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Non-Hereditary Angioedema Treated with Tranexamic Acid

A 6-Month Placebo Controlled Trial with Follow-up 4 Years Later

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Ten patients with frequent attacks of non-hereditary angioedema were treated with tranexamic acid or placebo in a double blind manner, each period lasting 3 months. During the tranexamic acid period nine patients became symptom-free, or substantially improved, while one was unaffected ($P < 0.05$). In four patients itching was a major accompanying complaint which was relieved in three. Diarrhoea and abdominal discomfort were more pronounced during tranexamic acid treatment ($P < 0.05$), but only necessitated dose reduction in one patient. Four years later contact was obtained with eight of the nine responders and six were still taking tranexamic acid regularly, while in two patients the attacks were so infrequent that the drug was not taken regularly.

Key words: follow-up; non-hereditary angioedema; placebo controlled trial; tranexamic acid.

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Patients with angioedema are often seen in allergy and dermatology clinics and are frequently in urgent need of treatment. In a small minority the angioedema is due to a hereditary defect of C1-esterase inhibitor, an allergic or immunologic disease, or a neoplasma. In the majority of cases, however, no apparent aetiology can be identified. These patients are often severely affected by large disfiguring swellings and have for years tried different ineffective treatments. This double-blind study indicates that a substantial part of these patients will become symptom-free or benefit significantly by long-term treatment with tranexamic acid. A starting dose of 1.5 g t.i.d. is recommended for a period long enough to determine whether the drug is effective. The lowest effective dose varies, and after it is identified should be used in the long-term treatment.

The treatment of non-hereditary angioedema (NAE) is unsatisfactory. The usual drugs applied in the treatment of allergic or immunologic disease have no or only doubtful value. The situation is very different for hereditary angioedema (HAE) which can be effectively treated prophylactically with antifibrinolytic drugs (2, 6), or androgen derivatives (4). During recent years we have had the impression that some of the NAE patients improved during treatment with antifibrinolytic drugs. This impression encouraged us to perform a controlled trial comparing tranexamic acid with placebo.

MATERIAL AND METHODS

Patients

Twelve patients were included in the study, but two were later excluded: one because of a change of address, the other because of spontaneous gradual improvement during the trial – an improvement that continued after termination of the trial. Median age was 58 years and the patients had suffered from the disease for 4–30 years (Table 1). The attacks occurred 4–10 times every month and consisted of localized, circumspective, firm swelling accom-

panied by a prickling and sometimes itching sensation. Five of the 10 patients also suffered from itching, but none of them had observed or reported classical urticarial wheals. The swellings were localized anywhere on the body, but especially on the face (chin, lips, eye region). No patient had a family history of angioedema. Minor trauma, stress, and tiredness were mentioned by the majority of patients as precipitating factors. Patient No. 5 described that herring, lemon, and tomato ketchup provoked attacks, but even avoidance of these foodstuffs did not prevent about four attacks every month. Secondary angioedema was excluded by a full medical history, physical examination, blood analyses, allergy investigation including skin prick tests, radio-allergo-sorbent test (RAST), IgE, and evaluation for food allergy or intolerance, including challenge tests.

The patients had previously been treated with antihistamines, oral steroids, calcium tablets, and elimination diets without improvement of the symptoms. Four patients (Nos. 1, 4, 7, and 10) had been treated with tranexamic acid in a previous period, apparently with some improvement. As the treatment had not been given in a controlled manner these four patients were included in the study.

Trial design

The controlled part of the study was performed in 1978 as a two-part, cross-over study using a double blind, double dummy technique. The patients were randomly allocated to receive either tranexamic acid or placebo in the first 3 months and crossed over to receive the alternative treatment in the consecutive 3 months. During the active period the patients were treated with 1.5 g tranexamic acid (3 tablets á 0.5 g) three times daily, while during the placebo period the patients received placebo tablets of identical appearance in the same dosage.

Medication

During acute attacks the patients were allowed to take antihistamines. Patient No. 1 took 20–30 mg prednisone for 3–4 days during the attacks which may have caused amelioration .

Diary

Each day the patients recorded in a diary the presence or absence of: skin symptoms (swelling, itching; the localization marked on a body figure), diarrhoea and abdominal discomfort.

Table 1

Patient characteristics

Patient No.	Age (years)/ sex	Disease duration (years)	Attack frequency/ month	Treated before with tranexamic	C1-INH chemic. (norm.: 80–140)	C1-INH funct. (norm.: 2.5–10)	Localization
1	52/F	17	4	yes	114	2.2	lips, extrem., eye region
3	70/M	19	5	no	123	3.3	"anywhere"
4	26/M	5	4	yes	123	2.5	tongue, neck, feet
5	59/F	23	4	no	128	3.2	extrem., lips, eye region
6	62/F	8	6	no	not done	2.5	abdominal wall, extrem., cheek
7	56/M	4	6	yes	118	3.6	tongue, cheek, extrem.
9	62/F	30	4	no	114	2.2	tongue, extrem., eye region
10	73/F	4	4	yes	137	2.6	tongue, cheek, neck
11	29/F	16	10	no	105	3.7	lips, cheek, extrem.
12	41/F	4	5	no	131	3.4	trunk, extrem., eye region

The diaries were checked once a month at the clinic. Based on the diaries the ratios between number of days with swelling and/or itching and the total number of treatment days were calculated and subsequently used in the statistical analysis.

Laboratory examinations

Before the trial and 3 and 6 months after the start of the trial the following examinations were performed: sedimentation rate, haemoglobin, leucocytes, thrombocytes, eosinophilocytes, se-creatinin, -bilirubin, -transaminase, -alkaline phosphatase, complement C3 and C4. C1-esterase inhibitor (C1-INH) was determined before the trial by means of immunochemical and enzymatic analysis (5) kindly performed by I. Gad, Ph.D., Clinical Chemical Dept., Kommunehospitalet, Copenhagen.

Follow-up questionnaire

A questionnaire was sent to the responding patients 4 years later, and information about attack frequency and use of tranexamic acid was obtained.

Table 2

No. of days with symptoms

Patient No.	No. days with symptoms/No. treatment days			
	Oedema		Itching	
	Placebo	Tranexamic acid	Placebo	Tranexamic acid
1	3/4	16/92	–	24/92
3	23/91	1/83	45/91	1/83
4	5/15	3/83	0/15	1/83
5	16/83	2/99	32/83	2/99
6	4/85	8/89	3/85	16/89
7	2/8	3/84	0/8	0/84
9	2/12	3/85	2/12	1/85
10	4/69	0/81	0/69	0/81
11	4/9	0/86	0/9	0/86
12	25/27	0/72	23/27	0/72
Total	88/403	36/854	104/401	45/854

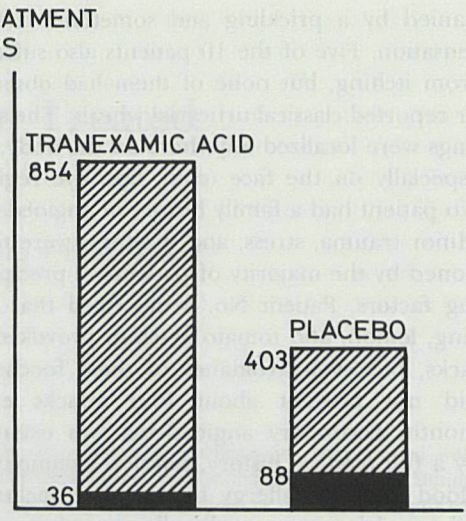

Fig. 1. Total number of days of treatment with tranexamic acid and placebo. Hatched area: days of treatment without symptoms; black area: days with symptoms (oedema).

Statistics

The data were evaluated by a non-parametric paired test (Wilcoxon matched-pairs signed-rank test) and by the Chi square test. Differences were considered significant at $P < 0.05$ (two-tailed).

RESULTS

Number of days with oedema

Five patients completed the study according to the protocol, while five did not complete the placebo period. The ratio between days with swellings and total treatment days is shown in Table 2. Nine of the 10 patients had a marked decrease in this ratio in the tranexamic acid period compared with the placebo period ($P < 0.01$).

The total number of treatment days and days with oedema in the active and placebo periods are demonstrated in Fig. 1. According to the protocol each treatment period was about 90 days. Because patients with frequent and severe attacks were allowed to cross over to the second period before scheduled, the total number of treatment days with placebo was only 403 days

compared with 854 days with tranexamic acid. This difference was significant ($P < 0.01$, binomial test). Patient No. 1 used prednisone during attacks which might have influenced their duration, although her reluctance to complete the placebo period suggests that tranexamic acid was the major cause of the decrease in attack frequency during the active period. If she is omitted from the statistical analysis there is still a significant difference in favour of tranexamic acid ($P < 0.01$).

Number of days with itching

Six of the 10 patients complained of itching (Table 2). In three of the most affected patients an obvious improvement was demonstrated. Due to the small number this difference was not significant.

Side effects

Patient No. 1 was considerably troubled by diarrhoea during the active period (Table 3). A reduction in tranexamic acid dose to 1 g three times daily reduced the abdominal symptoms without recurrence of angioedema. All other patients ingested the prescribed dose throughout the 3 months of active treatment. Patient No. 3 had persisting abdominal symptoms during both periods due to a hernia hiatus oesophageus and oesophagitis not related to the trial. Even if he is excluded there were significantly more days with abdominal discomfort during tranexamic acid treatment compared with placebo treatment.

Table 3

Side effects

Patient No.	Abdominal discomfort		Diarrhoea	
	Placebo	Tranexamic acid	Placebo	Tranexamic acid
1	0	8	0	21
3*	64	76	1	0
4	0	1	0	0
5	0	0	0	0
6	4	13	3	16
7	0	1	0	15
9	0	7	0	25
10	0	0	5	0
11	0	0	0	17
12	0	0	0	0
Total No. days with side effects*	4	30	8	94
Treatment days*	312	771	312	771
	$P < 0.05$		$P < 0.01$	

* Patient No. 3 excluded from total.

After the trial started we had the impression that the patients experienced less abdominal discomfort when they ingested tranexamic acid in connection with meals, and were subsequently advised to do so.

There was no significant change in the laboratory analysis during active treatment compared with placebo.

Follow-up

Four years after ending the trial contact was obtained with eight of the nine patients that responded to tranexamic acid. Six were still using the drug in doses from 1 to 4.5 g daily. They had tried stopping treatment several times, but this had resulted in relapse in all six. Two patients had stopped the treatment, one because attacks had become very seldom (1–2 each year), and one had been operated for nephrolithiasis a year ago and had no further attacks, but she still carried a supply of three tablets.

DISCUSSION

Angioedema can be classified into three groups: 1) hereditary angioedema, 2) secondary angiodema, and 3) idiopathic angioedema.

The hereditary type is a rare but life-threatening disease that is possible to treat effectively, and therefore, important to identify. Most often there is a family history and the disease has its debut in early life. The swellings are non-itching and often localized to the viscera. The diagnosis is verified by immunochemical analysis of C1-INH and – if the ana-

lysis is normal – by functional analysis of C1-INH because in 15–20% of patients with HAE the enzyme is present in normal or increased amount as determined by immunochemical methods, but is functionally defective. Any sign of functional deficiency can be obtained by immunoelectrophoresis, where the defective enzyme shows altered mobility (5). The symptoms can be effectively controlled by antifibrinolytic or androgen treatment (2, 4, 6).

The secondary form of angioedema is seen in neoplastic diseases, liver diseases, virus infections, collagenoses and in intolerance or allergy to drugs (penicillin, aspirin) or food. The swellings are often itching or accompanied by urticaria. The diagnosis is made by a thorough medical history and physical examination, appropriate blood analysis and allergy testing and/or provocation.

More frequently, however, there is no clue to the aetiology in patients with angioedema, and different symptomatic treatment with antihistamines, sympatomimetica, steroids, calcium, etc. are tried, often with discouraging effect. Antifibrinolytic treatment has been tried in a non-controlled study by Zachariae in 1975 (8), who found it of no value in eight patients with NAE and with significant effect in eight patients with HAE. However, several case records indicate that antifibrinolytics are valuable in some cases of NAE (3, 7).

The mechanism behind the action of antifibrinolytics in HAE is believed to be an inhibitory effect of plasminogen activation (1), while androgens exert their effect by increasing the level of functionally active C1-INH (4). Our patients had normal values of functionally active C1-INH with the exception of two with subnormal levels, although far from the very low values in HAE. No patient had a family history of angioedema, thus it is hardly possible that any of the patients were suffering from unrecognized HAE. In our trial the therapy with tranexamic acid was so effective that most of the patients entering the trial in a tranexamic acid period refused to complete the following placebo period because of the immediate relapse of symptoms. Nine of the 10 patients became free from oedema or experienced a substantial improvement. In four patients itching was a major complaint and in three of these the symptoms disappeared or were markedly ameliorated.

No serious side effects were observed and blood analyses were not affected by the drug. Five patients were troubled with diarrhoea, but only in one did this necessitate a dose reduction. We received fewer complaints of gastrointestinal side effects after the patients were instructed to take the drug after meals.

According to a questionnaire answered 4 years later, all the responders were still taking tranexamic acid regularly, except two who experienced symptoms so infrequently that regular treatment was not necessary. The individual maintenance dose varied from 1 to 4.5 g daily and all patients had experienced prompt recurrence of symptoms after attempts to stop the treatment. Four patients had been treated with tranexamic acid earlier, thus the material was not unselected. The 90% success rate is therefore higher than can be expected in a random material. Nevertheless, tranexamic acid is presumably a very effective drug for a substantial fraction of patients with HAE.

Conclusion

Patients with angioedema should undergo a full medical examination to identify the few cases of herditary angioedema or the secondary forms of angioedema. The remaining cases of angioedema, where no aetiology or specific provocative factor can be identified, should be considered for a therapeutic trial with tranexamic acid. It is recommended to start the treatment with 3–4.5 g daily in 3–4 divided doses taken after meals to minimize gastrointestinal side effects. The trial should be carried out for a period long enough for at least three or four attacks to have normally occurred. The treatment is expensive and should continue perhaps for many years, therefore, if the therapeutic trial shows that the drug is effective, the dosage should gradually be decreased to find the individual daily maintenance dose.

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