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Pollen Count and Presentation of Angiotensin-Converting Enzyme Inhibitor-Associated Angioedema

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Abstract

BACKGROUND—The incidence of angiotensin-converting enzyme (ACE) inhibitor-associated angioedema is increased in patients with seasonal allergies.

OBJECTIVE—We tested the hypothesis that patients with ACE inhibitor-associated angioedema present during months when pollen counts are increased.

METHODS—Cohort analysis examined the month of presentation of ACE inhibitor-associated angioedema and pollen counts in the ambulatory and hospital setting. Patients with ACE inhibitor-associated angioedema were ascertained through (1) an observational study of patients presenting to Vanderbilt University Medical Center, (2) patients presenting to the Marshfield Clinic and participating in the Marshfield Clinic Personalized Medicine Research Project, and (3) patients

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enrolled in The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). Measurements include date of presentation of ACE inhibitor-associated angioedema, population exposure to ACE inhibitor by date, and local pollen counts by date.

RESULTS—At Vanderbilt, the rate of angioedema was significantly associated with tree pollen months ($P = .01$ from χ^2 test). When separate analyses were conducted in patients with a history of seasonal allergies and patients without, the rate of ACE inhibitor-associated angioedema was increased during tree pollen months only in patients with a history of seasonal allergies ($P = .002$). In Marshfield, the rate of angioedema was significantly associated with ragweed pollen months ($P = .025$). In ONTARGET, a positive trend was observed between the ACE inhibitor-associated angioedema rate and grass season, although it was not statistically significant ($P = .057$).

CONCLUSIONS—Patients with ACE inhibitor-associated angioedema are more likely to present with this adverse drug event during months when pollen counts are increased.

Keywords

Angiotensin-converting enzyme inhibitor; angioedema; pollen; bradykinin; substance P; seasonal allergies

Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in patients with congestive heart failure, risk factors for coronary artery disease, and nephropathy.¹⁻³ Occasionally, ACE inhibitors cause a potentially serious adverse event called angioedema, characterized by swelling of the lips, tongue, pharynx, face, and sometimes the hands, feet, or abdominal viscera.⁴

The presumed mechanism of ACE inhibitor-associated angioedema involves decreased degradation of the vasoactive peptides bradykinin and substance P. Bradykinin increases vascular permeability directly by stimulating its B₂ receptor and also stimulates the release of substance P from nerve terminals; substance P, in turn, increases vascular permeability via the neurokinin 1 receptor.^{5,6}

The reported incidence of ACE inhibitor-associated angioedema varies from 0.1% to 0.7% in epidemiologic studies to as high as 6% in prospective clinical trials.⁷⁻⁹ The incidence of ACE inhibitor-associated angioedema is increased in African Americans, women, smokers, patients who have received a transplant or are immunosuppressed, and in patients with seasonal allergies, whereas the risk of angioedema is reduced in diabetics.^{7,10,11} Angioedema often occurs after prolonged ACE inhibitor use, suggesting some environmental factor(s) may trigger an episode.^{12,13}

For >9 years, Vanderbilt investigators have collected and analyzed blood and DNA from patients with ACE inhibitor-associated angioedema.^{7,11} This experience suggested that patients were more likely to present with angioedema during the spring and late summer, relative to other seasons. Because ACE inhibitor-associated angioedema is associated with a history of seasonal allergies, we hypothesized that ACE inhibitor-associated angioedema may be more common during months when pollen counts are high. To test this hypothesis, we examined the relationship between the month of presentation of patients with ACE inhibitor-associated angioedema and pollen counts in the Nashville area. We also examined

the relationship between the month of presentation of ACE inhibitor-associated angioedema and periods with high pollen counts to assess replication in 2 other studies: the Marshfield Clinic Personalized Medicine Research Project and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET).

METHODS

Ascertainment of Nashville cases

The study was approved by the Vanderbilt University Institutional Review Board, and all patients provided written informed consent.

This is a cohort study. Cases were identified prospectively at presentation with angioedema via activation of a study pager by the emergency department or clinic physician, retrospectively by referral by their primary care physician, or retrospectively by search of the electronic medical record for the diagnosis of angioedema in a patient taking an ACE inhibitor from January 2004 through December 2010. The whole cohort (population) at risk for these angioedema cases (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) was estimated on the basis of the number of patients who had been prescribed an ACE inhibitor each month during this time period with the use of the Vanderbilt University Medical Center's electronic prescribing system.

One hundred seventy-three cases were identified and were interviewed by a research nurse or physician, and the medical history, including history of angioedema and history of seasonal allergies, was confirmed with a detailed case report form. Cases were defined as having ACE inhibitor-associated angioedema if they had swelling of the lips, pharynx, or face while taking an ACE inhibitor, but had never had angioedema while not taking an ACE inhibitor. Patients were asked if they had a history of seasonal allergies and what their symptoms were, as well as if they had any food or medication allergies. A detailed medication history was taken. Eighteen patients were excluded from this analysis because they could not recall the date of presentation of angioedema and documentation was not available.

Information on pollen exposure in Nashville was obtained from the Metro Nashville and Davidson County Public Health Department. Counts of various types of pollen were measured daily from a monitoring station located in the Lentz Public Health Department. Daily pollen counts were available for the period from January 2004 through December 2010. Of the 155 patients with a known date of onset of ACE inhibitor-associated angioedema, 109 presented with angioedema during this period. These 109 patients were included in the analysis.

Ascertainment of Marshfield angioedema cases and pollen exposure

The Marshfield Clinic Personalized Medicine Research Project is a large population-based biobank linked to an electronic medical record that includes all events and encounters of patients within the Marshfield Clinic system of care. It includes a complete retrospective medication use history, as well as International Classification of Diseases, Ninth Revision, codes, and textual documentation such as office notes, operative reports, discharge

summaries, and other patient information to allow for the development of algorithms to detect medication exposure and outcomes.

The study was approved by the Marshfield Clinic Institutional Review Board. Cases were identified retrospectively via electronic medical records, and the medical history of each potential study patient was reviewed by a trained research coordinator, as previously described.¹⁴ The research coordinator completed a case report form, similar to the one used in Nashville. From June 1996 through June 2009, a total of 30 patients who met the case definition were included in the analysis. Three patients had a documented recurrence of angioedema, bringing the total number of events to 33. Information about history of seasonal allergies was not available for these patients.

Information on pollen exposure in Wisconsin during the study period was obtained from the Allergy, Asthma & Sinus Center, S.C., in Milwaukee. Daily pollen counts were available for the months of March through November 1995 through 2009, but data were missing for 2002 and a portion of 2003. The Marshfield population at risk (Table E2 in this article's Online Repository at www.jaci-inpractice.org) for angioedema was calculated on the basis of the number of patients who had been prescribed ACE inhibitor each month with the use of the Marshfield electronic medical record.

Ascertainment of ONTARGET angioedema cases and pollen exposure

ONTARGET was a randomized clinical trial that compared the ACE inhibitor ramipril, the angiotensin receptor blocker telmisartan, and the combination of the 2 drugs in patients with vascular disease or high-risk diabetes. A detailed description of the trial can be found elsewhere.¹⁵ During the trial, investigators at 54 centers reported episodes of angioedema in 60 ACE inhibitor-exposed patients and provided the date of presentation (from May 2002 through September 2007).

For participating centers in the ONTARGET trial, local pollen season information was obtained from <http://www.hon.ch/Library/Theme/Allergy/Glossary/calendar.html> and <http://www.theweathernetwork.com/pollenfx>. Pollen season data were not available for 8 patients presenting in the United Arab Emirates, Argentina, and Brazil, and these patients were excluded from the analysis. The ONTARGET exposure (Table E3 in this article's Online Repository at www.jaci-inpractice.org) for angioedema was calculated as the number of patients in each center times their mean follow-up time on study.

Statistical analysis

For each site we conducted a χ^2 test to assess the association between angioedema rate and pollen season combined over the years. For Nashville and Marshfield, pollen season was defined as those months during which the pollen count exceeded 20 grains/ cubic meter (gr/M^3) per day. This is at the 75th percentile for grass pollen and between the 50th and 75th percentile for tree and weed pollen, according to the American Academy of Allergy, Asthma, and Immunology.¹⁶ Because pollen data for Wisconsin were missing for some periods, we used the average pollen count from 1995 through 2009 for each day of the calendar year. For ONTARGET, we used the pollen season defined for each site in the databases noted earlier. The expected numbers of angioedema cases in pollen season and off

season as in Tables I to III were calculated by assuming that angioedema had occurred at the same rate during the 2 seasons.

We also fit a Poisson regression model to examine the effect of pollen exposure on monthly angioedema rate. For the Nashville sample, monthly average pollen count was used as the exposure in the model. For the Marshfield sample, pollen season, as defined previously for use in the χ^2 test, was used in the model. For the ONTARGET study, we treated each individual center as the observation unit in the Poisson regression model to examine the effect of pollen season on angioedema rate. The 95% confidence interval of the rate ratio was constructed with Wald statistics.

On the basis of the assumption that the number of patients prescribed an ACE inhibitor ascertained through the electronic prescribing systems or the ONTARGET database was in constant proportion to the population of patients prescribed an ACE inhibitor, we were able to quantify the effect of pollen exposure on the ratio of the underlying angioedema rates. We were not able to calculate the absolute angioedema rates, however, because of incomplete data on the total number of patients prescribed an ACE inhibitor. A two-sided P value $< .050$ was considered statistically significant. Analyses were conducted with the R 2.13.1 statistical package (<http://www.r-project.org>).

RESULTS

Vanderbilt

One hundred nine patients presented with ACE inhibitor-associated angioedema on a known date during a month for which pollen data were available. Subject characteristics appear in Table I.

From January 2004 to December 2010, there were 35 months during which the pollen exceeded 20 gr/M³ on at least 1 day, defined as months of pollen season. The specific months varied with the year and type of pollen. On average, 3.1 months of the year were defined as tree pollen season, 3.4 months as grass pollen season, 4.9 months as tree/grass pollen season, 3.6 months as grass/ragweed pollen season, 4.4 months as tree/ragweed pollen season, and 1.3 months as ragweed pollen season. Fifty-three of the 109 total patients presented with ACE inhibitor-associated angioedema during any pollen month, compared with 56 patients during non-pollen season (Figure 1 and Table II). When separate pollen seasons were defined for specific types of pollen, the presentation of angioedema was significantly associated with tree pollen months, but not with grass or ragweed pollen months (Table II).

Among the 109 patients who had angioedema, 67 (61%) had a history of seasonal allergy. Patients with a history of seasonal allergies were significantly more likely to be taking an antihistamine or corticosteroid or sympathomimetic nasal spray (36% vs 16%; $P = .01$). We conducted a subgroup analysis to determine whether the relationship between presentation of angioedema and months with high pollen counts differed in patients with and without a history of seasonal allergy. For this analysis, we assumed a stable ratio between ACE inhibitor users with seasonal allergy and without seasonal allergy. A significant association

was observed between angioedema rate and tree pollen season (Table II). This association was not statistically significant in patients without a history of seasonal allergies (Table II). ACE inhibitor-associated angioedema was actually decreased during ragweed pollen season, but the period during which ragweed exceeded 20 gr/M³ was short and included grass pollen.

In the Poisson regression model, the monthly angioedema rate was significantly associated with the pollen count ($P = .047$ for all patients; $P = .022$ for ACE inhibitor users who reported a history of seasonal allergy). For each increase in monthly average pollen count of 10 gr/M³, the rate of angioedema increased by 4.6% (95% CI, 0.12%–9.3%) for all subjects and by 6.4% (95% CI, 1.0%–12.1%) for subjects with a history of seasonal allergy.

The distribution of race, sex, smoking history, or diabetes history among patients presenting with angioedema did not vary by tree, grass, or ragweed pollen season (Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Marshfield

Thirty patients presented with 33 episodes of ACE inhibitor-associated angioedema during the time period when pollen data were available. Their mean age was 65.5 ± 11.4 years. Eighteen were women, and all were of European ancestry. At presentation with angioedema, the patients were taking the following ACE inhibitors: lisinopril ($n = 8$), enalapril ($n = 6$), benazepril ($n = 6$),trandolapril ($n = 5$), moexepiril ($n = 3$), captopril ($n = 2$), fosinopril ($n = 2$), and quinapril ($n = 1$). Eight patients were taking an antihistamine or nasal spray. Seven smoked, and 13 had diabetes. Four months of the year were defined as tree pollen season, 2 months as grass pollen season, 5 months as weed pollen season, and 3 months as ragweed pollen season. The rate of angioedema was significantly associated with ragweed pollen months ($P = .025$ by χ^2 test) but not with months when counts of other types of pollen were elevated (Figure 2 and Table III). In the Poisson regression model, the ratio of angioedema rate in ragweed pollen season compared with the rate in the off season was estimated to be 2.16 (95% CI, 1.085–4.315).

ONTARGET

Fifty-two patients presented with ACE inhibitor-associated angioedema at 48 centers for which pollen season information was available. Their mean age was 66.5 ± 7.5 years and 34 were men. Forty-six were of European ancestry, 3 of African ancestry, 2 Asian ancestry, and 1 Hispanic white ancestry. Twelve of the 52 smoked and 15 were diabetic.

Among these 52 patients, 36 presented with ACE inhibitor-associated angioedema during pollen season and 16 presented during other months (Figure E1 in this article's Online Repository at www.jaci-inpractice.org). A positive trend was observed between the ACE inhibitor-associated angioedema rate and grass season, although it was not statistically significant ($P = .057$ from χ^2 test; Table IV). In the Poisson regression model, the ratio of ACE inhibitor-associated angioedema rate during grass pollen season compared with the rate during other months was estimated to be 1.69 (95% CI, 0.98–2.91).

DISCUSSION

We report for the first time an association of the timing of presentation of ACE inhibitor-associated angioedema with elevated pollen counts. We found this association in 3 different populations, which differed in geographic location and in racial composition. Although the precise months and specific types of pollen involved differed in the 3 populations, this may reflect regional differences in season duration, associated risk factors, and genetic predisposition among the populations studied. It may be that the atopic predisposition to specific aeroallergens may lead to inflammation and, in turn, trigger ACE inhibitor-associated angioedema. These data suggest that environmental exposure may explain why patients can present with angioedema even after prolonged ACE inhibitor use and remind physicians to be vigilant to this possibility.

Prior epidemiologic studies have reported an increased incidence of ACE inhibitor-associated angioedema among patients with seasonal allergies.^{7,10} For example, in the Omapatrilat Cardiovascular Treatment Assessment versus Enalapril trial, patients with a history of seasonal allergy had an odds ratio for ACE inhibitor-associated angioedema of 1.79 (95% CI, 1.06–3.00).¹⁰ Byrd et al⁷ reported an odds ratio for angioedema of 2.40 (95% CI, 1.42–4.07) among patients with a history of seasonal allergies. Nevertheless, the mechanism of this association has not been clear. ACE inhibitor-associated angioedema itself is not a typical hypersensitivity reaction.⁴ Rather, ACE inhibitor-associated angioedema, like hereditary angioedema, likely results from excess concentrations of vasoactive peptides. Although hereditary angioedema results from increased generation of bradykinin,¹⁷ ACE inhibitor-associated angioedema is thought to result from defective degradation of bradykinin and substance P via other enzymes when ACE is inhibited.⁴

We studied the relationship between ACE inhibitor-associated angioedema in 3 separate populations. We note the limitation of a small number of cases presenting to the Marshfield, Wisconsin, and ONTARGET cohorts. Nevertheless, the Nashville study population is the largest sample of ACE inhibitor-associated angioedema cases of which we are aware. In the Omapatrilat Cardiovascular Treatment Assessment versus Enalapril trial, by comparison, there were 86 cases of angioedema.⁹ In addition, patients were defined as having seasonal allergies on the basis of clinical history and did not undergo formal IgE sensitization testing. The ability to detect a direct association between sensitivity to specific pollen and concentrations of that pollen would have strengthened the study.

This study did not examine the relationship between ACE inhibitor-associated cough and season or pollen count. The pathophysiologic relationship between cough and angioedema is not known. However, at least 1 epidemiologic study suggests that ACE inhibitor-associated cough is a risk of angioedema.¹⁸ However, Asian populations, whereby rates of ACE inhibitor-associated cough are high, have decreased risk of angioedema.^{18,19}

The observation that angioedema can occur long after initiation of therapy and remit and recur spontaneously^{12,13} suggests that an environmental stimulus may be necessary to trigger the formation of bradykinin or substance P. Seasonal exposure to antigens could represent such a stimulus for some patients. Natural allergen exposure induces the

expression of bradykinin²⁰ and substance P²¹ on the surface of the human nasal mucosa. In addition, patients with allergic rhinitis show increased responsiveness to bradykinin²² and substance P.²¹ Thus, it can be postulated that allergic inflammation increases the production and vasoactive effects of bradykinin and substance P, rendering patients with defects in non-ACE degradation pathways and seasonal allergies more susceptible to angioedema during certain months of the year.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

ACE	Angiotensin-converting enzyme
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

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What is already known about this topic?

The incidence of angiotensin-converting enzyme (ACE) inhibitor-associated angioedema is increased in patients with seasonal allergies.

What does this article add to our knowledge?

This article reports an association of the presentation of ACE inhibitor-associated angioedema with elevated pollen counts. Patients are more likely to present with this adverse drug event during months when pollen counts are increased.

How does this study impact current management guidelines?

These data suggest that environmental exposure may explain why patients can present with angioedema even after prolonged ACE inhibitor use and remind physicians to be vigilant to this possibility.

FIGURE 1.

Presentation of patients with ACE inhibitor-associated angioedema and associated pollen count, Vanderbilt. Patients were significantly more likely to present with ACE inhibitor-associated angioedema during peak pollen season. This pattern was observed in patients with a history of seasonal allergies but not in patients without a history of seasonal allergies. The natural log of pollen count is presented for each date.

FIGURE 2.

Presentation of patients with ACE inhibitor-associated angioedema and associated pollen count, Marshfield. Patients were significantly more likely to present with ACE inhibitor-associated angioedema during peak pollen season. Allergy history was not available for patients at Marshfield. The natural log of pollen count is presented for each date.

TABLE I

Vanderbilt patient characteristics

Parameter	Value
Age (y), mean $\pm$ SD	55.9 $\pm$ 14.1
Sex	
Male, no. (%)	47 (43.1)
Female, no. (%)	62 (56.9)
Ethnicity	
African, no. (%)	64 (58.7)
European, no. (%)	45 (41.3)
Smokers, no. (%) [*]	64 (59.3)
Diabetes, no. (%) [*]	34 (31.5)
Seasonal allergies, no. (%) [*]	67 (61.5)
ACE inhibitors, no. (%)	
Lisinopril	78 (71.5)
Enalapril	9 (8.2)
Benazepril	9 (8.2)
Ramipril	6 (5.5)
Quinapril	5 (4.6)
Fosinopril	1 (1)
Unknown	1 (1)
Antihistamines, no. (%)	21 (19.3)
Nasal spray (corticosteroid, sympathomimetic), no. (%)	20 (18.3)
Inhalers, no. (%)	11 (10.1)

* Percentage among those patients for whom data were available. Data were available for >98% of patients for each of these categories.

χ^2 Test for association between ACE inhibitor-associated angioedema and pollen season, based on type of pollen, Vanderbilt

TABLE II

	All patients		History of seasonal allergies		No history of seasonal allergies	
	Observed	Expected*	Observed	Expected*	Observed	Expected*
Tree						
Pollen season	39	27	28	17	11	11
Off season	70	82	39	50	31	31
P value	.01		.002		.864	
Grass						
Allergy season	33	32	16	20	17	12
Off season	76	77	51	47	25	30
P value	.789		.346		.105	
Ragweed						
Pollen season	9	14	2	9	7	6
Off season	100	95	65	58	35	36
P value	.134		.014		.494	

* Expected was calculated with the assumption that angioedema occurs evenly during the whole year.

TABLE III

χ^2 Test for association between ACE inhibitor-associated angioedema and pollen season, based on type of pollen, for all patients at Marshfield

	Observed	Expected*
Tree		
Pollen season	9	11
Off season	24	22
<i>P</i> value	.466	
Grass		
Pollen season	4	6
Off season	29	27
<i>P</i> value	.475	
Weed		
Pollen season	19	14
Off season	14	19
<i>P</i> value	.064	
Ragweed		
Pollen season	14	8
Off season	19	25
<i>P</i> value	.025	

* Expected was calculated with the assumption that angioedema occurs evenly during the whole year.

TABLE IV

χ^2 Test for association between ACE-inhibitor-associated angioedema and pollen season, based on type of pollen, for all centers except United Arab Emirates and South American, ONTARGET

	Observed	Expected*
Tree		
Pollen season	22	20
Off season	30	32
<i>P</i> value	.642	
Grass		
Pollen season	27	20
Off season	25	32
<i>P</i> value	.057	
Weed		
Pollen season	20	21
Off season	32	31
<i>P</i> value	.767	

* Expected was calculated with the assumption that angioedema occurs evenly during the whole year.