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Letter

Evaluating for seasonal variation in angiotensin-converting enzyme inhibitor–and angiotensin receptor blocker-induced angioedema

Angioedema that occurs as an episodic, adverse effect of angiotensin-converting enzyme inhibitors (ACEIs) presents the emergency physician with some of the most challenging and distressing airway emergencies encountered in common clinical practice.^{1,2} It is characterized by a bland, nonpainful, nonurticarial swelling of the lips, face, tongue, and the soft tissues of the pharynx and larynx. It may result in airway compromise and rapid progression to respiratory failure and death.³ The benefits of the use of ACEIs are remarkable and include the control of hypertension and positive effects on the progression of coronary artery disease, kidney injury, peripheral vascular disease, diabetes, and stroke. These effects appear to be mediated by the antagonism of angiotensin II.⁴ Angioedema has also been shown to occur, although at a lower frequency, in patients using angiotensin receptor blockers (ARBs).⁵ The extensive benefits of ACEIs and ARBs have resulted in high rates of prescription and use. In 2007 an estimated 40 million people in the United States were using these agents. Angioedema occurs in a small fraction of users (0.1%–0.8%)^{2,6}; however, the widespread use of these medicines guarantees a significant number of occurrences. Although the overwhelming benefits of these agents are believed to greatly outweigh the adverse effects, considering the rarity, the consequences for the individual who experiences them can be life altering or ending.³

Interestingly, little is known about the timing and triggers of ACEI angioedema. It may occur within days to years of the initiation of therapy and is sometimes known to occur in the setting of a surgical intervention or other stressors.² Epidemiologically, ACEI-induced angioedema most commonly occurs in African American women between the ages of 32 and 92 years.⁷ In one series, ACEI angioedema accounted for 64% of all patients with angioedema presenting for acute care.² The angioedema associated with ACEIs is widely believed to result from an excess of bradykinin, which some studies have suggested may interact with histamine.^{8,9} Despite this potential link to an allergic type response, no published data support an association of ACEI angioedema with seasonal variation and common allergy triggers.

We sought to determine whether there is a seasonal variation in the incidence of ACEI and ARB angioedema and if a correlation exists with temperature, dew point, or pollen counts, hypothesizing from clinical observation that this may be so. We performed a retrospective medical record review using a single institution's electronic health records to identify all cases of angioedema (*International Classification of Diseases, Ninth Revision*, code 995.1) from all emergency department patient visits from 2009 to 2011. Cases that had an ACEI or ARB recorded as an active patient medication were included for analysis. Patients with discharge

diagnoses of angioedema who were not taking ACEIs or ARBs were excluded, and there were also no patients at our institution younger than 18 years. Daily mean temperature and dew point were obtained for the region from the National Oceanic and Atmospheric Administration website. Local pollen counts were obtained from the US Army Centralized Allergen Extract Lab, the local American Academy of Allergy, Asthma, and Immunology–certified counting station.

Data were analyzed using Poisson regression to evaluate for variation in seasonal incidence and multivariate logistic regression to evaluate for temperature and dew point correlation (Stata statistical software, version 12.1; StataCorp, College Station, Texas). A separate analysis was performed for pollen count correlations because counts are only recorded a mean of 3.8 days per week, yielding 605 observations in the 1,095-day study period. The study site is a 901-bed urban teaching hospital in Washington, DC, with an emergency department with approximately 90,000 patient encounters per year. The study was approved by the MedStar Washington Hospital Center Institutional Review Board.

A total of 217 cases were included for analysis. Multivariate logistic regression of temperature and dew point revealed a nonstatistically significant model with ($P = .63$) and individual odds ratios of 0.99 ($P = .64$) and 1.00 ($P = .47$), respectively. Poisson regression analysis for seasonal variation also produced a nonsignificant model with P values for spring, summer, and fall (winter was used for reference) of .07, .47, and .12, respectively.

A separate multivariate logistic regression of temperature, dew point, and pollen counts restricted to the 605 days with pollen count observations also produced a nonstatistically significant model with a $P = .67$. The above analyses were also repeated excluding cases where an ARB but not an ACEI was documented on the patient's medication list ($n = 210$), and the models were again not statistically significant, yielding P values for temperature, dew point, and pollen count of .21, .42, and .64, respectively.

During a 3-year period at a single institution in the mid-Atlantic region, no seasonal variation was identified in cases of ACEI- and ARB-induced angioedema. Furthermore, no association was identified with mean daily temperature, dew point, or pollen counts for the region. Limitations to this study include a lack of information on patient's baseline atopic status, the retrospective nature of the study, and the fact that the study was limited to a single institution.

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