Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy

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Background: Case reports have raised concern about concurrent use of angiotensin-converting enzyme inhibitors (ACE-Is) in patients receiving venom immunotherapy (VIT). No surveys have been performed on the number of venom allergic patients who take ACE-Is and their outcomes.

Objective: To survey the use of ACE-Is and systemic reaction (SR) characteristics in patients receiving VIT.

Methods: A retrospective medical record review was performed on all patients evaluated for Hymenoptera venom allergy at a single center from 2000 to 2005. Patient records were evaluated for presenting symptoms, specific IgE testing, VIT treatment course, ACE-I use during VIT, and the presence of any SRs to field stings or VIT.

Results: Of 288 patients evaluated from 2000 to 2005 for Hymenoptera venom allergy, 157 were found to have venom specific IgE. Of these 157 patients, 79 (50%) of those with Hymenoptera venom allergy underwent VIT. Seventeen of these 79 patients (21%) were taking an ACE-I during VIT. The mean overlap of a patient taking an ACE-I with the time they were receiving VIT was 30.9 months (range, 3–114 months). Patients taking ACE-Is were older (mean age, 56.2 vs 36.4 years; $P < .001$) and received VIT for a longer period (mean, 72.3 vs 29.9 months; $P < .04$). Thirteen of 62 patients not taking an ACE-I (21%) experienced an SR during their VIT. No patients taking an ACE-I experienced an SR to VIT while taking an ACE-I ($P = .03$).

Conclusions: This study suggests that there is not an association between ACE-I use and increased frequency of SRs to venom immunotherapy.

Ann Allergy Asthma Immunol. 2008;101:426–430.

INTRODUCTION

Venom immunotherapy (VIT) is life saving for venom-induced anaphylaxis.[1] Data have emerged during the last 2 decades regarding a potential risk for venom allergic patients who take angiotensin-converting enzyme inhibitors (ACE-Is). It is not known whether this risk is potentially extended to other patients at risk for anaphylaxis. Several case reports have been published of severe systemic reactions (SRs) in venom allergic individuals to either VIT or field stings when taking ACE-Is.[2–5] In 2 of the reported cases, reactions ceased when the ACE-I was withheld for at least 24 hours before VIT injection, then recurred when the ACE-I was reintroduced.[2] The other case reports described severe SRs in patients taking an ACE-I at the time of a Hymenoptera sting, but a rechallenge was not performed after stopping use of the ACE-I.[3–5]

Several studies have demonstrated a correlation between decreased levels of serum angiotensin I and II and increased risk for more severe Hymenoptera anaphylaxis and increased incidence of VIT failure.[6–9] It has also been found that serum levels of angiotensin I and II approached those of healthy controls in allergic patients after successful VIT.[7,8] Urinary angiotensin I and II levels have been found to be elevated in patients shortly after anaphylactoid reactions; this observation has been suspected to be due to release during stress.[10] ACE-Is have been implicated as a possible cause or contributor to anaphylactoid reactions in dialysis patients using high-flux dialysis membranes through increased bradykinin levels.[11–15]

In reflecting on these data, the Stinging Insect Hypersensitivity Practice Parameter[1] and ACE-I package inserts[16] mention a possible increased risk of SR to VIT when patients are concomitantly taking an ACE-I. Because the clinically driven end points for these statements appear to be limited to case reports, we elected to explore this question more thoroughly by examining ACE-I use and clinical outcomes in a population of patients receiving VIT at a single medical center.

METHODS

At our medical center, records are kept of all venom allergy clinic referrals. In addition, an electronic medical record has been in existence for patients followed up in the allergy clinic since the year 2000. After local institutional review board approval, this record was queried from the years 2000 to 2005 to examine patients who had been evaluated for venom allergy at our facility. Because we are a tertiary referral center, some of our patients are referred for venom evaluation from outside the area. Patients receiving VIT from outside the area

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Disclosures: Authors have nothing to disclose.

Disclaimer: The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Department of the Air Force, the US Department of Defense, or the US government.

Previous Presentation: Data from this letter were presented as a 10-minute slide presentation during the 2007 meeting of the American College of Allergy, Asthma and Clinical Immunology in Dallas, Texas, November 2007. It has not been otherwise disseminated or published.

Received for publication March 19, 2008; Received in revised form June 4, 2008; Accepted for publication June 15, 2008.

were not followed up in this study. Review and recording of information from the electronic medical record included patient demographics, presenting symptoms, specific IgE testing (skin and/or serologic testing), treatment course, SR to VIT (as documented by the allergist), and SR to field stings (as reported during the VIT by the patient during follow-up). In assessing the presenting symptoms and the subsequent SRs to VIT and field stings, the following anaphylaxis classification was used: grade 1, cutaneous symptoms only (eg, urticaria and/or angioedema); grade 2, cutaneous symptoms and evidence of other system involvement but not hypoxia or hypotension (eg, urticaria and wheezing); and grade 3, multisystem involvement, including hypotension or hypoxia.[17] Flying Hymenoptera are first tested with skin prick testing at 1 μg/mL. If the results are negative, intradermals (IDs) are placed: first ID, 0.001 μg/mL; second ID, 0.01 μg/mL; third ID, 0.1 μg/mL; and fourth ID, 1 μg/mL; stopping when a positive test result occurs or the patient reaches the last ID test. Imported fire ant testing is performed with whole body extract with corresponding doses as follows: prick, 1:1,000 wt/vol; first ID, 1:1,000,000 wt/vol; second ID, 1:100,000 wt/vol; third ID, 1:10,000 wt/vol; and fourth ID, 1:1,000 wt/vol. The patients' demographic information was cross-referenced with our medical center's electronic pharmacy database to determine the type and duration of ACE-I therapy if prescribed. An ACE-I was considered to be taken if it was prescribed with refills and if at least 1 refill was obtained. In our clinic, we do not routinely stop ACE-I therapy in patients receiving VIT. For statistical analysis, the Student *t* test was used to evaluate the significance of differences in age, sex, and length of time receiving immunotherapy between groups, and the Fisher exact test was used to evaluate the difference in SR between the 2 groups.

Table 1. Overview of Patients Receiving Venom Immunotherapy at our Facility in 2000–2005

Variable	No. (%) of patients (n = 79)[a]
Age, mean (SD), y	36.4 (16.8)
Male	46/79 (58)
Asthmatic	20/79 (25)
Reaction at presentation[b]	
Grade 1	10/79 (13)
Grade 2	57/79 (72)
Grade 3	12/79 (15)
Hymenoptera monosensitized	48/79 (61)
Imported fire ant	36/48 (75)
Honeybee	7/48 (15)
Wasp	4/48 (8)
Yellow jacket	1/48 (2)
Hornet	0/48 (0)
Hymenoptera polysensitized	31/79 (39)
Imported fire ant and flying insect	8/31 (26)
Mixed flying insect	23/31 (74)
No. of months receiving VIT, mean (SD)	39 (46)

Abbreviation: VIT, venom immunotherapy

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] See the "Methods" section for an explanation of the presenting reactions (grades 1–3).

RESULTS

Of 288 patients evaluated from 2000 to 2005 for Hymenoptera venom allergy, 157 were found to have specific IgE (90 to imported fire ant, 54 to yellow jacket, 54 to hornet, 60 to wasp, and 43 to honeybee; many patients had a positive skin test result to more than one). VIT was recommended for patients with a history of a SR and evidence of venom specific IgE, with the exception of patients younger than 16 years who had grade 1 reactions only.[1] Seventy-nine of the 157 allergic patients (50%) underwent VIT at our facility. An overview of the patients who underwent VIT is given in Table 1. Seventeen of the 79 patients receiving VIT (21%) took an ACE-I during their immunotherapy (Table 2). The average overlap of a patient taking an ACE-I with the time they were receiving VIT was 30.9 months (range, 3–114 months). Fifteen patients took lisinopril, 6 took ramipril, and 1 patient took benazepril (5 patients took more than 1 ACE-I during VIT). Of the 17 patients receiving ACE-Is and VIT, 10 patients started taking the ACE-I after starting VIT (1 during buildup) and 7 patients continued taking the ACE-I at the time VIT was started. Patients taking ACE-Is were significantly older (mean age, 56.2 vs 36.4 years; $P < .001$) and received VIT for a longer period than those who were not taking an ACE-I (mean, 72.3 vs 29.9 months; $P < .04$). Of the 17 patients taking ACE-Is, 14 had the concentration at which their skin test result became positive recorded (82%). Those without a level were recorded as having a positive result. Of those 14 patients, their average skin test response (using the more sensitive result if there were multiple positive results) was between the first and second ID tests (0.001 μg/mL and 0.01 μg/mL for flying Hymenoptera, 1:1,000,000 wt/vol and 1:100,000 for imported fire ant). Of the 62 patients not taking ACE-Is, 44 had the level at which their skin test result turned positive recorded (71%). Of those 44 patients, their average skin test response was also between the first and second ID tests.

Thirteen of 62 patients (21%) not taking an ACE-I experienced an SR to VIT during their VIT. No patient taking an ACE-I experienced an SR to VIT or field stings while taking an ACE-I ($P = .03$) (Table 3). In the 13 patients not taking ACE-Is who had SRs to VIT, 8 had symptoms of a similar grade on SR (all were grade 2), 4 had symptoms of a lesser grade, and 1 patient who had grade 1 symptoms on presentation had grade 2 symptoms on SR to VIT. Twenty-two of the 62 patients (35%) not taking an ACE-I reported having a field sting during their VIT course, and 5 of the 22 (23%) had an SR to the sting. In the 5 patients not taking ACE-Is who had SRs to a field sting, 4 had symptoms of a lesser grade on SR and 1 patient who had grade 2 symptoms on presentation had grade 2 symptoms on field sting. Twelve of the 17 patients (71%) taking an ACE-I reported having field stings,