

Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor

To the Editor:

In October 1991, French investigators reported 2 cases of severe anaphylactic reactions to low-dose venom immunotherapy injections in patients taking an angiotensin-converting enzyme (ACE) inhibitor.¹ Patient 1 was a 52-year-old hypertensive male who had been taking enalapril (20 mg daily) for 2 years. A few minutes after his first venom immunotherapy injection, he had generalized pruritis, with a decrease in blood pressure. He recovered quickly after administration of intravenous dextran. After enalapril administration was stopped 24 hours before his venom injections, he was able to achieve a monthly maintenance dose of 100 µg of wasp venom. On the third month of venom therapy, the patient again experienced a severe anaphylactic reaction requiring oxygen, dextran, and epinephrine. The patient admittedly had forgotten to stop his enalapril the day before. No more reactions were observed after enalapril was consistently discontinued 24 hours before venom administration.

Patient 2 was a 34-year-old hypertensive male taking a β -blocker drug who was changed to the ACE inhibitor enalapril before initiating venom immunotherapy. After his second injection of venom immunotherapy, he experienced an anaphylactic reaction. His ACE inhibitor was replaced with a calcium blocker (nifedipine), and venom immunotherapy was continued. A few months later, after nifedipine was discontinued and enalapril was reintroduced, venom immunotherapy again triggered an anaphylactic reaction. Enalapril was then stopped, and venom therapy was continued without adverse effects. The authors postulated the alterations in the kinen system, possibly a buildup of bradykinin induced by ACE inhibitor drugs, predisposed these 2 patients to anaphylactic reactions. They cautioned that ACE inhibitors be used with caution in allergic patients undergoing desensitization and avoided in those undergoing venom immunotherapy.

The following case report describes our recent experience with a patient taking an ACE inhibitor while undergoing venom immunotherapy. The patient is a 43-year-old hypertensive male with type II diabetes who had been taking ACE inhibitors for 2 years (40 mg of lisinopril for 5 months) and had a long history of shellfish (shrimp) anaphylaxis. In November 2001, he experienced a grade IV (hypotensive) systemic reaction to a stinging insect that responded to appropriate emergency department care. Subsequent skin tests demonstrated sensitivity to shrimp, crab, and lobster and all hymenoptera venoms (at the 0.1 µg level), except honeybee venom. In March 2002, he was started on venom immunotherapy. In July

2002, 5 minutes after receiving venom immunotherapy maintenance doses of 0.80 mL of wasp venom (100 µg/mL) and 0.80 mL of mixed vespoid venom (300 µg/mL), he became flushed, dizzy, diaphoretic, and hypotensive (ie, blood pressure of 60/40 mm Hg). A code blue was called, and the patient was given 50 mg of intramuscular Benadryl, intravenous saline, oxygen, and 1:1000 epinephrine (0.30 mL) times 3. After 25 minutes of therapy, his blood pressure stabilized at 105/70 mm Hg. He was then transported to a local emergency department and given intravenous Solu-Medrol. Four hours later, he was discharged in stable condition. After the ACE inhibitor was replaced with a calcium blocker, he was restarted on venom immunotherapy. He now tolerates full-strength venom immunotherapy injections. This patient has no signs or symptoms of systemic mastocytosis, and his serum tryptase level is normal.

These reports and the published literature suggest that the combination of ACE inhibitors and venom immunotherapy might be a risk factor for anaphylaxis in a subset of patients. Kemp and Lieberman² cited that the 1996 Physician's Desk Reference prescribing information for 9 ACE inhibitors all warned of the potential for anaphylaxis when prescribed to patients who receive venom immunotherapy. Reports from Germany have described patients with stinging insect allergy taking ACE inhibitors and receiving venom immunotherapy who had recurrent anaphylaxis either from immunotherapy or sting provocation.³ These patients had significantly lower rennin, angiotensinogen, angiotension I, and angiotension II levels than patients who did not have repeated episodes of anaphylaxis with immunotherapy or stings.^{4,5} None of the 17 patients who died after skin tests and immunotherapy were taking ACE inhibitor drugs.⁶ A preliminary report by the Immunotherapy Committee at the 2003 American Academy of Allergy, Asthma, and Immunology meeting noted that one of 17 patients who died after immunotherapy was taking an ACE inhibitor medication. The increased risk of anaphylaxis posed by use of ACE inhibitor drugs in patients undergoing renal dialysis has been well documented in several studies.⁷

The 1998 Practice Parameter on the Diagnosis and Management of Anaphylaxis notes that there are data indicating that patients taking ACE inhibitors might be at increased risk for development of anaphylaxis, as well as being more refractory to treatment if anaphylaxis develops.⁸ The 1999 Practice Parameter on Stinging Insect Hypersensitivity states, "Patients who are taking β -adrenergic blocking agents and possible patients taking ACE inhibitors are at greater risk if they experience an allergic reaction and in the case of ACE inhibitors, might be at greater risk of having an allergic reaction. Therefore, patients who have stinging insect hypersensitivity should not be prescribed β -adrenergic blocking agents or ACE inhibitors unless absolutely necessary. If the

patients who has stinging insect hypersensitivity cannot discontinue these medications, venom immunotherapy should still be given, but with greater caution.”⁹ The recently published Practice Parameters on Allergen Immunotherapy do not address the ACE inhibitor issue and cite only β -adrenergic blocking agents as a risk factor or relative contradiction for immunotherapy.¹⁰

Systemic anaphylaxis can trigger catecholamine release and activate the rennin-angiotension-aldosterone system. Because ACE inhibitors inhibit the metabolism of angiotension, leading to a buildup of bradykinin and substance P, one can postulate that ACE inhibitor therapy might predispose some individuals to anaphylaxis. Because the use of these important ACE inhibitors is constantly expanding throughout medicine, case reports should be gathered and studies undertaken to determine whether there is an association between ACE inhibitors and anaphylactic events triggered by inhaled, oral, or injected allergens, especially venom. In light of our recent experience, we are now advising our patients undergoing venom immunotherapy who require ACE inhibitor therapy not to take their ACE inhibitor 24 hours before their venom injection visit.

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