remained nearly symptom-free on a dosage of 1 g 2-3 times daily. Even the third one had shorter and milder attacks. One patient, however, had to stop taking AMCA after 6 weeks' treatment, because of fatigue and nausea. Follow-up time for the others was 9-11 months. For comparative purposes, 3 patients were given continuous treatment with an antihistamine, cinnarizine in a dosage of 20-30 mg daily. Two of the patients were helped by it, one becoming nearly symptom-free and the other having fewer and milder attacks; follow-up time 9-10 months.

Key words: Hereditary angioneurotic edema; Complement; Tranexamic acid; Cinnarizine

Hereditary angioneurotic edema (HANE) is a disease with an autosomal dominant inheritance, in which the complement either has a low esterase inhibitor of the first component (C1-INH) or else this is biochemically inactive (7, 24). Even the fourth (C4) and second (C2) components of the complement are reduced (1, 8). The clinical features are paroxysmal edema of subcutaneous tissues and mucosa, abdominal pain and laryngeal edema, which may prove fatal. Some patients have red streaks and rings on their skin in conjunction with swellings. Less frequent symptoms are urine retention due to edema of the urinary tract, and cerebral symptoms such as severe headache, aphasia, and hemiplegia.

No definitely specific treatment exists so far. Some patients have obtained relief by continuous methyl-testosterone treatment (27), Trasylol® (Bayer) (14), fresh-frozen plasma (21), antifibrinolytic epsilonaminocaproic acid (EACA) and tranexamic acid (AMCA) (2, 3, 5, 11, 12, 18, 19, 26), cinnarizine (10) and suramine (4).

The effect of AMCA treatment was tested on Finnish HANE patients. Some of these were given cinnarizine for purposes of comparison.

MATERIAL AND METHODS

Patients

The material is composed of 7 HANE patients belonging to 5 different families. The patients are presented in Table 1 with age, sex, age at onset of symptoms, trigger factors, prodromal symptoms and C1-INH and C4 levels. Patients 1 and 2 have been described earlier (20).

Medication

The AMCA preparation used was Cyklokapron® (Kabi) in 0.5 g tablets, and was given as follows: 1) Only during attacks, to all 7 patients, dosage 1-1.5 g 2 or 3 times daily. 2) As continuous treatment to 3 patients, dosage 0.5-1.5 g 3 times daily.

For comparative purposes, cinnarizine (Marisan®, Leo) was given in 10 mg tablets continuously, dosage 20-30 mg daily. This treatment was started with 4 patients, but one of them had to give it up within 2 days because of the severe fatigue it produced. The patients kept records of their attacks and medication, and reported on them at 1-2 month intervals.

Laboratory investigations

C1-INH, C4 and C3 have been measured by radial immunodiffusion at the Laboratory of Clinical Immunology, Helsinki, Finland. In addition, SR, blood counts, Latex, Waaler-Rose, cold agglutinins, anti-streptolysin O, anti-staphylococcal, direct Coombs, cryoprecipitation, antinuclear antibodies, GOT, GPT, creatinine, CPK, and aldolase tests have been performed.

During treatment, blood counts, liver and kidney functions, and muscle enzymes, were monitored continually.

CASE REPORTS

Symptoms and treatment are shown in Fig. 1 for all patients except nos. 4 and 7, whose attack recordings were

Table 1. Main symptoms and age of onset, trigger factors, C₁-INH and C₄ in 7 HANE patients

Case No.	Age	Sex	Age at onset of symptoms				Triggering factors							C ₁ -INH % of normal ^a	C ₄ g/l ^b
			Abdominal pain	Peri-pheral edema	Laryngeal edema	Prodromal symptoms	Trauma	Mental stress	Menstruation	Pregnancy	Contraceptive pills				
1	25	♂	4	19	19	+	±	+						7	<0.04
2	41	♀	5	22	22	±	+	—	+	+				9	<0.04
3	31	♀	5	6	28	+	+	—	+	+	n.u.			8	<0.04
4	24	♀	10	10	12	—	+	+	+	+	+			18	<0.04
5	66	♀	34	54	64	+	±	—	—	—	n.u.			19	<0.04
6	62	♀	28	28	52	+	—	+	—	—	n.u.			25	0.09
7	29	♀	26	22	—	+	—	—	—	—	+			26	0.12

^a Normal range 60–160%.^b Normal range 0.2–0.65 g/l.

not satisfactory. To complement the information in Fig. 1, case reports nos. 4 and 7 follow below.

Case 4

A 24-year-old woman. No other HANE patients known in the family.

From the age of 10, swellings and attacks of abdominal pains, and from the age of 12 laryngeal edema more than ten times. Attacks of swelling have appeared irregularly once or twice a month, but when the patient was 16, she was symptom-free for a year and a half. The swellings appear most often on the extremities and on the face, remaining for 4–7 days. The swelling site is often surrounded by a red ring. Swellings are often triggered by some trauma, which may be as minute as the pressure of an elastic in the underwear, or just sitting on a sharp-edged chair. Mental stress is also an accessory factor. More frequent swellings in the pre-menstrual period, almost continuously during the fourth month of pregnancy, but towards the end of pregnancy no symptoms. Contraceptive pills caused such strong abdominal pains as to prohibit their use. Otherwise, abdominal pains occur only 2–3 times a year, often in conjunction with vomiting and diarrhea. No prodromal symptoms.

The patient's health is otherwise good. No atopy.

HANE was diagnosed in 1972 at Seinäjoki Central Hospital. For 3 years, the patient has had hydro-cortisone treatment during attacks, and in her opinion this has had some effect.

AMCA treatment during attacks was started in December 1972, but by mistake the patient took only 0.5 g 2 or 3 times daily, and thus she was unable to perceive any effect of the medication.

In March 1974 she was started on cinnarizine, 10 mg 3 times daily. During the following 9 months, attacks were less frequent and were milder and shorter. No abdominal pains occurred at all.

In December 1974, medication reverted to AMCA, to be taken only during attacks, dosage 1.5 g 3 times daily. This treatment has now continued for 3 months, and attacks have been mild and passed off quickly. No side effects have appeared. Laboratory findings: normal apart from reduced C₁-INH and C₄ values.

Case 7

A 29-year-old woman, daughter of a sister of Cases 5 and 6. Mother died from laryngeal edema at the age of 50. One sister and one of the patient's two children have HANE blood changes, without symptoms.

At the age of 22, 6 months after her first delivery, the patient began to have attacks of edema, usually on the extremities and in the genitals, sometimes over large areas of the body. The skin often showed red streaks at the sites of swelling. Edema appeared 1–2 times a month, irregularly, and lasted 1–2 days. Prodromal symptoms were fatigue and tenderness over site of swelling. The patient did not notice any special trigger factor. At the age of 26, she had her first severe attack of abdominal pain and was hospitalized. She has had no laryngeal edema.

At the same time as the edema attacks, an allergic rhinitis developed, and slight asthmatic attacks occurred, especially when working in the cow house. Skin tests revealed sensibility to animal epithelium and to some species of pollen; the patient received desensitization treatment for a period of 2 years, and these symptoms were alleviated.

HANE was diagnosed in March 1973 at South Saimaa Central Hospital in connection with a HANE family investigation. Cortisone and antihistamines have been without effect on the HANE attacks.

AMCA treatment during attacks was begun in March 1973 with a dosage of 1.5 g 3 times daily. In the patient's opinion the medication had an evident effect, the edema became milder and did not last so long. When it was found that the patient had taken contraceptive pills for 3 years and that the HANE attacks coincided with this period, the pills were discontinued in May 1973. Since then, the patient has been symptom-free apart from a slight edema in conjunction with a tooth extraction, and which subsided quickly when treated with 1.5 g AMCA. After a symptom-free period of 11 months, contraceptive pills were reintroduced as a provocation, and the attacks of edema started within 2 weeks and appeared almost daily during the 6 weeks the patient was taking contraceptive pills and even during the monthly pill-free week. When the contraceptive pills were abandoned, HANE symptoms ceased within 2 weeks and the patient has again been

symptom-free for 6 months. Instead, dermographism has appeared for some months, and also numbness and pains in the extremities. Laboratory findings: In addition to lowered C $\bar{I}$ -INH and C4 levels, cryoprecipitins were found temporarily on one occasion. Other findings were normal.

RESULTS

The results are shown in Table II. AMCA given only during attacks seemed to be effective in 6 of the 7 cases. The attacks became milder and of shorter duration. The best effect was obtained when the patient took the medicament immediately at the onset of the attack, in doses of 1.5 g 3 times daily. Follow-up time 3–25 months. During continuous AMCA treatment, 2 patients out of 3 were kept almost symptom-free on a dose of 1 g 2–3 times daily. One of these (case 5) was the only one who obtained no relief by taking AMCA only during attacks. The other, however, a sister of the above-mentioned (case 6), had to stop her medication after 6 weeks because of severe fatigue, nausea and vertigo. Nothing pathological was found in her laboratory tests. Also the third patient who was given continuous AMCA treatment had milder and fewer attacks during this period. Follow-up time 3–11 months.

Of the 3 patients treated with cinnarizine, 2 have had evident help from this medication in doses of 30 mg daily. One of these (case 6) has been almost symptom-free. She is the one who had to interrupt her AMCA treatment. The other one (case 4) has had fewer and milder attacks. On the other hand, the third patient (case 3) interrupted her cinnarizine treatment after 3 weeks' medication, when she had a severe HANE attack and had to be hospitalized.

No other side effects of the above-mentioned treatment were found.

DISCUSSION

During HANE attacks, C1 is activated into an active esterase C1s which reacts with C4 and C2. This process liberates C kinins which increase the permeability of blood vessels, thus causing edema. The activator of this reaction is plasmin, a fibrinolytic enzyme, together with kallikrein and antigen-antibody complexes (22). The presence of C $\bar{I}$ -INH in normal plasma also inhibits (except C1s) kallikrein and plasmin (15, 23). Since the C $\bar{I}$ -INH deficiency is a permanent feature in HANE patients, it is so far impossible to say what

triggers the attacks. In some cases there is, however, an evident connection with trauma, mental stress, and menstruation. This may be explained by the fact that in these conditions plasmin levels are increased (7, 8, 9). The effect of EACA and AMCA treatment of HANE is due to their inhibiting plasmin as well as the activation of plasminogen into plasmin. The effect of cinnarizine on HANE is, in its turn, attributed to its blocking influence on C4 (6). Cinnarizine is mainly known as an antihistamine and usually other antihistamines have not been of any help in HANE cases. However, in one case, 3 years' treatment with antihistamine promethazine has diminished the severity—though not the frequency—of the attacks (17).

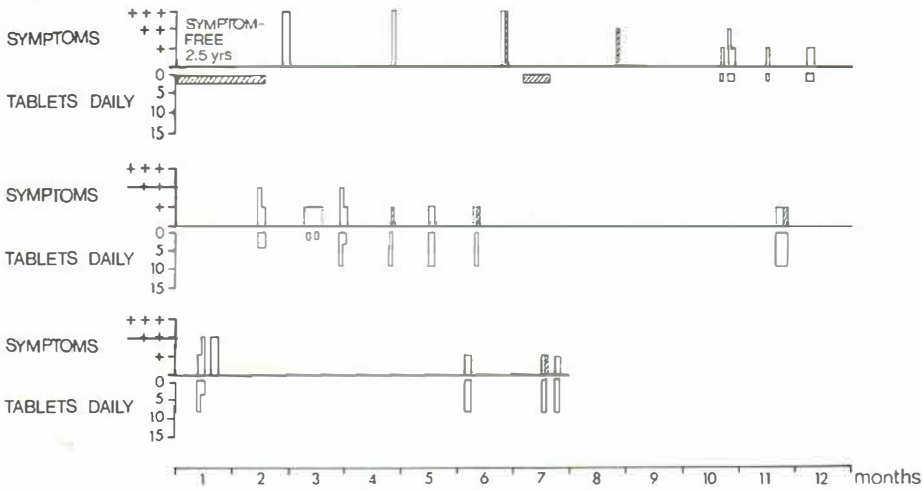
EACA and AMCA have not proved effective in all HANE cases (13, 17). In a double-blind crossover study performed with AMCA, Blohmé (3) obtained results in 3 cases out of 5, 2 of which were treated continuously and 1 intermittently, the continued dosage being 1 g 2–3 times daily. Sheffer et al. (26) performed corresponding tests, with a positive effect in 11 cases out of 12, when treated continuously with the above-mentioned AMCA dose.

Placebo was not given to the patients in this material. It was considered too hazardous, because all except one had laryngeal edema, and because 4 patients belonged to families where there had been several HANE deaths.

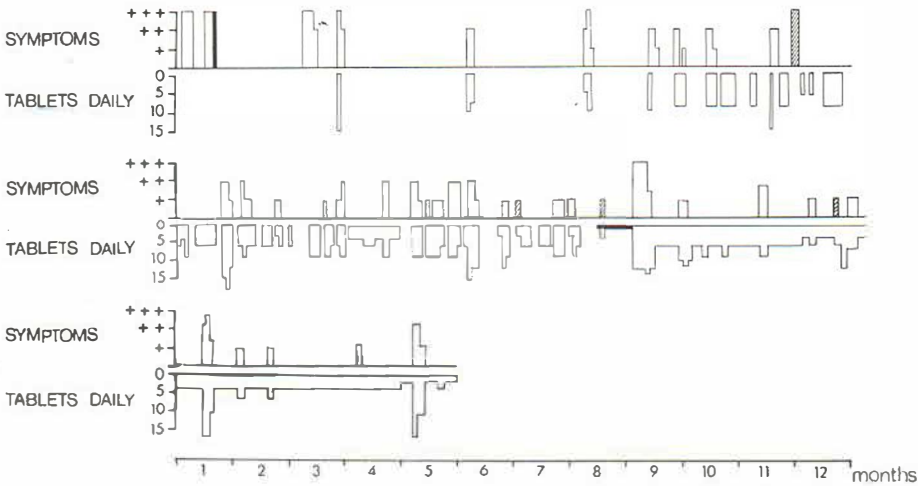
It seems likely that EACA and AMCA are most effective in cases where any one of the above-mentioned trigger factors is involved. Only one (case 5) of the 7 patients in this material did not seem to receive definite help from AMCA given only during attacks. She was also the only one who was not conscious of any trigger factor. However, AMCA helped even her when it was given continuously.

It is interesting to note that aggravating effect of contraceptive pills on the 2 patients who have taken them. In one of these cases (case 4), contraceptive pills caused such severe abdominal pain that the pills had to be discontinued. In the other (case 7), HANE attacks appeared only during the 3 years she was taking such pills. When these were discontinued, she became symptom-free for nearly 2 years, except for one short episode of swelling in connection with a tooth extraction, and which was quickly cured by a 1.5 g dose of AMCA. When this patient was submitted to a provocation test and

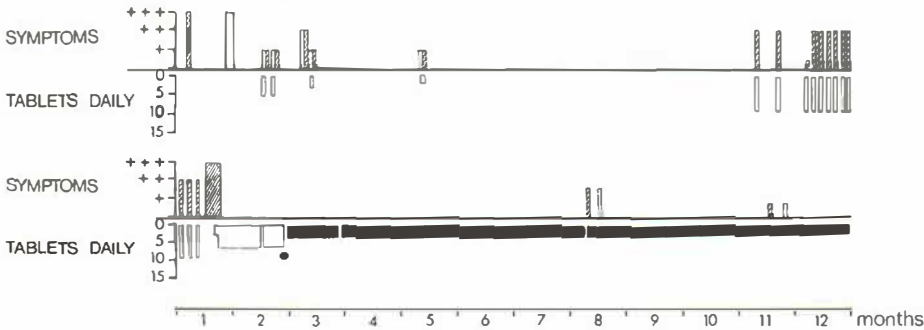
CASE 1
O* 25 yrs



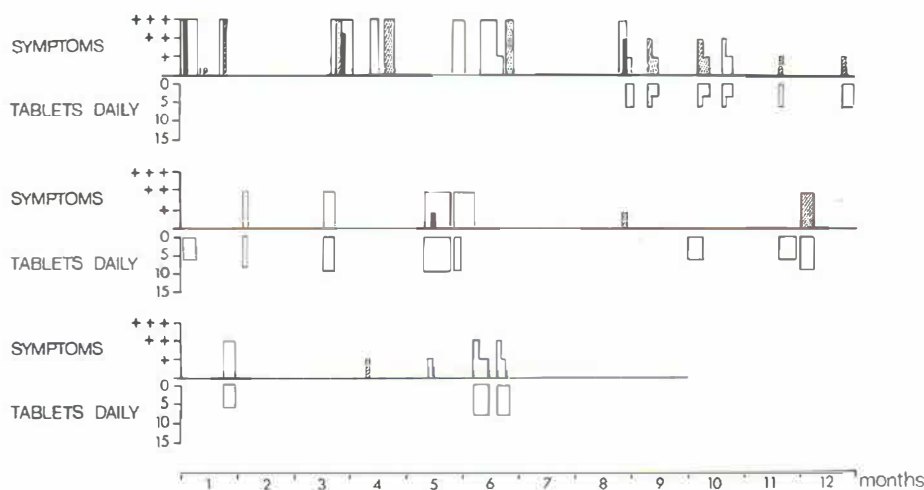
CASE 3
O 31 yrs



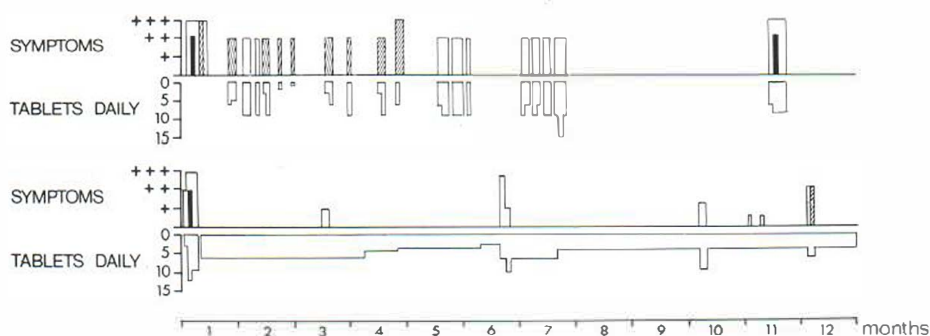
CASE 6
O 62 yrs



CASE 2
 ♀ 41 yrs



CASE 5
 ♀ 66 yrs



□ AMCA (0.5 g)

■ CINNARIZINE (10 mg)

▨ METHYL-TESTOSTERONE (25 mg)

• INTERRUPTED THERAPY DUE TO SIDE EFFECTS

+++ SEVERE
 ++ MODERATE
 + SLIGHT

□ SKIN EDEMA

▨ ABDOMINAL PAIN

■ LARYNGEAL EDEMA

Fig. 1. Symptoms and therapy in cases 1-3, 5 and 6.

took contraceptive pills for 6 weeks, HANE edema appeared within 2 weeks from the start and continued almost daily, not ceasing until 2 weeks after the end of the contraceptive series.

Fatigue, nausea, diarrhea and pruritus ani have been described as side effects of AMCA. On the other hand, there has been no evidence of the principal adverse side effects of EACA—muscle

pain and weakness, accompanied by elevations in the serum enzymes creatine phosphokinase and aldolase (11) or massive muscle necrosis (16). In this material only one patient (case 6) had to interrupt the AMCA treatment because of fatigue, nausea and vertigo. No other side effects were found. This patient has since been kept nearly symptom-free with a daily dose of 30 mg cinnari-

Table 11. *The results of treatment with AMCA and cinnarizine in 7 HANE patients*

++=good response, a few mild attacks, +=moderate response, the attacks shorter and milder

Case No.	AMCA				Cinnarizine	
	During the attacks		Continuously		Continuously	
	Duration of treatment (months)	Response	Duration of treatment (months)	Response	Duration of treatment (months)	Response
1	22	+				
2	25	+				
3	15	+	9	+	21 days	-
4	3	+			9	+
5	11	-	11	++		
6	11	+	1.5 ^a	++	10	++
7	13	+				

^a Interrupted therapy due to side effects.

zine, for 10 months. Another patient (case 4) in this material, who obtained relief from cinnarizine, in the form of milder and shorter attacks, was helped to the same extent by taking AMCA during attacks, in doses of 1.5 g 3 times daily. A dose of AMCA 0.5 g 3 times daily had no effect however. Neither patient had any side effects from cinnarizine. Except in one instance mentioned above (10), I have not found anything published concerning the use of cinnarizine in HANE treatment. We have not tested the possible effect of cinnarizine given only during attacks. The patients find it difficult to continue daily medication, especially if they are symptom-free. For instance, the only male patient (case 1) in our material, whose father and grandfather had died from laryngeal edema at an age of 33-35, and who himself had had two episodes of incipient laryngeal edema, stopped the continuous methyltestosterone treatment during which he had been symptom-free for 2.5 years. Now he has managed on AMCA taken only during attacks, for 22 months, and does not want to begin any continuous medication.

EACA, AMCA and cinnarizine have been of considerable help to HANE patients who have been living in fear of laryngeal edema. Even the knowledge that easily obtainable and effective medications exist will relieve the mental stress which is one of the trigger factors of these attacks. In the future we shall perhaps have a specific C1-inhibitor concentrate at our disposal for the treatment of attacks. Experiments are already under way (25, 28).

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K. Ohela, M.D.
South Saimaa Central Hospital
SF-53130 Lappeenranta 13
Finland