

Original article

Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema

Background: Skin swellings are the most frequent symptoms in hereditary angio-oedema (HAE) arising out of C1-inhibitor (C1-INH) deficiency. They may be painful and impact daily activities of patients. Detailed clinical data concerning the treatment of skin swellings by C1-INH concentrate have not been reported yet.

Methods: From 1976 through 2007, a total of 2104 skin-swelling attacks in 47 patients with HAE were treated with the C1-INH concentrate. Time to relief and duration of the swellings were documented during personal interviews using standardized questionnaires. The results were compared with 9046 untreated skin swellings in the same patients.

Results: The first clinical sign of efficacy was a slowdown of progress of symptoms accompanied by a decreased feeling of tension and pain in the swollen area. The mean time to the first relief of symptoms was 1.1 ± 1.4 h in treated skin swellings and 50.4 ± 33 h in untreated skin swellings. Improvement of facial skin swellings took longer than swellings of the extremities, genitals or trunk. The duration of treated skin swellings was 1.7 day in treated and 3.2 day in untreated ones. In treated swellings, there was long-lasting control and no rebound within the 48 h following the drug administration and no laryngeal oedema following facial oedema were observed. No severe side-effects occurred.

Conclusions: The C1-INH concentrate has proven to be highly effective and safe for treating skin swellings in patients with HAE arising out of C1-INH deficiency.

K. Bork¹, P. Staubach¹, J. Hardt²

¹Department of Dermatology, Johannes Gutenberg University, Mainz; ²Clinic for Psychosomatic Medicine, Heinrich Heine University, Duesseldorf, Germany

Key words: angio-oedema; C1-inhibitor deficiency; hereditary angio-oedema; pasteurized C1 inhibitor concentrate; skin swellings.

Konrad Bork, MD
Department of Dermatology
Johannes Gutenberg University
Langenbeckstr. 1
55131 Mainz
Germany

Accepted for publication 2 October 2007

Hereditary angio-oedema (HAE) types I and II constitute a defined autosomal-dominant disease (Mendelian Inheritance in Man no. 106100) caused by a genetic deficiency of functionally active C1-esterase inhibitor (C1-INH), which is the primary control protein for the complement system (1–5). More than 180 different C1-INH gene mutations have been described (6, 7). The low plasma concentration of functionally active C1-INH in type I and type II HAE permits activation of the kallikrein-kinin system, the classical complement pathway, the fibrinolytic system and the coagulation system, with release of vasoactive peptides among which bradykinin is considered to be most important (8–10). Recently, another type of HAE (HAE type III) was reported in which the patients have normal C1-INH in plasma (11). In some of the families, missense mutations in the coagulation factor XII were found to be the underlying cause of the disease (12, 13). Clinically, HAE arising out of C1-INH deficiency is characterized by skin swellings, abdominal pain attacks, episodes of life-threatening upper airway obstruction and rarely oedema of other body sites. Oedema attacks typically last for

1–7 days and are followed by disease-free intervals of variable duration.

Treatment with C1-INH concentrate from human plasma has been used in HAE arising out of C1-INH deficiency, since 1973 (14). In the early years, this kind of treatment was regarded as an emergency therapy only. Later, after virus inactivation measures had been introduced during the manufacturing process, the indication was extended stepwise to milder symptoms of the disease. Purified and virus-inactivated C1-INH concentrates were shown to be effective in treating and preventing laryngeal oedema and abdominal pain attacks of HAE arising out of C1-INH deficiency (15–21). They are the treatment of choice for these conditions wherever they are available (22).

Though skin swellings are the most frequent symptoms of HAE (23), many skin swellings do not require treatment. On the other hand, some of the skin swellings may be a severe symptom: (i) facial swellings are disfiguring and may be followed by a potentially life-threatening laryngeal oedema (23, 24); (ii) skin swellings of the extremities may be painful and may affect not only

one hand or one foot but may involve one whole extremity; (iii) limb swellings may extend to parts of the trunk and (iv) limb swellings may be followed within 24 or 48 h by swellings of one or more other limbs. In these cases, the clinical symptoms become disabling and cause inability to work for a few days. In these kinds of skin swellings, treatment with C1-INH concentrate should be considered. However, until now only limited information had been published about the efficacy and safety of the administration of C1-INH concentrate for skin swellings in HAE patients.

Aim of the following study was to assess the efficacy and safety of a pasteurized C1-INH concentrate in the treatment of skin swellings in patients with HAE arising out of C1-INH deficiency.

Patients and methods

Study design

Analysis was based retrospectively and prospectively on clinical case reports. Untreated skin swellings before the use of C1-INH concentrate were compared with those treated with C1-INH concentrate in the same individuals. Data were generated by asking patients about symptoms they experienced during skin swellings of HAE. Documentation was performed by structured questionnaires.

Patients

Patients were surveyed at the Angio-oedema Outpatient Service (AOS) at the Department of Dermatology, University of Mainz, Germany. Of the 302 patients with HAE arising out of C1-INH deficiency, 47 patients had received C1-INH concentrate for treating skin swellings – these represent the study group. The survey ranged from 1976 through May 2007. Diagnosis of HAE was based on personal history, family history and plasma examination. All diagnoses were performed or confirmed at our AOS.

Laboratory

Laboratory diagnosis of C1-INH deficiency was made on the basis of plasma levels of C1-INH activity, C1-INH antigen and C4 antigen. Plasma levels of C1-INH antigen and C4 antigen were assayed by radial immunodiffusion (NOR Partigen C1 INH and C4; Dade-Behring, Marburg, Germany), and C1-INH activity was determined using the chromogenic substrate $C_2H_5CO-Lys(e-Cbo)-Gly-Arg-pNA$ (Technochrom C1-Inhibitor; Technoclone, Vienna, Austria).

Treatment

Patients were provided with pasteurized C1-INH concentrate (Berinert® P; CSL Behring, Marburg, Germany) for treatment in case of acute oedema attacks. Before 1985, the unpasteurized version of the product was used. Forty-seven patients presenting with skin swellings received intravenous C1-INH concentrate via their general practitioner, at their local hospital or at our AOS. The usual dose comprised 500 U of C1-INH concentrate, which corresponds to a C1-INH plasma activity of about 500 ml of fresh plasma. For treatment of skin swellings, 500 U C1-INH concentrate were rec-

ommended. If the patient felt that this dose was not sufficiently effective, the administration of 1000 U of C1-INH concentrate for subsequent skin swellings was recommended. Patients were counselled that mild skin swellings should not be treated. Mild skin swellings were defined as swellings limited to the back of one hand or foot or swellings at one extremity or at the trunk with a diameter of < 20 cm. Treatment was recommended for all facial and genital swellings. In skin swellings of the extremities, treatment was only recommended when the swellings were > 20 cm in diameter or if the whole extremity was affected or when the swelling of one extremity was followed by a swelling of another extremity or parts of the trunk within 24 h. All patients received vaccination for hepatitis B virus.

Data collection

At first visit to our AOS, all prior attacks including skin swellings were recorded with respect to clinical symptoms, severity and course of the attacks. At their first visit, patients also were instructed to record in a diary, the date, duration, symptoms, severity and course of future skin swellings. Patients were then seen twice a year and personally interviewed and examined by physicians experienced in HAE symptomatology. Information about untreated and treated attacks was obtained by a personal interview and by analysing the patient's diary twice a year. In untreated swellings, the time between onset and the first improvement of the swelling was recorded, as well as the time between onset and end of the swellings. In treated swellings, the following were recorded: time between onset of the swelling and the administration of the C1-INH concentrate, the time to the initial symptom relief after injection of C1-INH concentrate and finally, the time between onset and end of the skin swelling. Furthermore, the patients were questioned about the dose of the drug, side-effects including relapse, recurrence of a swelling in the same or in a different location, and their personal opinion about the efficacy of C1-INH concentrate. Statistics were performed with STATA9. All tests were two-tailed (25).

Results

The baseline data of the 47 patients are listed in Table 1. The 47 patients experienced a total number of 11 150 skin swellings, occurring on the face (10.0%), of the hands and/or arms (53.0%) (Fig. 1), of the feet and/or legs

Table 1. Basic data regarding 47 patients with hereditary angio-oedema (HAE) who received C1-INH concentrate because of skin swellings

HAE type I	
Patients	41
Families	40
HAE type II	
Patients	6
Families	5
Age at end of the study (years)	42.2 ± 16.1 (range 7–70)
Gender (M/F)	15/32
Laboratory results*	
C1-INH protein (g/l) (HAE type I)	0.048 ± 0.04
C1-INH protein (g/l) (HAE type II)	0.28 ± 0.14
C1-INH activity (%) (all patients)	16.8 ± 9.4
C4 (g/l) (all patients)	0.08 ± 0.041

*Normal range for C1-INH protein, 0.15–0.35 g/l. Normal range for C1-INH activity, 70–130%. Normal range for C4, 0.20–0.50 g/l.



Figure 1. Swelling of hand and forearm in hereditary angio-oedema.

(29.9%), of the genitals (5.6%) and on the trunk (1.5%). A total of 9046 skin swellings were untreated. For 2104 skin swellings, C1-INH concentrate was administered. The localization of the treated and untreated skin swellings in the various body sites is shown in Table 2.

All 47 patients received 500 U for their first-treated skin swelling. Later on, in 400 attacks of 13 patients, higher doses of 1000 U were necessary. Only two of them had a body weight >80 kg. Table 2 shows the doses of C1-INH concentrate related with the various body sites. No patient received >1000 U C1-INH concentrate for treating a skin swelling. The average time until injection after onset of the attack was 3.4 h (SD 4.9 h, range 1–24 h). Table 3 shows that the time taken for the administration of C1-INH concentrate is longer in oedema involving the skin of the trunk than other sites of the body.

Time to relief

Time interval between the injection of C1-INH concentrate and first manifestation of efficacy, i.e. the time to the first relief of symptoms, was seen as a slowdown in the progression of the swelling followed by a decrease in symptoms, i.e. a reduction in tension and in pain (if the swelling had been painful). The mean time to first relief of symptoms of all treated skin swellings was 1.1 h (SD 1.4, range 10 min–10 h). Onset of relief started within 1 h after infusion of C1-INH concentrate in 1428/2104 (67.9%) skin swellings and within 2 h after infusion in 1843/2104 (87.6%) skin swellings. In 211 skin swellings, relief started between 2 and 3 h after infusion and in 49 further attacks between 3 and 6 h after infusion. In one facial swelling, the time to first relief was 10 h. The mean time to the first relief of symptoms of all untreated skin swellings was 50.4 h (SD 33 h, range 10–120 h). Figure 2 demonstrates the shorter time to relief in treated skin swellings compared with untreated skin swellings (mean shortening 49.3/50.4 h, 97.8%). Table 3 shows that the time to relief differs in swellings of the various body regions.

Duration of attacks

The mean duration, i.e. the time interval between onset and end of symptoms, of the 9046 untreated skin swellings was 3.2 days (SD 1.7 days, range 1.5–7 days). The mean duration of the 2104 treated skin swellings was 1.7 days (SD 1.3 days, range 0.3–5.5 days). So the mean duration of treated skin swellings was considerable shorter than in untreated ones (1.5/3.2 days, 46.9% shortening; Fig. 3). A series of *t*-tests shows a significant shorter duration of attacks under treatment (Table 3). In

Table 2. Skin swellings untreated and treated with 500 or 1000 U C1-INH concentrate related to localization, type of hereditary angio-oedema (HAE) and prospective and retrospective data

	Patients	Total number attacks	Untreated attacks	Number of treated attacks		
				Total	500 U C1-INH concentrate	1000 U C1-INH concentrate
Body site of swelling						
Face	35	1111	628	483	451	32
Hands and/or arms	27	5915	5084	831	645	186
Feet and/or legs	18	3330	2692	638	538	100
Genitals	14	628	505	123	62	61
Trunk	4	166	137	29	8	21
Total	47*	11 150	9046	2104	1704	400
HAE types						
Type I	41	10 779	8749	2030	1633	397
Type II	6	371	297	74	71	3
Prospective and retrospective parts						
Prospective	47	7025	4950	2075	1678	397
Retrospective	36	4125	4096	29	26	3
Treatment before pasteurization of the drug						
Before 1985	2	474	469	5	5	0

*N's do not add up to 47 because of multiple occurrences.

Table 3. Time from symptom onset to administration of C1-INH concentrate, time to first relief, and time from onset to end of symptoms in treated and untreated skin swellings related to localization, type of hereditary angio-oedema (HAE) and prospective and retrospective data

	Time from onset of symptoms to injection of C1-INH concentrate	Time to first symptom relief		Length of attacks		
		After injection of C1-INH concentrate	Untreated	Treated	Untreated	Test for differences
	Hours (mean $\pm$ SD)	Hours (mean $\pm$ SD)	Day (mean $\pm$ SD)	Day (mean $\pm$ SD)	Day (mean $\pm$ SD)	t-value P-value
Body site						
Face	2.8 (6.0)	1.2 (1.9)	3.1 (1.7)	3.9 (1.6)	7.1 (1.9)	$t_{(1109)} = 29.8$ <0.001
Hands and/or arms	3.6 (3.4)	1.1 (1.0)	1.9 (0.8)	1.0 (0.9)	3.2 (1.7)	$t_{(5913)} = 36.5$ <0.001
Feet and/or legs	3.4 (2.7)	1.1 (0.9)	2.1 (1.1)	1.1 (0.9)	3.0 (1.3)	$t_{(3328)} = 35.0$ <0.001
Genitals	3.5 (4.2)	1.0 (0.6)	1.9 (0.6)	1.5 (0.9)	3.0 (1.5)	$t_{(626)} = 10.6$ <0.001
Trunk	9.0 (9.1)	0.5 (0.6)	2.2 (0.7)	1.3 (0.5)	3.4 (0.7)	$t_{(164)} = 15.3$ <0.001
Total	3.4 (4.9)	1.1 (1.4)	2.1 (1.4)	1.7 (1.3)	3.2 (1.7)	$t_{(11148)} = 38.0$ <0.001
HAE types						
Type I	3.4 (4.9)	1.1 (1.4)	2.2 (1.1)	1.6 (1.3)	3.3 (1.7)	$t_{(10777)} = 42.3$ <0.001
Type II	3.3 (4.7)	1.3 (1.1)	2.6 (1.1)	1.4 (1.0)	3.5 (1.6)	$t_{(369)} = 10.8$ <0.001
Prospective and retrospective parts						
Prospective	3.4 (4.9)	1.1 (1.4)	2.1 (1.4)	1.7 (1.3)	3.2 (1.7)	$t_{(7023)} = 36.0$ <0.001
Retrospective	4.2 (3.1)	1.3 (1.6)	2.0 (3.1)	1.8 (1.4)	2.9 (1.8)	$t_{(4123)} = 3.3$ <0.001
Treatment before pasteurization of the drug						
Before 1985	5.3 (3.7)	1.7 (1.5)	2.9 (1.6)	3.1 (1.6)	5.6 (1.8)	No test

No test was performed in the last row because of the small number of treated attacks (see Table 2).

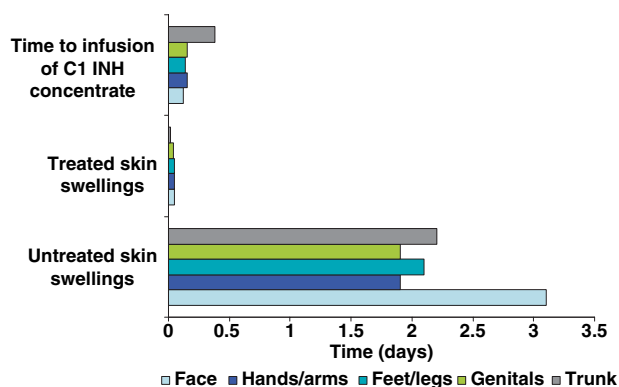


Figure 2. Time between onset of skin swellings and injections of C1-INH concentrate, time to first relief of symptoms in skin swellings of various body regions, and time to first relief in untreated skin swellings of the same patients.

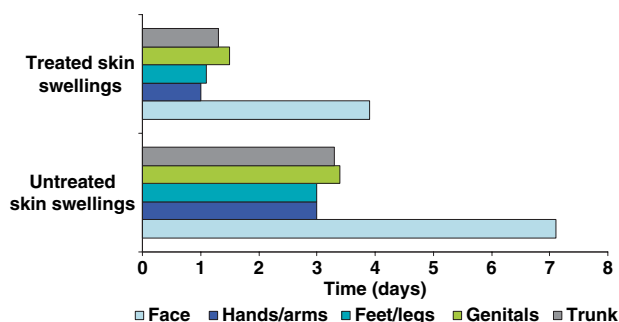


Figure 3. Duration of skin swellings in various body regions of patients treated with C1-INH concentrate and in untreated skin swellings of the same patients.

24 attacks involving four patients, the course of the skin swellings treated with C1-INH concentrate was not shorter, but symptoms were milder compared with untreated swellings.

According to Tables 2 and 3, there were no major differences in time to relief and duration of the attacks when related with types I or II of HAE or to the prospective or retrospective part of the study ($\chi^2_{(1)} = 0.29$, $P = 0.59$).

Patients' judgement

All 47 patients judged the treatment with C1-INH concentrate as helpful in their skin swellings. No patient felt that the injections were not effective. All 23 patients with more than 10 injections reported that treatment with C1-INH concentrate was more effective when injected early after onset of skin swellings compared with late injections.

Extension of treated skin swellings to other body sites or organs

None of the 483 treated facial swellings were complicated by laryngeal oedema, compared with 51 out of 628 untreated facial swellings. None of the treated skin swellings at the extremities were complicated by a further skin swelling at another limb or an extension of the swelling to larger skin areas; this was reported in 29% of the untreated swellings.

Rebounds

No rebound or recurrence of a treated skin swelling was observed, i.e. a skin swelling in the same location or at

another site or organ after a complete or nearly complete resolution within 48 h after administration of C1-INH concentrate.

Safety

We did not observe any major side-effects in the 2104 treated skin swellings. Furthermore, we did not observe adverse effects in patients with numerous treatments. There was no reported viral transmission of hepatitis C or because of human immunodeficiency virus (HIV).

Discussion

This is the first study to report detailed quantitative data of treated and untreated skin swellings of HAE in a sample of the given size. The time between injection and first relief of symptoms was <2 h in average, i.e. only 2.2% of the time to relief obtaining in the natural course of these skin swellings. In the study of Waytes et al. (16), a mean time to response of 120 min for treated extremity oedema, and 14 min for treated facial oedema was found. Furthermore, a considerable shortening of the total attack time in most attacks and patients was observed. Both, time to relief and total duration of skin swellings were longer than that obtaining in abdominal pain attacks or laryngeal oedema treated with C1-INH concentrate (19, 20). This may indicate that the resolution time of the oedema depends on the texture of the tissue, and that resolution occurs more rapidly in mucosal tissues than in skin attacks.

We can only speculate why the concentrate needed a longer time to work in some of the skin swellings. First, the degree of oedema at the time of treatment might play a role. Secondly, on average, the untreated facial oedema in our patient series lasted considerably longer than the oedema of the limbs. Correspondingly, the time to first relief and length of the treated facial oedemas was longer than that of skin swellings at other body sites. So the different courses of skin swellings may be related with different tissue features of the skin of the various body regions.

Facial oedema may progress to laryngeal oedema, which is potentially life-threatening; in the past, numerous patients with HAE suffocated on account of laryngeal oedema (26–29). In earlier studies, 13.9–28.5% of facial swellings were complicated by laryngeal oedema either simultaneously or within the subsequent 24 h (23, 24). In 35 patients with facial swellings in the present patient series; however, only 51 untreated facial swellings (8.1%) were associated with or followed by laryngeal oedema. Thus, 8.1–28.5% episodes of laryngeal oedema could have been anticipated in the patients with facial oedema had they not been treated with C1-INH concentrate. However, no laryngeal oedema occurred. So, we can assume that treatment of facial swellings is an effective

protection against progression to laryngeal oedema. Therefore, we recommend that all facial swellings in patients with HAE arising out of C1-INH deficiency be treated with C1-INH concentrate.

Concerning swellings of the extremities, many patients reported progression of the swellings to other body sites, and moreover, many of the untreated skin swellings led to a feeling of illness enough that they were unable to work for several days. This progression to other limbs or to larger areas of the trunk was not observed in any of the treated attacks. So, besides the shortening of the time to relief and, in most cases, the shortening of the attack duration, treatment with C1-INH concentrate led to avoidance of progress and extension of the skin swellings to other body sites and to other organs and was not associated with rebound oedema.

Major drug-related side-effects were not observed in the patient series reported here. However, side-effects of treatment with C1-INH concentrate were mentioned in other studies; in four patients, anaphylactic reactions occurred and in a number of other patients, mild side-effects occurred, generally symptoms lasting for a few minutes (20, 30). All these side-effects occurred when the concentrate was injected either too rapidly or when it was too cold (20). Because C1-INH concentrate is derived from human plasma, virus transmission is an important factor. Before the introduction of virus-inactivation steps, transmission of hepatitis had been observed with use of a different C1-INH concentrate that has been withdrawn from the market in 2003 (27, 30, 31). We treated only two patients because of skin swellings before 1985, i.e. before introduction of the practice of pasteurization of the C1-INH concentrate; neither of the two patients had signs of hepatitis (see Table 2). After the introduction of virus-inactivation steps, one clinical study showed that a vapour-heated C1-INH concentrate did not transmit HIV-1 infections, and another (which followed the recommendations of the Committee for Proprietary Medicinal Products) found no proven virus transmissions since the registration of Berinert® P (31, 32). As the introduction of virus inactivation measures, no transmission of infectious agents via the pasteurized C1-INH concentrate has been reported (32).

A systematic cost-benefit approach for the use of C1-INH concentrate has not been made until now. Extended and severe skin swellings cause illness for several days including being away from work. In Europe, the cost of 500 U of C1-INH concentrate is about 500 Euros or less depending on the country.

The present study has several limitations. First, and most importantly, it describes a case series of clinical records and not a randomized controlled trial. Hence, there is no control of confounders or blinding of assessment and a bias in results cannot be ruled out. Even though a large effect for C1-INH concentrate is undoubtedly visible in the various response criteria, efficacy of the drug is not proven in a rigorous

methodological manner. Secondly, analysis was based on data that were not collected in a prespecified design, but in clinical routine over a long period of time. There is additional uncertainty that the data may have some unreliability. Thirdly, central response parameters were assessed by single items, and it is known that there is some variation in measurement in this case. Fourth, data are partly retrospective reports of the patients, which may have incorporated additional bias.

In spite of these limitations, the study has the strengths of a relatively large sample of patients with a rare disease and data collected over a long timespan. It includes aspects that cannot be covered in double-blind studies, e.g. rare but potentially life-threatening complications such as laryngeal oedema. In such situations, serious doubt on the external validity of a controlled trial is to be contended with (33). It is a matter of

subjective view whether the limitations mentioned above would justify a randomized controlled trial, which implies withdrawing a seemingly effective treatment from some patients for some period. Until today, there was only one randomized controlled trial with C1-INH concentrate (vapour-heated) in HAE comparing 11 patients receiving the concentrate with 11 patients receiving placebo (16).

In light of these considerations, C1-INH concentrate can be expected to be an efficacious treatment in HAE. We conclude that the pasteurized C1-INH concentrate is effective and safe in treating skin swellings in patients with HAE. The risk of laryngeal oedema following facial swelling within 24 h is avoided when patients are treated with a C1-INH concentrate. Furthermore, risk of further extension or progress of extremity swellings to other limbs or body regions is minimized.

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