

C1 INH Concentrate in the Therapy of Hereditary Angioedema

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Ten acute attacks were managed in nine patients with hereditary angioedema by means of the infusion of a C1 INH concentrate produced on large scale. No side effects were observed.

Key words: C1 INH concentrate; hereditary angioedema.

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CLINICAL ASPECTS

Hereditary angioedema is a disorder characterized by deficiency of the C1 esterase inhibitor (C1 INH). The edema involves subcutaneous and/or mucous tissues. Laryngeal edema may cause the death of the patient by asphyxia. Antifibrinolytic agents and androgen-derivatives are useful in the prophylactic treatment of the disease. Acute attacks can be successfully managed with the infusion of C1 INH concentrate. Replacement therapy resolves mucous edema in 15-20 min.

The clinical signs of hereditary angioedema (HAE) were first recognized a century ago by Osler (4), but the biochemical abnormality was first defined by Donaldson & Evans in 1963 (6). The disease is related to the genetically transmitted absence or functional deficiency (CRM⁺ variant) of the inhibitor of C1-esterase (C1 INH). It is characterized by recurrent spontaneous attacks of subcutaneous and mucous swelling lasting 24-48 h. When edema involves the gastrointestinal tract, nausea, vomiting, diarrhea and abdominal pain may occur. If swelling involves the upper respiratory tract the patient may die of asphyxia as a result of laryngeal edema.

Although in many patients the edema occurs following a direct trauma (psychological or mechanical) about half of the attacks have no relation to a triggering event (5).

HAE patients can be prophylactically treated with antifibrinolytic agents (7) or androgen-derivatives (8). In our experience with 120

patients good results were obtained with tranexamic acid, which reduced the severity of the attacks in about 70% of treated subjects without serious side effects even in long-term therapy (3). Better results were obtained with 17 α -alkylated androgen-derivatives (danazol, stanazolol) which induce clinical remission in patients by producing a 4-5-fold increase in serum C1 INH activity (2, 10). However, the 17 α -alkylated androgens seem to be implicated in the development of liver tumors, cholestatic jaundice, and peliosis hepatis (5). Long-term administration of drugs is not recommended in patients whose disease activity does not justify continuous prophylactic treatment. In pregnant women and in children an alternative to androgen or antifibrinolytic therapy is needed. Moreover, neither androgen nor antifibrinolytic agents can be successfully used when edema formation has begun. For these reasons an alternative to prophylaxis is needed to manage the acute attacks of life-threatening

severity. Good results have been obtained by our group using C1 INH concentrate prepared by The Netherlands Red Cross Blood Transfusion Service, Amsterdam, in 19 severe HAE attacks (1). Similar results were obtained by Gadek et al. (9) with the infusion of a different preparation in eight acute episodes of mucous and subcutaneous swelling. We have recently been supplied with a new C1 INH preparation, produced by Immuno AG, Vienna.

In this paper we report the *in vivo* efficacy and safety of this protein preparation in nine HAE patients during 10 acute attacks. In seven cases we were also able to evaluate the biochemical response determining the serum levels of C1 INH and C4 at several time intervals after the infusion.

MATERIAL AND METHODS

Patients

In each patient hereditary angioedema was diagnosed according to the accepted clinical and laboratory criteria (8). All patients had decreased functional activity of C1 INH, one patient (C.L.) had normal serum level of C1 INH representing the CRM⁺ variant. In all cases the C4 serum level was decreased. Three patients (V.Mo, V.Ma, C.L.) were children not suitable for long-term treatment with androgen or antifibrinolytic drugs, the remainder were not prophylactically treated because of limited disease activity (less than one attack per month).

C1 INH and C4 serum levels

Antigenic and functional determinations of C1 INH and antigenic C4 serum levels were performed immediately before the infusion and at several time intervals during the course of the study (15, 60, 120 min and 24 h). Antigenic determinations of C1 INH and C4 were performed by single-radial immunodiffusion on cellulose acetate strips (4). C1 INH functional activity was determined according to the Lachmann method (12).

C1 INH preparation

C1 INH preparation was supplied by Immuno AG, Vienna (Austria). The partially purified preparation was obtained by selective absorption of C1 INH from a cryoprecipitate of pooled human plasma. Radioimmunoassay showed that the starting material and C1 INH concentrate were hepatitis B surface antigen (HbsAg)-free. The concentrate was reconstituted with 10 ml of sterile distilled water. The final concentration (55 U/ml) was (v/v) 70-fold higher than fresh human plasma. The preparation was infused intravenously in about 10–15 min.

RESULTS

We treated nine patients for 10 acute attacks with 1,100–2,200 U. No side effects were observed in any of the subjects, particularly, there was no evidence of allergic reaction. 15–20 min after the infusion swelling ceased to increase, and within 30–60 min mucous edema began to subside as evidenced by the disappearance of abdominal pain or a subjective sensation of reduced airway obstruction. Subcutaneous edema began to subside after a longer time period (2–3 h). In each case patients could be discharged within 3–4 h of the infusion.

Pretreatment C1 INH activity ranged from 2 to 29% of the normal standard pool, 15 min after the infusion it increased up to 44–136% and slowly began to decrease after approx. 24 h. There was a consistent lag between infusion and the increment of C4 serum levels that results from decreased catabolism of this protein (Table I). The different antigenic levels of C1 INH in serum of three HAE children (V.Mo, V.Ma, C.L.), with about the same body weight, after the infusion of 1,100 U of concentrate, probably reflects the equilibration time of the protein from the intravascular to the extravascular compartment.

During two severe attacks of laryngeal edema, patient G.A. was treated with 1,650 and 1,100 U of C1 INH concentrate, respectively, but both infusions gave the same clinical response.

Table 1
Biochemical and clinical effect of intravenous infusion of C1 INH concentrate in patients with hereditary angioedema.
(Values are expressed as percentage of normal mean)

Patient	Sex	Age (years)	Site of edema	Dose (U) of C1-INH	C1 INH (immunochem. assay)					C1 INH (enzymatic assay)					C4 (immunochem. assay)					Clinical response**
					0	15'	60'	120'	24h	0	15'	60'	120'	24h	0	15'	60'	120'	24h	
S.G.	F	43	Pharynx	2,200	10	74	126	120	58	10	75	94	90	55	22	22	24	30	58	20 min
G.A.	M	19	Larynx	1,650	16	45	41	41	36	29	63	63	60	54	24	27	25	28	33	15 min
G.A.	M	19	Larynx	1,100	10	38	40	40	35	7	44	37	35	39	24	22	22	25	67	20 min
V.Ma.	M	4	Face	1,100	19	198	182	180	150	20	122	140	140	105	13	11	12	12	15	3 h
V.Ma.	F	8	Bowel	1,100	28	226	182	168	130	25	136	112	123	80	18	20	19	19	38	15 min
C.L.*	M	6	Face	1,100	78	148	-	-	164	3	65	-	-	60	8	12	-	-	40	3 h
F.G.	F	40	Larynx	1,650	10	59	90	85	43	2	59	62	60	61	6	10	10	15	31	15 min
P.A.	F	18	Bowel	1,100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20 min	15 min
G.C.	M	43	Bowel	1,100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
S.A.	M	48	Face	1,100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3-4 h

* Patient with variant HAE (CRM⁻).

** Beginning of symptom regression after start of infusion.

None of the treated patients suffered any untoward consequences from the infusions and there was no clinical or biochemical evidence of transfusion hepatitis.

DISCUSSION

The infusion of C1 INH concentrate is the treatment of choice in acute attacks of hereditary angioedema (1, 9).

Although the management of an attack with kallikrein inhibitor (Trasylol®) is satisfactory (12) we prefer replacement therapy with C1 INH concentrate because it gives a more rapid remission of clinical symptoms and avoids the risk of the allergic reaction reported with kallikrein inhibitor (15). On the other hand, transfusion of fresh plasma, in addition to being a less convenient volume to administer, provides C1-esterase substrates (C4, C2), a source of the kinin-like peptide of HAE (10).

In this study we report the clinical and biochemical results obtained with a large-scale preparation of C1 INH protein the storage of which, in some cases, exceeded 12 months at 4°C. A rapid positive clinical result was observed in all the patients treated for mucous edema, particularly those treated for laryngeal edema, who reported a clear improvement within 20-30 min of the infusion, and emergency tracheostomy was never necessary.

The patients receiving this C1 INH preparation showed a lag of the C4 serum increment providing *in vivo* evidence of the efficacy of this concentrate. Similar results have recently been reported with other C1 INH preparations (1, 9).

These current data suggest that a C1 INH preparation, even produced on a large-scale, provides a safe and definitive approach to the management of acute attacks of hereditary angioedema. Thus for patients not suitable for long-term prophylactic treatment a stock of the C1 INH preparation could be maintained and self-infusion authorized in order to reverse the incapacitating or life-threatening manifestations of hereditary angioedema.

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