
C1-esterase inhibitor transfusions in patients with hereditary angioedema

D E Visentin, W H Yang, and J Karsh

Background: Hereditary angioedema results from the deficiency of C1-esterase inhibitor (C1-INH), and C1-INH replacement would represent definitive treatment for angioedema attacks. In Canada, C1-INH is available only on a compassionate basis at select medical facilities. Our objective is to assess the efficacy of C1-INH transfusions during angioedema attacks at a single Canadian institution.

Methods: A retrospective chart review of transfusion data between January 1, 1995 and June 30, 1996 was performed. Phone interviews with patients elicited their opinions of the treatment. Data collected included the number and duration of angioedema attacks, dose of transfused C1-INH, and side effects of treatment.

Results: Of a cohort of 13 patients with hereditary angioedema, seven received transfusions with C1-INH. Attacks totaled 87, and more than 100,000 units of the product were transfused. The mean time for abatement of an attack after initiation of transfusion was 50 ± 8 minutes (1 SD). There were no reports of adverse effects. Although patients were satisfied with the treatment, they raised concerns regarding long-term safety and availability.

Conclusions: C1-INH transfusion is a satisfactory means of treating angioedema attacks.

Ann Allergy Asthma Immunol 1998;80:457-61.

INTRODUCTION

Quincke¹ reported angioedema in 1882 and Osler² described the hereditary form in 1888. Hereditary angioedema occurs in 1:50,000 to 150,000 people, and accounts for 2% of all cases of angioedema.^{3,4} Half of the patients are affected by age 7 and two-thirds by adolescence.⁴ Hereditary angioedema is an autosomal dominant inherited disease with incomplete variance.⁴ It has two phenotypical presentations. Type 1 accounts for 80% to 85% of all cases and is characterized by a deficiency of functionally active C1-esterase inhibitor protein (C1-INH).^{5,6} Type 2 accounts for 15% of cases^{6,7} and is

characterized by normal or elevated levels of a functionally defective C1-INH. Hereditary angioedema has significant morbidity sometimes resulting in endotracheal intubation,⁸⁻¹⁰ and when severe the mortality rate approaches 25% without appropriate treatment.¹¹

Clinically, hereditary angioedema is recognized by the presence of subcutaneous or submucosal tissue swelling with often normal appearing skin.^{12,13} Areas of swelling are predominantly in the face, extremities, gastrointestinal tract, and upper airways.^{3,14} Symptoms can include nonpruritic, nonpitting edema of the extremities, colicky abdominal pain, nausea, vomiting, watery diarrhea, hoarseness, and dysphagia.¹⁵

There are a number of "triggers" that can precipitate an angioedema attack including trauma, dental work, stress, menstruation, and medications, especially estrogen-containing compounds.¹¹ Remission has been observed after menopause and during pregnancy.⁸ The attacks generally progress over 12 to 36 hours and remit

spontaneously in one to three days if not fatal.¹²

C1-INH is a protein with significant roles in the regulation of the fibrinolytic and complement pathways. It is synthesized in the liver by fibroblasts, monocytes, and megakaryocytes, and by the placenta.¹² It is up-regulated by androgens, gamma-interferon, and interleukin-6.¹² Its half-life is 64 hours.⁴

C1-INH inhibits the proteolytic activation of C2 and C4 along the classical complement pathway; lack of inhibitor results in increased C2 kinin levels which contribute to angioedema.¹⁶ Within the fibrinolytic pathway, C1-INH inhibits the amplification pathway for factor XII proteolysis (Hageman factor); lack of inhibitor results in increased bradykinin activity which also contributes to angioedema.⁴ A plasma level less than 38% of normal of C1-INH is associated with a risk of angioedema.¹⁷

Treatment of hereditary angioedema consists of the long-term prophylaxis or prevention of attacks and the management of acute episodes.¹⁸ The mainstay of prophylaxis has been androgen therapy in the forms of danazol and stanozolol.^{19,20} These medications increase hepatic synthesis of functional C1-INH resulting in increased serum concentrations of inhibitor and offer control of symptoms in greater than 90% of patients.^{21,22} Treatment with androgens, however, is not without side-effects which include acne, virilization, hepatitis, weight gain, myalgias, altered lipoprotein profiles, altered libido, and menstrual irregularities.^{12,15,23} These medications are also not suitable for children, during pregnancy, and are futile in the management of acute attacks. Antifibrinolytic agents, such as tranexamic acid and epsilon-aminocaproic acid (EACA), are alternative

Diana E. Visentin, MD, Medical Resident.
William H. Yang, MD, FRCPC, Head, Section of Allergy and Clinical Immunology, Ottawa Civic Hospital, and Clinical Assistant Professor, University of Ottawa.
Jacob Karsh, MDCM, FRCPC, Division of Rheumatology, Ottawa General Hospital, and Professor of Medicine, University of Ottawa.
Received for publication July 8, 1997.
Accepted for publication in revised form March 2, 1998.

therapies and have been used with an attack reduction rate of around 80% to 90%. They are a treatment option for children. Potential side-effects include thrombosis, myonecrosis, and postural hypotension.^{12,15}

Acute attacks of angioedema have always been a potentially fatal situation because until the availability of C1-INH, there had been no effective means of interrupting an attack once it had begun.²⁷ Treatment with epinephrine, antihistamines, and corticosteroids provide little or no significant change in the course of the attack. C1-esterase inhibitor (C1-INH) has been used effectively as procedure prophylaxis,²⁴⁻²⁶ but its true value lies in the abatement of acute angioedema attacks.^{8,28} What follows is a description of our experience with C1-INH transfusion for attacks of hereditary angioedema.

METHODS

The C1-INH product (Immuno, Vienna, Austria) was made available on compassionate grounds by the Drugs Directorate of Health and Welfare, Canada. A workshop was conducted for Emergency Room physicians outlining the transfusion protocol. Two vials of product (573 plasma units of lyophilized human vapor heated C1-INH), reconstituted in sterile water, were added to 50 mL of 2:3 to 1:3 normal saline-D5/W and administered intravenously over 10 to 15 minutes. If the patient did not improve within the hour, a third vial would be transfused upon patient request. Patient 1, a male with a body surface area of 2.99 m², had three vials transfused with an attack.

Immuno, a freeze-dried, sterile, human plasma fraction containing concentrated and purified C1-INH, is prepared from pooled human plasma obtained from Central Europe and the USA. The pooled plasma—non-reactive in approved tests for hepatitis B surface antigen, and human cytomegalovirus and immunodeficiency virus-1 and -2 antibodies—is vapor-heated at 60 °C for ten hours which surpasses

Table 1. Characteristics of Ottawa Patients with Hereditary Angioedema

Patient	Age/Sex	C1-INH (245-543 mg/L)	C4 0.16-0.49 g/L	Interval Between Attacks	Use of C1-INH	Other Therapy
1	32/M	68	0.12	4 wk	Yes	Stanozolol
2	32/M	159	0.09	4 wk	Yes	Danazol
3	37/F	<48	<0.08	4 wk	Yes	No
4	19/F	<48	<0.08	3 wk	Yes	No
5	20/F	<48	<0.08	4 wk	Yes	No
6	35/F	<48	<0.08	8 wk	Yes	No
7	9/F	76	0.10	12 mth	Yes	No
8	13/M	<48	<0.10	12 mth	No	No
9	20/F	<48	<0.10	6 wk	No	No
10	45/F	60	0.11	4 wk	No	No
11	16/M	103	0.19	>24 mth	No	No
12	46/F	<48	<0.16	5 mth	No	No
13	52/F	<48	<0.06	12 mth	No	Stanozolol

the time required to destroy the human immunodeficiency virus. Heat-treating plasma has also been successful in reducing hepatitis C transmission.²⁹ The shelf-life of the preparation is 2 years when stored between 2 to 8 °C. Immuno has been used in Europe since the early 1980s and there have been no reports of adverse reactions, incidents of viral hepatitis, human immunodeficiency virus transmission, or anti-C1-INH antibody production with over 5,400 treatments.³

At the end of the study period of January 1, 1995 to June 30, 1996, a retrospective review was conducted on an established cohort of 13 patients in the Ottawa area known serologically to have hereditary angioedema. Transfusion records were obtained from the hospital blood bank. Date of angioedema episode, number of vials transfused per episode, and duration of attack were recorded. The duration of an attack was defined as the total time from initiation of the transfusion to the time recorded on the Nurses' Progress Notes indicating when the patients' symptoms had resolved. If this was not noted, the time of discharge from the Emergency Department was taken as the indication of attack resolution. All times were recorded to the nearest 15-minute interval.

A standardized Quality of Life Questionnaire pertinent to the presentation of a transient, acute illness was

not available. Subjective comments were elicited from all 13 patients regarding the use of this treatment by telephone interview. The questions asked were as follows:

- (1) What are your thoughts regarding the use of C1-INH for attacks of angioedema?
- (2) How does this treatment compare to previous treatments?
- (3) Do you have any concerns regarding the use of this product?

For those patients who had not used the transfusion product, these questions were asked the following:

- (1) Are you aware that there is a transfusion of C1-INH available for angioedema attacks?
- (2) Why have you not used the product?

RESULTS

Serum levels of C1-INH were measured by radioimmunoassay and complement components by nephelometry (Clinical Immunology Laboratory, University Hospital, London, Ontario).

Thirteen patients constituted the Ottawa cohort (Table 1). Patients 3 and 6 are sisters. Patients 4 and 5 are the children of patient 3 and patients 7 and 8 are the children of patient 6. Patients 9 and 11 are the children of patient 10, and patient 12 is the first cousin of patient 10. Patient 12 has 2 other sib-

lings with hereditary angioedema in other cities.

Patients 2 and 11 had decreased circulating C1-INH levels, although they were above 38% of the lower limit of the normal range. They were not on androgens when testing was performed. Assessments of the functional status of the C1-INH in these two patients were not performed. Despite the higher level of C1-INH somewhat atypical for hereditary angioedema, patient 2 had frequent attacks of angioedema and a decreased C₄. Patient 11 was identified during screening of his family, had rare and only mild attacks of swelling of the feet, and was the only patient with a normal level of C₄. Concentrations of C₃ were normal and the ANA was negative in all.

Patient 2 was receiving 900 mg of danazol a day, and patients 1 and 13 were receiving stanozolol 2 mg every other day during the study. The other patients were not on androgens, the females because of the undesired side effects and the two young males (patients 8 and 11) because of rare and mild attacks of angioedema. None of the patients was known to have behavioral problems such as seeking narcotics and none was under psychiatric care. Patients were not screened before or after the study for evidence of infection with the human immunodeficiency virus or strains of hepatitis.

Of the 13 patients, seven received C1-INH transfusions during the study period and six did not (Table 2). Patient 1 used the transfusions only for attacks of laryngeal edema and the others predominantly for GI attacks. A total of 87 attacks were treated, with the number of attacks per person ranging from 3 to 33. A total of 190 vials of Immuno were used. Patient 1 always received three vials and the other patients always responded to the two vials of product. The mean duration of attack was 50 ± 8 minutes (1 SD) with a range of 15 to 150 minutes. This duration contrasted strikingly with the typical attack duration of one to four days. There were no reported adverse effects with this treatment.

Table 2. Characteristics of Attacks and Treatment in Patients with Angioedema

Patient*	Typical Location	Typical Duration (days)	Total No.† of Attacks	Total No. of Vials	Total‡ Units × 10 ³	Mean Duration of Attacks with C1-INH (min)
1	Hands/feet/larynx	1-3	5	11	5.5	71
2	GI/larynx	2-4	4	14	7	53
3	GI	1-2	8	17	8.5	48
4	GI/hands/feet	2-3	33	71	35.5	46
5	GI/faces/hands	2	27	58	27	61
6	GI/hands/arms feet	1-2	7	14	7	43
7	GI/hands/arms	1	3	6	3	30
8	Hands/face/GI	1	0	No C1-INH		
9	GI/hands/feet	3	0	No C1-INH		
10	GI/hands/feet/ back	3-4	unknown	No C1-INH		
11	Feet	5	0	No C1-INH		
12	GI/feet	2-3	unknown	No C1-INH		
13	Face/eyes/ hands/larynx	1-3	1	No C1-INH		

* Patients 1-7 treated with C1-INH.

† During observation period of this study.

‡ 573 units per vial.

Patient 13 refused C1-INH transfusions because of a fear of blood products. On stanozolol, 2 mg every other day she had only one significant attack of angioedema during the duration of the study; however, she had hepatotoxicity attributable to androgens. She used analgesics during her attacks of angioedema. Patients 10 and 12 had been on androgens but stopped them because of virilizing side effects. They treated angioedema attacks which were predominantly of the peripheries with analgesics at home.

The subjective comments from the patients were insightful. Those who had used the product were unanimously content with the rapid alleviation of symptoms. Two patients found that if they waited to obtain the transfusion, the symptoms persisted for a longer duration. Those who had received the transfusion wished that it was more accessible at different centres as they felt "stuck" in having to report to only one facility. Several were disappointed with the wait in the emergency room before receiving their transfusion. A common concern was the risk of either human immunodeficiency

virus infection or an infection yet unknown from receiving a blood product.

Of those who had not yet received the product, all were aware that it existed and how to obtain it. Several reasons accounted for not having received a transfusion. Patient 13 was fearful of blood products in general. The other patients either had infrequent, predominantly peripheral, angioedema attacks of manageable severity, or were serologically positive for hereditary angioedema but yet to experience a significant attack.

DISCUSSION

In Canada, C1-INH transfusions are presently only available on a compassionate basis and their use has been a positive and effective experience in the treatment of our patients undergoing angioedema attacks. The abatement of symptoms was rapid, and the treated patients acknowledged that C1-INH treatment surpassed their experiences with traditional treatments offered in the past, namely hydration and symptom control with analgesics and anti-

emetics. Their concerns are valid in that there may always be a risk of viral transmissibility with the transfusion of blood products. Preventing transmission of present day known viruses is favorably affected by the method of preparation of the particular product.

This study is limited by its unblinded nature, the small sample size, the short duration of observation, and by the indefinite nature of determining the duration of attack. It can be inferred that there were both overestimations and underestimations of the duration of an attack, a common data error in retrospective studies. Yet, the overall conclusion based on both objective data and subjective experiences is that C1-INH transfusion has been very effective in reducing the duration of angioedema attacks.

In this regard, our experiences are identical to the results of the American double-blind, placebo-controlled study of Waytes et al.²⁸ He and his colleagues observed a rapid increase in circulating concentrations of C1-INH and a similar shortened duration of attacks in 11 treated patients, also in the range of one hour, with the same C1-INH product. Equally important, after 4 years of follow-up, no evidence of transmission of the immunodeficiency virus or hepatitis B or C has been noted by this group of investigators.

Europeans have more than a decade's experience with the use of purified C1-INH products. Agostini et al³ from Italy describe the favorable and safe treatment of 28 patients receiving 83 transfusions with the same purified C1-INH product to treat acute attacks of angioedema. Purified C1-INH has also been used prior to surgery in Australia and France to prevent attacks.^{24,25} In two German patients, successful continuous prophylactic therapy with C1-INH has been described.²⁶

We feel our experience has provided additional evidence that C1-INH transfusion is effective treatment for the abatement of angioedema attacks. Long-term concerns over the safety of human blood derived products are certainly justified and will require contin-

ued surveillance of all patients treated with the product.

REFERENCES

1. Quincke H. Uber akutes umschriebenes Hautodem. *Monatsh Prakt Dermatol* 1882;1:129-31.
2. Osler W. Hereditary angioneurotic oedema. *Am J Med Sci* 1888;95:362-7.
3. Agostini A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine* 1992;71:206-15.
4. Elnicke DM. Hereditary angioedema. *South Med J* 1992;85:1084-90.
5. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C1-esterase. *Am J Med* 1963;35:37-44.
6. Rosen FS, Charache P, Pensky J, Donaldson VH. Hereditary angioneurotic edema: two genetic variants. *Science* 1965;18:957-8.
7. Aulak KS, Pemberton PA, Rosen FS, et al. Dysfunctional C1-inhibitor (At), isolated from a type II hereditary-angio-edema plasma, contains a P1 'reactive centre' (Arg⁴⁴⁴-His) mutation. *Biochem J* 1988;253:615-8.
8. Sim TC, Grant JA. Hereditary angioedema. Its diagnostic and management perspectives. *Am J Med* 1990;88:656-64.
9. Megerian CA, Arnold JE, Berger M. Angioedema: 5 years' experience, with a review of the disorder's presentation and treatment. *Laryngoscope* 1992;102:256-60.
10. Shah TJ, Knowles WO, McGeady SJ. Hereditary angioedema with recurrent abdominal pain and ascites. *J Allergy Clin Immunol* 1995;96:259-61.
11. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976;84:580-93.
12. Huston DP, Bressler RB. Urticaria and angioedema. *Med Clin N Amer* 1992;76:805-40.
13. Davidson AE, Miller D, Settupane G, Klein D. Urticaria and angioedema. *Clev Clin J Med* 1992;59:529-34.
14. Cicardi M, Bergamaschini L, Marasini B, et al. Hereditary angioedema: an appraisal of 104 cases. *Am J Med Sci* 1982;284:2-9.
15. Orfan NA, Kolske GB. Angioedema and C1-inhibitor deficiency. *Ann Allergy* 1992;69:167-72.
16. Kaplan AP, Silverberg M. The coagulation-kinin pathways of human plasma. *Blood* 1987;70:1-15.
17. Spath PJ, Wuthrich B, Butler R. Quantification of C1-inhibitor functional activities by immunodiffusion assay in plasma of patients with hereditary angioedema-evidence of a functionally critical level of C1-inhibitor concentration. *Complement* 1984;1:147-59.
18. Hardie J, Ringland T, Yang WH, Wagner V. Potentially fatal hereditary angioedema: a review and case report. *J Can Dental Assoc* 1990;56:1096-9.
19. Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanazolol. *J Allergy Clin Immunol* 1987;80:855-60 (also correction 1988;81:1208).
20. Hosea SW, Santaella ML, Brown EJ, et al. Long-term therapy of hereditary angioedema with danazol. *Ann Intern Med* 1980;93:809-12.
21. Arreaza EE, Singh K, Grant JA. Hereditary angioedema: clinical and biochemical heterogeneity. *Ann Allergy* 1988;61:69-74.
22. Sheffer AL, Fearon DT, Austen KF. Clinical and biochemical effects of stanazolol therapy for hereditary angioedema. *J Allergy Clin Immunol* 1981;68:181-7.
23. Zurlo JJ, Frank MM. The long-term safety of danazol in women with hereditary angioedema. *Fertil Steril* 1990;54:64-72.
24. Langton D, Weiner J, Fary W. C1-esterase inhibitor concentrate prevents upper airway obstruction in hereditary angioedema [Letter]. *Med J Aust* 1994;160:383-4.
25. Laxenaire M, Audibert G, Janot C. Use of purified C1-esterase inhibitor in patients with hereditary angioedema [Letter]. *Anesth* 1990;72:956-7.
26. Bork K, Witzke G. Long-term prophylaxis with C1-inhibitor (C1-INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 1989;83:677-82.
27. Gadek JE, Hosea SW, Gelfand JA, et al. Replacement therapy in hereditary angioedema. *N Engl J Med* 1980;302:542-6.
28. Waytes AT, Rosen FS, Frank MM.

Treatment of hereditary angioedema with a vapor treated C1 inhibitor concentrate. *N Engl J Med* 1996;334:1630-4.

29. Cicardi M, Mannucci PM, Castelli R,

et al. Reduction in transmission of hepatitis C after the introduction of a heat-treatment step in the production of C1-inhibitor concentrate. *Transfusion* 1995;35:209-12.

Request for reprints should be addressed to:
Dr W H Yang
1081 Carling Ave
Suite 800
Ottawa, Ontario
Canada K1Y 4G2
