
Angiotensin converting enzyme inhibitor-induced angioedema more prevalent in transplant patients

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Background: Angioedema in association with angiotensin converting enzyme inhibitor (ACEI) use is rare, but serious. Which patients are predisposed to the reaction and whether it involves an immune mechanism remain unclear.

Objectives: To determine the frequency of ACEI angioedema in immunosuppressed cardiac and renal transplant patients.

Methods: This was a retrospective chart review of all adult cardiac (n = 156) and renal (n = 341) transplant patients followed at our hospital (years 1985 to 1995).

Results: Of 105 cardiac and 91 renal transplant patients on a combination of immunosuppressive and ACEI therapy, 5 (4.8%) cardiac and 1 (1%) renal patients developed angioedema. This prevalence of ACEI angioedema among cardiac and renal transplant patients is 24 times and 5 times higher, respectively, than that observed in the general population (0.1% to 0.2%). Reactions often appeared after prolonged ACEI use (average 19 months; range 3 days to 6.3 years). African-Americans were significantly more likely to experience ACEI-associated angioedema ($P = .034$), especially among the cardiac patients where 4 of 5 reactors were African-American.

Conclusions: For unclear reasons, ACEI-induced angioedema (often late-onset) is more prevalent among immunosuppressed cardiac and renal transplant patients. Additionally, African-Americans are over-represented among those developing the reaction.

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INTRODUCTION

Angioedema has been recognized as a rare, yet potentially life-threatening complication of angiotensin converting-enzyme inhibitors (ACEI) for nearly 15 years. Although a few case reports have described sudden occurrences of angioedema after months or years of ACEI use, most reactions occur within the first week of therapy. The mechanism by which ACEI cause angioedema is not understood and in-

volvement of the immune system remains speculative. Furthermore, there are no drug or patient-related risk factors to identify susceptible individuals.

We present 6 cases of transplant recipients on chronic immunosuppressive therapy in whom ACEI-induced angioedema developed, often after many months or years. In addition, most patients (5/6) were African-American, a finding unrecognized in the past.

PATIENTS AND METHODS

A retrospective chart review of 156 consecutive cardiac transplant patients and 341 renal transplant patients (1985 to 1995) was undertaken to determine the prevalence of ACEI-induced angioedema in this population. Six transplant patients (1 renal, 5 cardiac) developed ACEI angioedema.

All 5 cardiac patients underwent transplantation for either viral or idiopathic cardiomyopathy. The renal patient had end stage renal disease due to chronic glomerulonephritis. All cardiac patients were maintained on ACEIs at some point prior to transplantation without reported adverse reactions. All cardiac patients except one were initially started on captopril shortly after transplantation and tolerated it well. All were later converted to enalapril, a longer acting agent. All cardiac and renal transplant patients were maintained on cyclosporine and azathioprine; some additionally on prednisone or medrol. The amount of immunosuppression administered to the study patients at the time of the episodes of angioedema did not significantly differ from the amount given to the remaining patients on ACEI who did not develop angioedema.

In all six patients, the reaction of angioedema involved either the lips (patient 6) and entire face (patients 2 and 5) or tongue (patients 1, 3 and 4), which is consistent with the unique propensity of ACEI to involve the head and neck region. In patients 1, 4, 5, and 6, the angioedema was objectively witnessed by a physician.

In some patients, the relationship between ACEI use and symptoms was not immediately recognized. Patient 1 developed episodic tongue swelling 4 months after enalapril use. His reactions were erroneously attributed to metabisulfite sensitivity as the patient was frequenting restaurant salad bars. Almost 2 years later, after developing angioedema with lisinopril-hydrochlorothiazide, the patient was finally taken off ACEI. Patient 4 first noted tongue and cheek swelling 2 years af-

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ter starting enalapril. Her symptoms were attributed to tension and anxiety and she remained on the enalapril. Seven months later, she required hospitalization for laryngeal edema with upper airway compromise. All cases have now been followed an average of 2.5 years since discontinuation of ACEI therapy with no recurrence of angioedema.

RESULTS

Of all patients studied, 105/156 (cardiac) and 91/341 (renal) were on ACEI at some point during their posttransplant care. Overall, 6 patients (5 cardiac and 1 renal) were found to have one or more typical reactions of isolated angioedema (9 reactions in 6 patients). Virtually all cardiac and 27% (25/91) of the renal transplant patients were on daily aspirin (ASA). Seven of 9 reactions occurred in patients on concomitant ASA therapy.

Patient characteristics are shown in Table 1. The drug reaction in the renal transplant patient occurred within 7 days. A total of 8 ACEI-induced angioedema reactions occurred in 5 cardiac transplant patients and were usually late in onset (patient 1: 4 and 14

months; patient 2: 6.3 years; patient 3: 3.5 years and 3 days; patient 4: 2 years; patient 5: 4 months and 1 year). The mean age of the cardiac transplant patients was 50 (range 39 to 59). The renal transplant patient was 61 years old. There was a total of 4 males, 2 females; 1 Caucasian, 5 African-Americans. Overall, the prevalence of African-Americans among cardiac transplant patients was 14% (15/105), whereas this group represented 80% (4/5) of ACEI reactors ($P = .034$ by chi square).

The reported frequency of ACEI-induced angioedema is 0.1% to 0.2%.¹ Our findings demonstrate a prevalence of 4.8% (8 reactions per 5 patients out of 105) in cardiac transplant patients and 1% in renal transplant patients. These rates are 24 times and 5 times higher, respectively, than that reported in the literature.

DISCUSSION

It is known that beyond the first week of therapy, the incidence of ACEI-induced angioedema declines sharply with no clear temporal trend thereafter.¹ Most of the first time reactions we present occurred many months (aver-

age 19 months, range 3 days to 6.3 years) after ACEI use. Two patients (patient 1 and patient 4) had intermittent episodes of angioedema either dismissed or erroneously attributed to food allergy or psychologic factors by the patient and/or physician. These cases demonstrate the need for both patients and physicians to maintain a high index of suspicion for any swelling episodes with the use of ACEI, regardless of duration of therapy.

Our cases corroborate previous observations that angioedema with one agent does not guarantee a similar reaction with a different agent.¹ Conversely, previous tolerance to one agent does not exclude risk for angioedema with another agent.² Additionally, a previous reaction with one agent does not necessarily predict earlier onset of a subsequent reaction with a different agent, as demonstrated by patients 1, 3, and 5.

The recognition of personal, genetic, or other risk factors for drug allergy can make clinical reactions to drugs more predictable.³ Pigman et al⁴ reported that patients with ACEI-induced angioedema compared with patients with non-ACEI angioedema

Table 1. Clinical Features of Six Adult Transplant Recipients with ACEI Angioedema

Patient Number*	Age	Race	Sex	Agent† (duration of therapy‡)		Immunosuppressive Regimen (mg/day)			ASA Use
				No Reaction	Angioedema	Prednisone	Azathioprine	Cyclosporine	
1	48	African-American	Male	1) captopril (18 m)	2) enalapril (4 m)	2.5	150	250	yes
				3) lisinopril§ (8 m)	4) lisinopril-HCTZ (14 m)				no
2	59	African-American	Male	1) captopril (3 m)	2) enalapril (6.3 y)	5	250	320	yes
3	53	African-American	Female	1) captopril (4 m)	2) enalapril (3.5 y)	none	100	200	yes
					3) lisinopril-HCTZ (3 d)				yes
4	51	Caucasian	Female		1) enalapril (2 y)	none	50	140	yes
5	39	African-American	Male	1) captopril (1 m)	2) enalapril (4 m)	12.5	175	660	yes
					3) lisinopril (1 y)				no
6	61	African-American	Male		1) lisinopril (7 d)	none	50	300	yes

* Patients 1–5 have had cardiac transplants and patient 6 has had a renal transplant.

† Listed in chronologic order of use.

‡ In days (d), months (m), and years (y).

§ Lisinopril refers to Prinivil® throughout the manuscript.

|| Hydrochlorothiazide.

were older and had less of an allergic history. Jain et al⁵ identified risk factors for upper airway obstruction with ACEI use including marked obesity, previous intubations, and face and neck surgery. In our study, African-Americans were more likely to develop angioedema. This corroborates recent data showing African-Americans to be at increased risk for ACEI angioedema, presumably due to their increased sensitivity to bradykinin.⁶

While sustained immune responses to drugs are more likely in adults with specific human leukocyte antigen (HLA) phenotypes,³ we found no HLA phenotypes unique to the 5 cardiac transplant patients who developed angioedema.

Bacteria, viruses, and parasites can produce factors that have immunoregulatory properties. This is exemplified by the high frequency of cutaneous reactions to ampicillin in patients with infectious mononucleosis.³ None of the angioedema episodes we describe, however, were associated with apparent clinical infections. Furthermore, the total white blood cell counts of the patients close to the time of the reactions were within the expected range.

There is evidence that certain drug reactions are more prevalent among immunocompromised patients. Adverse reactions to sulfonamides, dapsone, and rifampin occur in human immunodeficiency virus (HIV)-infected patients at rates at least 10 times higher than that in the general population. The disordered immunoregulatory environment in HIV-infected patients favors formation of IgE, G, M, and A antibodies to sulfamethaxazole.³ Previous animal studies of the effects of irradiation, adult thymectomy or splenectomy, or immunosuppressive agents have revealed an enhancement of IgE antibody production. Marked elevations of serum IgE concentrations have been reported in both acute and chronic graft-versus-host-disease (GVHD). These elevations are thought to be due to a deficiency of T cells important in the down regulation of IgE synthesis. Patients with GVHD

may develop allergic reactions to antibiotics or dietary antigens without history of such reactions occurring prior to transplantation.⁷

While it is attractive to theorize that immunosuppression is responsible for the increased prevalence of ACEI angioedema in our study, it should be pointed out that drug-specific antibodies have not been consistently detected in ACEI angioedema reactions.^{8,9} Immunosuppression may, however, modulate ACEI angioedema by its effects on the control of inflammatory mediators.

Bradykinin accumulation and its effects on prostaglandins, leukotrienes, and substance P is thought to be the cause of cough and/or angioedema induced by ACEI. Concurrent inhibition of prostaglandin formation with non-steroidal anti-inflammatory drugs (NSAIDs) would be expected to attenuate these reactions.¹⁰ One uncontrolled study showed that sulindac (an NSAID) inhibited ACEI cough; however, another study found that patients with ACEI cough were more likely to be taking ASA.¹¹ It is well known that a subset of patients with chronic urticaria experience flares of hives with or without angioedema after ingesting ASA or NSAIDs.¹² Since 7 of 9 reactions we present occurred in patients on daily ASA, we question whether ASA is playing a role as cofactor in mediating ACEI-induced angioedema.

Treatment with the recently introduced angiotensin II receptor blocker Losartan (Cozaar, Merck) has resulted in two reported cases of angioedema. One occurred in a patient with a prior history of ACEI cough¹³ and the other in a patient with a history of ACEI angioedema.¹⁴ Such reports cast doubt on bradykinin accumulation as the sole mechanism responsible for ACEI angioedema as angiotensin II receptor blocker medications should not affect bradykinin levels. Other factors, such as dysregulation of the plasma renin-angiotensin system (RAS) may contribute to angioedema formation. Previous findings suggest a possible role of the RAS in hymenoptera venom anaphylaxis. Angiotensin II itself has been shown to modulate some inflam-

matory and immune functions such as proliferation and differentiation of lymphocytes in vitro.¹⁵ While data in the literature suggest an interaction between the RAS and the immune system, it is too preliminary to directly explain our findings. Clearly, further studies are needed to better characterize the impact of immunosuppression on the development of ACEI angioedema.

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