

Treatment of 193 Episodes of Laryngeal Edema With C1 Inhibitor Concentrate in Patients With Hereditary Angioedema

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Background: Hereditary angioedema (HAE) is an autosomal dominant disease (*Mendelian Inheritance in Man* 106100) caused by an inherited deficiency of C1 inhibitor (C1-INH) function. The clinical symptoms include skin swelling, abdominal pain, and life-threatening episodes of upper airway obstruction. We evaluated the efficacy of C1-INH concentrate for treating sudden airway compromise.

Methods: A series of 95 patients with HAE and a functional deficiency of C1-INH belonging to 59 families underwent screening for laryngeal edema. Double-blind treatment of randomized patients was not justifiable because of the life-threatening nature of this condition. Efficacy was evaluated by determining the interval from injection of C1-INH concentrate to the beginning of resolution of symptoms. The mean duration of episodes of laryngeal edema was compared in treated and untreated patients. Clinical information was obtained from emergency department physicians, the hospitals in-

volved, reports of the general practitioners, and patients and their relatives.

Results: Forty-two patients had 517 episodes of laryngeal edema. Eighteen patients received 500- or 1000-U injections of C1-INH concentrate in 193 episodes. The C1-INH concentrate was effective in all laryngeal edemas. The interval from injection to interruption in progress of symptoms ranged from 10 minutes to 4 hours (mean \pm SD, 42.2 \pm 19.9 minutes). The mean \pm SD duration of laryngeal edema was 15.3 \pm 9.3 hours in patients who received C1-INH concentrate and 100.8 \pm 26.2 hours in those who did not.

Conclusions: Injected C1-INH concentrate is highly and rapidly effective in the treatment of laryngeal edema of HAE. Relief and resolution of symptoms begins 30 to 60 minutes after injection, and duration of the upper airway obstruction is substantially reduced.

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HEREDITARY angioedema (HAE), first described clinically by Osler in 1888,¹ is a well-defined autosomal dominant disease (*Mendelian Inheritance in Man* 106100²) caused by an inherited deficiency of functional C1-esterase inhibitor (C1-INH). Donaldson and Evans³ discovered the defect in 1963. The defective *C1-INH* gene produces no C1-INH (type I HAE [HAE I]) or a dysfunctional C1-INH (type II HAE [HAE II]). In HAE I, which represents 85% of patients, plasma levels of C1-INH are 5% to 30% of normal values. In HAE II, levels of C1-INH are normal or elevated. Both forms are clinically indistinguishable. Until now, more than 100 different *C1 INH* gene mutations have been described in HAE, including missense and nonsense mutations, large deletions, and frame-shift and splice-site mutations.^{4,5} The exact prevalence of HAE is unknown; current estimates suggest that the disease affects between 1 in 10000 and

1 in 50000 persons.⁶ The clinical features of the disease are recurrent transient episodes of skin swelling and intestinal and laryngeal edema. These transient episodes of edema last 2 to 5 days, after which they regress spontaneously. The episodes of intestinal wall edema may be accompanied by transient ascites.⁷ Asphyxiation due to obstruction of the upper airways is the most common cause of death.⁸ Upper airway obstruction is usually due to laryngeal and glottal edema. In some patients, however, laryngeal edema may extend into lower parts of the airway, and some patients may have pulmonary edema also. Since this is rare, we use the term *laryngeal edema*. The unexpected occurrence of laryngeal edema associated with the risk for asphyxiation is the most important feature of this disease.

Treatment of HAE includes the following: (1) long-term prophylaxis to prevent skin swelling, abdominal attacks, and predominantly laryngeal edema; (2) short-

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PATIENTS AND METHODS

PATIENTS

A series of 95 patients with HAE from 59 unrelated kindreds have been followed up at the angioedema service of the Department of Dermatology of the University of Mainz, Mainz, Germany, for up to 20 years. The patients were from various regions of Germany. Deficiency of C1-INH was confirmed for all 95 patients; 92 had HAE I, and 3 had HAE II. All patients had the typical clinical symptoms of HAE, ie, relapsing attacks of skin swelling and abdominal pain. Forty-two of the patients had 1 or more episodes of sudden airway obstruction; 18 of them, all with HAE I, received C1-INH concentrate for sudden airway obstruction. Information about the patients with laryngeal edema is given in **Table 1**.

C1-INH CONCENTRATE

The C1-INH concentrate used (Berinert HS; Aventis Behring, Liederbach, Germany) is derived from pooled plasma of healthy donors seronegative for hepatitis B surface antigen, anti-human immunodeficiency virus 1 (HIV-1), anti-HIV-2, and anti-hepatitis C virus (HCV). Furthermore, all donations were tested for the absence of hepatitis A virus (HAV), hepatitis B virus (HBV), HCV, and HIV-1 as well as high titers of Parvovirus B 19 by means of polymerase chain reaction (PCR) analysis. In addition, a plasma pool for fractionation is only released for further processing if results of a sensitive and selective PCR are nonreactive for HBV DNA, HCV RNA, and HIV-1 RNA. Therefore, the high virus reduction capacity of the manufacturing procedure of Berinert HS is facilitated by the starting material, nonreactive for transfusion-relevant viruses on PCR findings. Important steps in the production procedure included heat treatment in aqueous solution at 60°C for 10 hours (pasteurization). One clinical study showed that Berinert HS does not transmit HIV-1 infections,¹⁷ and another (which followed the International Committee on Thrombosis and Haemostasis protocol) found no transmission of HBV or non-HAV/HBV.¹⁸

METHODS

At the beginning of the study, all 95 patients received a vial containing 500 U of C1-INH concentrate and stored it in their refrigerators at home. When patients experienced an episode of laryngeal edema, they received an injection from this vial administered by their general practitioner or at the nearest hospital. If the general practitioner gave the injection, the patient was admitted to the nearest hospital, where immediate intubation, tracheostomy, cricothyrotomy, or other emergency procedures were possible if the laryngeal edema progressed rapidly and asphyxiation threatened. If the symptoms of laryngeal edema did not resolve within 30 to 60 minutes of the injection or had progressed further by that time, an additional 500-U injection of C1-INH concentrate was administered in the hospital. If this was necessary in 3 consecutive episodes of laryngeal edema in the same patient, the patient received 1000 U of C1-INH instead of 500 U initially for all subsequent episodes. The efficacy was evaluated by determining onset of symptom resolution. Symptoms included dyspnea, fear of asphyxiation, feeling of tightness in the throat, dysphagia, and voice changes (including hoarseness, roughness, and aphonia). The time from injection of C1-INH concentrate to the first signs of symptom resolution or the end of the symptom progression was determined, as well as the duration of laryngeal edema from the first symptoms (feeling of a lump in the throat, dysphagia, or voice changes) to the end of the involuntal period and attainment of normality. The duration of laryngeal edema was compared with the duration of a previous episode that was not treated with C1-INH concentrate in the same patient. Furthermore, the duration of laryngeal edema in patients treated with C1-INH concentrate was compared with the duration in a control group of patients with HAE who had never received C1-INH concentrate. The medical histories are based on reports by the general practitioners, emergency department physicians, and hospitals involved. Additional information was obtained from the patients and their relatives.

Unless otherwise indicated, data are given as mean (\pm SD).

term prophylaxis before elective surgical procedures; and (3) treatment of acute attacks.

Long-term prophylactic treatment may include attenuated androgens, tranexamic acid, and C1-INH concentrate. Attenuated androgens, such as danazol or stanozolol, reduce the number of HAE attacks considerably.⁹⁻¹¹ However, a number of adverse effects may limit their use, including weight gain, menstrual irregularities, and arterial hypertension.^{12,13} Recently, hepatocellular adenoma has been reported in 3 patients with HAE who took danazol for more than 10 years.¹⁴ Furthermore, a hepatocellular carcinoma has also been observed with long-term use of attenuated androgens.¹⁵ Therefore, despite the proven efficacy in preventing HAE attacks, treatment with attenuated androgens cannot be recommended routinely to all patients. Continuous prophylactic treatment of HAE is also possible with tranexamic acid, an antifibrinolytic agent. Its efficacy, however, is lower than that of androgens.¹⁰ Furthermore, antifibrinolytic agents bear the risk for thromboembolic events. Con-

centrate of C1-INH is effective in preventing and treating acute attacks of HAE, and it has also been tried for long-term prophylaxis for HAE.¹⁶ However, since the available preparations are concentrates from pooled human plasma, the risk of transmission of infectious agents cannot totally be excluded. Furthermore, the concentrate is expensive and not available in all countries. These drawbacks limit the use of these drugs as a life-long prophylactic standard treatment. Short-term prophylaxis before surgery, especially dental surgery, may be achieved with C1-INH concentrate or with attenuated androgens.⁶

Acute attacks of abdominal pain and skin swelling have been treated successfully with C1-INH concentrate. Information about the efficacy of C1-INH concentrate in the treatment of sudden upper airway obstruction in patients with HAE is sparse because of the rarity and unforeseen occurrence of these episodes and the limited number of patients who have been treated with C1-INH concentrate.

Table 1. Clinical Features of 42 Patients With Hereditary Angioedema Who Had 1 or More Episodes of Laryngeal Edema*

	Patients Treated With C1-INH Concentrate (n = 18)	Patients Not Treated With C1-INH Concentrate (n = 24)
HAE Type	All HAE I	22 With HAE I 2 With HAE II
Sex, No., M/F	8:10	9:15
Age, mean (range), y	46.3 (20-85)	50.1 (22-83)
No. of episodes of laryngeal edema	345	210
Mean \pm SD plasma C1-INH protein, g/L†	0.07 \pm 0.02	0.08 \pm 0.03
Mean \pm SD C1-INH activity, %‡	9.7 \pm 9.4	9.1 \pm 7.5
Mean \pm SD plasma C4, g/L§	0.10 \pm 0.05	0.10 \pm 0.06

*C1-INH indicates C1 esterase inhibitor; HAE, hereditary angioedema.

†Reference range is 0.15-0.35 g/L.

‡Reference range is 70%-130%.

§Reference range is 0.20-0.50 g/L.

This study evaluates the efficacy of C1-INH concentrate in the treatment of laryngeal edema of HAE in 18 patients with HAE I who received C1-INH concentrate for 193 episodes of upper airway obstruction. Because of the life-threatening nature of this condition, a study of double-blind treatment of randomized patients was not justifiable ethically. Laryngeal edema occurs rarely and is usually unforeseen, and another method of evaluating efficacy had to be used. Therefore, efficacy was evaluated by determining the interval between the injection of C1-INH concentrate and the start of relief and resolution of symptoms. In addition, the duration of laryngeal edema was compared between treated and untreated episodes of laryngeal edema in the same patients, as well as between patients who received C1-INH concentrate and a control group of patients with HAE who did not receive C1-INH concentrate.

RESULTS

From 1970 to 1999, 42 of the 95 patients with HAE experienced 1 or more episodes of laryngeal edema. Forty of the patients had HAE I, and 2 had HAE II. The patients experienced a total of 517 episodes of laryngeal edema; 24 patients who experienced 172 episodes of laryngeal edema had never received C1-INH concentrate because HAE and the causal C1-INH deficiency had not yet been diagnosed or because the C1-INH concentrate was not available on the market. The 18 patients who had received C1-INH concentrate experienced a total of 345 episodes of laryngeal edema. These patients were treated with C1-INH concentrate for 193 episodes of laryngeal edema. The other 152 episodes occurred before the C1-INH concentrate was available or before the C1-INH deficiency had been diagnosed.

In 48 episodes of laryngeal edema in 12 patients, only 500 U of C1-INH was needed for treatment. In 21 additional episodes in 8 patients, a second injection of 500

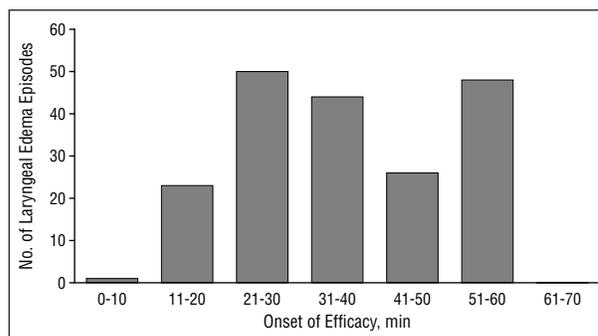


Figure 1. Onset of efficacy after injection of C1 inhibitor concentrate in 192 episodes of laryngeal edema in 17 patients with hereditary angioedema. In an 18th patient, resolution of symptoms in another episode did not begin until 4 hours after the injection.

U was warranted after the first 500 U. Two patients with 124 episodes of laryngeal edema started therapy with 1000 U of C1-INH concentrate. Four of the 18 patients received 500 U alone or, in other laryngeal edemas, 1000 U of C1-INH concentrate. None of the patients needed more than 1000 U. The C1-INH concentrate was effective in all episodes of laryngeal edema in all patients. None of the patients who received C1-INH concentrate required additional emergency procedures such as tracheostomy and cricothyrotomy.

In all patients, difficulty breathing and fear of asphyxiation were the first symptoms that resolved. Dysphagia, the sensation of a lump in the throat, and voice changes took longer to resolve completely. All patients experienced onset of relief within 4 hours after injection of C1-INH concentrate. In most patients, symptoms started to resolve between 30 and 60 minutes after administration of C1-INH concentrate (**Figure 1**). The therapeutic effect began within 1 hour in 17 patients with 192 episodes of laryngeal edema. In only 1 patient with 1 episode of laryngeal edema, resolution of symptoms did not start until 4 hours after administration of C1-INH concentrate. The mean interval between injection of C1-INH concentrate and the reversal of development of symptoms was 42.2 (\pm 19.9) minutes.

The mean duration (beginning of symptoms to resolution of last symptoms) of the 324 untreated episodes of laryngeal edema in the 24 patients who had never received C1-INH concentrate and in untreated episodes of laryngeal edema in the 18 patients who had received C1-INH concentrate for other episodes was 100.8 hours (\pm 26.2 hours) or 4.2 days (**Figure 2**). In the 18 patients, the mean duration of the 193 treated episodes of laryngeal edema was 15.3 hours (\pm 9.3 hours) and therefore was significantly lower than the duration of the untreated episodes of laryngeal edema of all patients ($P < .001$).

Among the 18 patients treated with C1-INH concentrate, 8 also had episodes that were not treated with C1-INH concentrate because it was not yet available for treatment of HAE or the C1-INH deficiency had not yet been diagnosed. The duration of the 144 episodes of laryngeal edema treated with C1-INH concentrate was significantly shorter than the duration of the 152 episodes that were not treated with C1-INH concentrate in the same

8 patients (Wilcoxon test, $\alpha = .05$; $P = .01$; highly significant) (**Table 2**).

In a subset of 3 patients with laryngeal edema, plasma concentration of C1-INH was determined by means of radioimmunoassay (reference range, 0.15-0.35 g/L) before and 1, 24, and 72 hours after administration of 500 U of C1-INH concentrate. The mean values were 0.03 ± 0.01 g/L before injection of C1-INH, 0.07 ± 0.01 g/L at 1 hour, 0.05 ± 0.01 g/L at 24 hours, and 0.03 ± 0.01 g/L at 72 hours.

Two patients received 500 U of C1-INH concentrate prophylactically 30 minutes before dental surgery and another patient, before 3 abdominal operations. No laryngeal edema or angioedema at other sites developed in these patients. There were no clinical signs of adverse drug reactions in any patients who had received C1-INH concentrate.

COMMENT

Hereditary angioedema is a potentially life-threatening disease. Although the most frequent symptoms, ie, relapsing attacks of skin swelling and abdominal pain, are not life threatening, sudden airway obstruction may lead to asphyxiation. Six asphyxiation-related deaths of patients with HAE have been reported recently.⁸ Even the first episode of laryngeal edema may be fatal.⁸ The possibility of sudden airway obstruction and asphyxiation must be emphasized in discussions with the patients and their relatives, and attending physicians should have a high degree of awareness of this aspect of HAE. Because of the danger of asphyxiation due to laryngeal edema, the 2 most important aims of treatment are interruption of an acute attack of laryngeal edema and prevention of laryngeal edema by means of long-term prophylaxis. Patients' early recognition of the beginning of an episode of laryngeal edema is crucial. For this purpose, patients should be carefully educated to recognize the first symptoms of upper airway obstruction such as dysphagia, sensation of a lump in the throat, feeling of tightness, and voice changes, including hoarseness and roughness. Dyspnea, fear of asphyxiation, and aphonia are features of a

fully developed episode of laryngeal edema. In choosing treatment for laryngeal edema, consideration should be given to the degree of the airway obstruction.^{19,20} In mild cases of airway edema, careful observation of the patient in the hospital may be sufficient, and oxygen therapy may be provided. When the edema progresses and dyspnea occurs, ventilation via mask and further emergency procedures, including intubation or tracheostomy, may become necessary. If no other treatment is possible and asphyxiation is imminent, an emergency cricothyrotomy should be performed without delay.

Replacement therapy with purified C1-INH preparation has proved to be effective in treating relapsing skin swelling and acute attacks of abdominal pain in patients with HAE.^{9,21-24} Information about treatment of laryngeal edema with C1-INH concentrate, however, is sparse. Gadek et al²¹ reported 2 attacks of laryngeal edema treated with a partly purified C1-INH. The times from infusion to resolution of symptoms were 7 hours and 1 hour in these patients. Agostoni and Cicardi with others^{9,25-27} reported on the treatment of 67 episodes of laryngeal edema in 23 patients with HAE with infusions of C1-INH concentrate. Resolution of symptoms started after 30 to 60 minutes. Kunschak et al²³ reported on the treatment of acute attacks of edema with C1-INH concentrate in 11 patients with acute edema. Among the 70 attacks in patients treated with C1-INH, there were only 4 episodes

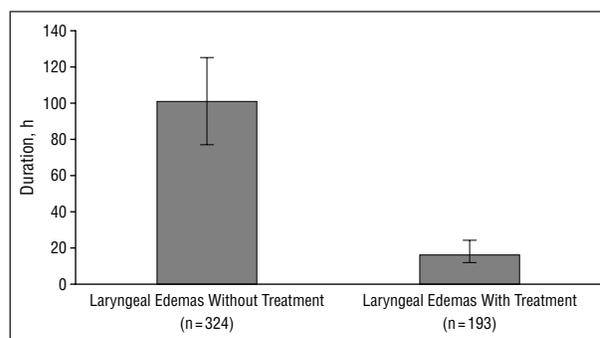


Figure 2. Mean duration of 193 episodes of laryngeal edema treated with C1 inhibitor concentrate and 324 episodes of untreated laryngeal edema.

Table 2. Duration of Episodes of Laryngeal Edema Not Treated and Treated With C1-INH Concentrate in the Same Patients*

Patient No.	Not Treated		Treated	
	No. of Episodes	Duration, h†	No. of Episodes	Duration, h‡
1	3	24	2	17.5
2	100	96 (25 times) 120 (75 times)	100	9
3	1	48	2	17
4	9	48	1	27
5	11	24	4	16
6	2	48 (1 time) 72 (1 time)	3	8
7	6	120	2	54
8	20	72	30	26
Total	152	...	144	...

*C1-INH indicates C1 esterase inhibitor; ellipses, not applicable.

†Mean \pm SD duration was 95.4 ± 32.1 hours.

‡Mean \pm SD duration was 14.5 ± 9.7 hours.

of difficult breathing or swallowing and no episodes of swelling of the respiratory tract. The number of patients who experienced these 4 episodes was not reported. Visentin et al²⁴ described 7 patients who received C1-INH transfusions. One of these patients was treated for 3 or 4 episodes of laryngeal edema. In this patient, the mean duration of the episodes of laryngeal edema treated with C1-INH concentrate was 71 minutes.

Because of the risks and adverse effects of long-term prophylactic treatment with attenuated androgens, antifibrinolytic agents, and C1-INH concentrate, having an appropriate treatment available for acute life-threatening events is very important. The present study shows, in a large number of laryngeal edemas in patients with HAE, that the administration of C1-INH concentrate is extremely helpful. Relief of the symptoms begins, on average, 42 minutes after the injection, and the course of the laryngeal edema is considerably shortened. Acute treatment must be administered early enough in the episode to interrupt its progression, and all steps must be discussed with the patient in detail.

CONCLUSIONS

Concentrate of C1-INH is rapidly effective (average, 42 minutes) in relieving and resolving symptoms of life-threatening laryngeal edema of HAE. The duration of the upper airway obstruction is significantly reduced.

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