

Are ACE inhibitors really safe in the patients receiving venom immunotherapy?

ACE inhibitörleri venom immünoterapisi alan hastalarda gerçekten güvenli midir?

Mehmet ÜNSEL¹, F. Ömür ARDENİZ¹, Nihal METE¹, Aytül Z. SİN¹

¹ Division of Immunology and Allergy, Department of Internal Medicine, Faculty of Medicine, Ege University, Izmir, Turkey
Ege Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İmmünoloji ve Allerji Bilim Dalı, İzmir, Türkiye

ABSTRACT

Few reports have been notified regarding systemic allergic reactions in patients being put on angiotensin converting enzyme (ACE) inhibitor during the course of venom immunotherapy. There have been conflicting suggestions with respect to ACE inhibitor use during the course of VI in the literature. There is no consensus report clarifying this issue in the clinical practice. Herein we reported a case experienced anaphylaxis after being put on angiotensin converting enzyme (ACE) inhibitor and beta-blocker therapy by reason of heart attack while receiving venom immunotherapy injections with *Apis mellifera* in the maintenance phase and discussed the likely causative factors.

(*Asthma Allergy Immunol 2012;10:100-103*)

Key words: Venom immunotherapy, ACE inhibitor, anaphylaxis, beta-blocker

Received: 20/01/2012 • Accepted: 19/02/2012

INTRODUCTION

Few reports have been notified regarding systemic allergic reactions in patients being put on angiotensin converting enzyme (ACE) inhibi-

ÖZ

Venom immünoterapisi sırasında anjiyotensin dönüştürücü enzim (ACE) inhibitörü başlandıktan sonra sistemik allerjik reaksiyon gelişimini bildiren olgu sunumları mevcuttur. Literatürde bu hastalarda ACE inhibitörü kullanımına ilişkin birbiriyle çelişen öneriler bulunmaktadır. Burada, *Apis mellifera* ile venom immünoterapisi almakta olan hastada idame fazında iken, kalp krizi nedeniyle ACE inhibitörü ve beta-bloker başlandıktan sonra sistemik allerjik reaksiyon gelişen bir olgu sunuldu. Ayrıca, sistemik allerjik reaksiyon gelişimine zemin hazırlayan olası mekanizmalar tartışıldı.

(*Asthma Allergy Immunol 2012;10:100-103*)

Anahtar kelimeler: Venom immünoterapi, ace inhibitörü, anafilaksi, beta bloker

Geliş Tarihi: 20/01/2012 • Kabul Ediliş Tarihi: 19/02/2012

tor during the course of venom immunotherapy^[1,2]. There have been conflicting suggestions with respect to ACE inhibitor use while receiving venom immunotherapy during the co-

urse of venom immunotherapy in the literature^[3-5]. There is no consensus report clarifying this issue in the clinical practice^[6]. Furthermore, the underlying mechanisms leading to systemic reaction are not known. Herein we reported a case experienced anaphylaxis after commenced on ACE inhibitor and beta-blocker therapy while receiving venom immunotherapy injections with *Apis mellifera* in the maintenance phase and discussed the likely causative factors.

CASE REPORT

A 42-year-old man with the history of grade 4 anaphylaxis (cardiac arrest and apnea) after being stung by a honeybee was evaluated^[7]. Skin prick test (ALK-Abello, Spain) and specific IgE measurement (CAP system Pharmacia Uppsala, Sweden) were found to be positive for *Apis mellifera*. Immunotherapy with *Apis mellifera* venom was introduced. The build-up period had been completed successfully and maintenance therapy was commenced. He was given 1 mL of the venom (100.000 SQ/mL, ALK-Abello, Spain) per month without any reaction. Nevertheless, the venom injections had to be stopped by reason of an heart attack two months after commencing maintenance therapy. His immunotherapy was reintroduced with the dose of 0.1 mL of the venom (100.000 SQ/mL, ALK-Abello, Spain) three months after this event. He tolerated the maintenance dose of 0.6 mL uneventfully. Nonetheless, he experienced itching all over the body followed by unconsciousness within five minutes following administration of 0.8 mL of the venom and his blood pressure could not be measured. Epinephrine was not administered because of recent heart attack and normalization of the blood pressure soon after intensive saline infusion and 100 mg intravenous methylprednisolone administration. The tryptase level measured in the blood sample taken one hour after the reaction was found to be increased (30 µg/L, normal value: < 11.4) compared with basal tryptase level of 10 µg/L. Since he had tolerated the maintenance dose of 1 mL before, his treatment was reevaluated. Questioning revealed

that the patient had been started on perindopril (ACE inhibitor) and carvedilol (beta-blocker) after the heart attack.

DISCUSSION

There have been few cases reported to experience systemic allergic reaction after commenced on ACE inhibitor therapy (two with enalapril and one with lisinopril) during venom immunotherapy. Authors reported that there had been no allergic reaction after stopping ACE inhibitor 24 hours prior to venom injections or replacing it with a calcium channel blocker^[1]. Therefore we stopped perindopril intake 48 hours before injections in taking into account of its longer half life (24 hours) when compared with enalapril and lisinopril in order to minimize the risk of anaphylaxis and avoid adrenaline use. Carvedilol was also discontinued. He did not experience an anaphylactic episode after re-introduction of the venom immunotherapy and completed his immunotherapy without any allergic reaction.

To our knowledge, there is no report of anaphylaxis in the patients commenced on ACE inhibitor while receiving immunotherapy with aeroallergens. This raises the question as to whether an interaction between the venom ingredients and bradykinin might play a role in development of anaphylaxis.

Our patient experienced anaphylaxis while on venom immunotherapy with *Apis mellifera*. It contains phospholipase A2, mellitin and hyaluronidase^[8]. Mellitin is known as a potent activator of membran-bound kallikreins leading to increase in kinin activity^[9]. Phospholipase A2 has been shown to enhance kallikrein activity that might lead to bradykinin synthesis^[9]. Bradykinin is known to activate mast cells and it can lead to mediator release such as tryptase^[10]. Tryptase has been shown to increase vascular permeability by means of enhancing bradykinin release^[11]. Therefore, it can contribute to significant bradykinin surge in the patients who have already high bradykinin levels due to ACE inhibitor use.

The vespid venom contains substances similar to *Apis mellifera* venom, which might also play role in activating kinin system^[8,12]. One of these, phospholipase A1, has been shown to activate mast cells. The interaction between this compound and kallikrein-kinin system, if any, is yet to be elucidated^[13]. Furthermore, wasp venom has been shown to contain bradykinin^[14].

A survey revealed that subjects experiencing systemic reactions with venom exposure had spontaneous kinin system hyperreactivity^[15]. Herman et al., suggested that patients experiencing anaphylaxis upon stung by bee during venom immunotherapy have significantly lower levels of plasma angiotensin I and angiotensin II compared with healthy and non-allergic subjects or patients without a history of anaphylaxis^[16]. The authors suggested that a defective renin-angiotensinogen system (RAS) might lead to increased tendency to anaphylaxis upon venom exposure^[17]. In this context, ACE inhibitors may play a contributory role to the tendency of systemic allergic reaction in the subjects who have already dysfunctional RAS by virtue of increased bradykinin levels and decrease in the generation of angiotensin II^[5].

Rueff et al. demonstrated that higher tryptase concentration and ACE inhibitor use were significantly associated with severe anaphylactic reaction after a field sting in untreated patients^[18]. They showed that systemic reaction risk markedly increased when serum tryptase level was above 5 µg/L. The authors suggested that ACE inhibitors be substituted to prevent severe anaphylactic reactions in the patients not protected by venom immunotherapy.

In a recent study, none of the 17 patients taking ACE inhibitors during venom immunotherapy had experienced a systemic reaction^[3]. The author suggested that ACE inhibitors should not necessarily be discontinued during venom injections. However, 8 of the 17 subjects were reported to receive immunotherapy with fire-ant known to contain less venom protein.

Additionally, the number of the patients was not enough to draw a definite conclusion regarding the safety of ACE inhibitor use.

Our patient was concomitantly on beta-blocker therapy. Carvedilol might have played a role in development of hypotension in the absence of tachycardia. However, the reduced blood pressure can not solely be explained by carvedilol taking into account of significantly raised tryptase level.

Rueff et al. cited that the effect of concomitant beta-blocker therapy on development of severe systemic reaction might be much smaller than that of ACE inhibitor medication and tryptase concentration^[18]. Several studies concluded that systemic reaction rate was very similar with and without beta-blockers^[19,20].

In summary, Hymenoptera venom consists of many proteases and allergens such as phospholipases which might enhance kallikrein-kinin activity. Increased kinin activity might pose an additive impact in the subjects taking ACE inhibitors especially those who have already impaired kinin metabolism. Larger population-based studies analysing these factors are needed to determine the patients prone to a systemic-reaction on ACE inhibitor therapy. It would be prudent to stop ACE inhibitor 24-48 hours prior to venom injections according to its half-life especially in patients with high serum tryptase level.

REFERENCES

1. Ober AI, MacLean JA, Hannaway PJ. Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor (letter). *J Allergy Clin Immunol* 2002;112:1008-9.
2. Tunon-de-Lara JM, Villanueva P, Marcos M, Taytard A. ACE inhibitors and anaphylactoid reactions during venom immunotherapy. *Lancet* 1992;340:908.
3. White KM, England RW. Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy. *Ann Allergy Asthma Immunol* 2008;101:426-30.

4. Kemp SF, Lieberman P. Inhibitors of angiotensin II: potential hazards for patients at risk for anaphylaxis? *Ann Allergy Asthma Immunol* 1997;78:527-9.
5. Stumpf JL, Shehab N, Patel AC. Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. *Ann Pharmacother* 2006;40:699-703.
6. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol* 2011;127:852-4.
7. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;1:466-9.
8. Bilo BM, Rueff F, Mosbech H, Bonifazi F, Oude-Eberink JN. EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60:1339-49.
9. Nishimura H, Alhenc-Gelas F, White A. Activation of membrane-bound kallikrein and renin in the kidney. *Proc Natl Acad Sci USA* 1980;77:4975-8.
10. Bandeira-Melo C, Calheiros AS, Silva PM, Cordeiro RS, Teixeira MM, Martins MA. Suppressive effect of distinct bradykinin B₂ receptor antagonist on allergen-evoked exudation and leukocyte infiltration in sensitized rats. *Br J Pharmacol* 1999;127:315-20.
11. Imamura T, Dubin A, Moore W, Tanaka R, Travis J. Induction of vascular permeability enhancement by human tryptase: dependence on activation of prekallikrein and direct release of bradykinin from kininogens. *Lab Invest* 1996;74:861-70.
12. Gökmen NM. Venom biochemistry. *Türkiye Klinikleri J Allergy-Special Topics* 2008;1:22-5.
13. Aoki J, Inoue A, Makide K, Saiki N, Arai H. Structure and function of extracellular phospholipase A1 belonging to pancreatic lipase gene family. *Biochimie* 2007;89:197-204.
14. Konno K, Palma MS, Hitara IY, Juliano MA, Juliano L, Yasuhara T. Identification of bradykinins in solitary wasp venoms. *Toxicon* 2002;40:309-12.
15. Neuman I, Ishay JS, Creter D. Hyperreactivity to bee stings: reevaluation. *Ann Allergy* 1983;50:410-2.
16. Hermann K, von Tschirschnitz M, Ebner von Eschenbach C, Ring J. Histamine, tryptase, norepinephrine, angiotensinogen, angiotensin-converting enzyme, angiotensin I and II in plasma of patients with hymenoptera venom anaphylaxis. *Int Arch Allergy Immunol* 1994;104:379-84.
17. Hermann K, Ring J. The renin-angiotensin system in patients with repeated anaphylactic reactions during hymenoptera venom hyposensitization and sting challenge. *Int Arch Allergy Immunol* 1997;112:251-6.
18. Rueff F, Przybilla B, Bilo MB, Müller U, Scheipl F, Aberer W, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol* 2009;124:1047-54.
19. Mueller UR. Cardiovascular disease and anaphylaxis. *Curr Opin Allergy Clin Immunol* 2007;7:337-41.
20. Hepner MJ, Ownby DR, Anderson JA, Rowe MS, Sears-Evald D, Brown EB. Risk of systemic reactions in patients taking beta-blockers receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990;86:407-11.