

Brief communications

An adverse reaction to angiotensin-converting enzyme inhibitors in a patient with neglected C1 esterase inhibitor deficiency

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CASE REPORT

The patient (FK) is a 66-year-old man with non-insulin-dependent diabetes mellitus, coronary heart disease, hypertension, and atrial fibrillation. In April 1996 he was referred to our department because of an anaphylactoid reaction with nausea and vomiting, diarrhea, angioedema, severe hypotension, and acute renal failure, which occurred 6 hours after an enalapril infusion test (mercaptoacetyltriglycerine [Mallinckrodt, The Netherlands] renography, performed March 26, 1996) because of suspected renovascular hypertension.

A personal history revealed a similar reaction, though less severe, after initial administration of lisinopril on March 12, 1996. The patient had a life-long history of episodic painless and non-itchy swelling of the extremities, face, and lips appearing spontaneously or after trauma. In addition, he had a familial history of episodic cutaneous angioedema affecting his father (already deceased), son (FJ), and grandson (FW). In view of these findings, a diagnosis of neglected hereditary angioneurotic edema (HAE) was suspected.

Test results

The erythrocyte sedimentation rate was 2 mm after 1 hour. Peripheral blood count and biochemical profile, including an electrophoresis and an immunoelectrophoresis, were within normal limits. Total serum IgE was 40 kU/L. The activated partial thromboplastin and prothrombin times, d-dimers, and plasminogen were normal. The result of a lymphocyte transformation test with enalapril was considered negative (stimulation index of 1.1). Results of skin prick tests with enalapril at 10^{-3} , 10^{-2} , and 10^{-1} dilutions were negative. Table I summarizes the results of serial analysis of C3, C4, C3d, functional complement activity (CH_{50}), C1q, and antigenic and functional C1 inhibitor (C1 INH) determinations. CH_{50} activity, C3, and antigenic and functional C1 INH levels were found to be repeatedly decreased. Blood samples incubated at 37°C, irrespective of the presence or absence of enalapril, demonstrated comparable activation of the complement cascade with reduction of CH_{50} and increased C3d.

Abbreviations used

ACE:	Angiotensin-converting enzyme
C1 INH:	C1 esterase inhibitor
HAE:	Hereditary angioneurotic edema

DISCUSSION

Angioedema can be a rare adverse effect resulting from the administration of angiotensin-converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, or ramipril). The overall incidence of ACE inhibitor-mediated angioedema has been reported to be 0.15% to 0.2%.¹ Several pharmacologic experiments and clinical studies have provided clear evidence that ACE inhibitors exhibit additional local vasodilator, non-renin-angiotensin-dependent mechanisms in their action on blood pressure and blood flow. Because ACE (identical to kininase II), by releasing the carboxy terminal dipeptide Phe-Arg, inactivates the nonapeptide bradykinin, accumulation and/or potentiation of bradykinin might well be responsible for these additional effects of ACE inhibitors.²⁻⁴ Bradykinin, which is cleaved from high-molecular-weight kininogens by plasma and tissue kallikrein,^{5,6} is a highly potent activator of the L-arginine nitric oxide system (i.e., endothelium-derived relaxing factor) that causes vasodilatation, increases vascular permeability, and also produces hypotension. Therefore inhibition of bradykinin degradation by ACE inhibitors might amplify kallikrein-kinin-mediated reactions on local vessel tone, in particular if kinin generation is enhanced.⁷

C1 INH, an α_2 -neuraminoglycoprotein of 105 kd, is synthesized primarily by hepatocytes and monocytes and is present in a normal serum concentration of 30 mg/dl. As a member of the superfamily of serine protease inhibitors (serpins), its spectrum of inhibitory activity, defined by a 444 arginine-445 threonine dipeptide at the reactive center, includes the target proteases C1r and C1s (complement system), factor XII and kallikrein (contact system), factors XIa, XIIa, and XIIf (coagulation cascade), and plasmin (fibrinolysis). In C1 INH deficiency, failure of homeostatic regulation of one or more of these protease systems that generate vasoactive mediators responsible for the localized enhanced vascu-

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TABLE I. Results of serial analysis

	Normal	FK	FK	FK	FJ	FW
Date		3/96*	7/96	8/96	8/96	8/96
CH ₅₀ (U)	133-243	ND	4	ND	5	16
C3 (mg/dl)	69-177	105	105	ND	116	128
C4 (mg/dl)	14-56	7	3	ND	10	8
C3d (mg/dl)	<0.38	ND	0.27	ND	0.24	0.20
C1q (mg/dl)	10-25	ND	16.4	17	20	16
C1 NH Ag (mg/dl)	21-39	19	12	13	18	17
C1 NH function (%)	60-150	40	17	8	13	11

ND, Not done; Ag, antigen.

*Blood sample was obtained 6 hours after adverse reaction; angioedema was still present.

lar permeability, which characterizes the disease, has been reported.^{8,9}

C1 INH deficiency is characterized by recurrent, circumscribed, nonpitting, and nonpruritic subepithelial edema that primarily involves the extremities, larynx, face, and bowel wall. There is no urticaria, but it may be associated with some erythema. Generally, angioedema develops fully within a few hours, lasts for 2 to 4 days, and resolves without harm. However, laryngeal or tracheal edema may result in asphyxiation and remains the major cause of death. Abdominal symptoms (colicky pain, nausea, vomiting, watery diarrhea) caused by intestinal wall edema, at times severe, may be the sole manifestations of the disease.⁹ In our patient the clinical presentation of the ACE inhibitor-mediated adverse reaction, however, differed from C1 INH deficiency-associated angioedema in that there was also hypotension and renal failure.

There has been controversy about the mediator or mediators responsible for the increased vascular permeability causing the bouts of edema in C1 INH deficiency. Histamine has no role in this type of edema, which seems to be due to an excessive production of kinin-like substances (e.g., bradykinin).^{9,10} With regard to this underlying mechanism, in a letter, Shepherd¹¹ expressed concern about the administration of ACE inhibitors (captopril, enalapril, and lisinopril) to patients with HAE. In 1991, Agostino et al.¹² presented two patients with C1 INH deficiency exhibiting adverse reactions after intake of an ACE inhibitor (captopril). The first patient, a 68-year-old man with a monoclonal gammopathy and acquired angioneurotic edema, was first seen with angioedema that occurred four times within 24 hours after taking captopril. The second patient, a 38-year-old woman with dysfunctional type II HAE, had severe hypotension immediately after initial administration of captopril. However, it had not been ruled out that the reaction is due to the hypotensive effect of captopril, eventually maximized by the presence of C1 INH deficiency. No other cases have been reported.

To our knowledge, our case report is the first presentation of a patient with quantitative HAE (type I) experiencing recurrent episodes of anaphylactoid reactions precipitated by the administration of an ACE inhibitor. The diagnosis of C1 INH deficiency was suspected on the basis of nearly absent hemolytic activity, measured by the CH₅₀ assay, and depressed levels of C4 and functional C1 INH activity. The diagnosis of type I HAE was based on the presence of life-long bouts of mucocutaneous edema, a familial history of angioedema, normal C1q levels, and decreased quantitative levels of C1 INH. The striking correlation between ACE inhibitor administration and the attacks of angioedema and hypotension suggested that they were probably drug-induced. The negative skin test and lymphocyte transformation test responses to enalapril did not contribute to the diagnosis of a primary enalapril-induced anaphylactoid reaction. Because complement activation occurred in incubated blood samples, irrespective of the presence or absence of enalapril, a complement-activation and/or C1 INH consumption by enalapril could not be evaluated. From our data, it seems that patients with hereditary C1 INH deficiency are particularly prone to develop anaphylactoid reactions to administration of an ACE inhibitor.

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