Brief Report

Angioedema After Long-term Enalapril Use

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A case of life-threatening angioedema occurring after 13 months of enalapril therapy is reported. Clinicians should be aware that such severe reactions can occur, even after long-term therapy. Patients who take angiotensin-converting enzyme inhibitors should be carefully questioned during each follow-up examination concerning angioedema symptoms.

Key words. Angioneurotic edema; enalapril; angiotensin-converting enzyme inhibitors; hypertension.
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Angioedema is an uncommon adverse effect of angiotensin-converting enzyme (ACE) inhibitors that is believed to occur in about 0.1% of patients who receive this class of drug.[1–3] It is a particularly serious adverse effect because of its remarkable predilection for the tongue and glottis, resulting in respiratory obstruction. Fatalities have been reported.[3,4]

Case Report

Enalapril, 5 mg orally, once a day, was prescribed in place of a long-acting verapamil preparation, for a 71-year-old female patient with well-controlled hypertension because of the development of mild cardiomegaly. She was examined by the physician five times at irregular intervals during the subsequent year, over which time her blood pressure ranged from 189/80 mm Hg to 132/58 mm Hg. Her compliance with the therapy was documented by her verbal report at four of these visits, and her enalapril prescription was not changed. There was no history of allergies, and no history of angioedema.

In April 1991, she had the sudden onset of rapidly progressive swelling of the tongue. She was unable to speak and consequently had much difficulty summoning help. When ambulance personnel arrived at the patient's home, she was short of breath and cyanotic, and her tongue was grossly swollen and protruding. A nasopharyngeal airway device was inserted to provide partial relief of dyspnea. The patient was given diphenhydramine intravenously and epinephrine subcutaneously.

On arrival in the emergency department, the patient was barely able to speak. Her tongue remained grossly swollen and protuberant, so that her posterior oropharynx could not be examined. There were superficial lacerations 3 to 4 cm in length on the inferolateral sides of the tongue that were evidently caused by pressure against her inferior denture, which she had been unable to remove. The nasal mucosa was pale and edematous, and the nasopharyngeal airway device provided the main breathing passage she was using. There was stridor during both inspiration and expiration. There was expiratory wheezing audible in all lung fields, which was believed to represent mild pulmonary edema caused by the negative intrathoracic pressure that the patient was generating when inhaling. There was no cyanosis on oxygen. Further emergency treatment consisted of repeat doses of epinephrine and diphenhydramine, maintenance of the patient in an upright sitting posture, and intravenous administration of furosemide and methylprednisolone. Because of substantial rapid improvement, tracheotomy was not required. Retrospectively, it is believed that endotracheal intubation would have been impossible.

The patient was admitted to the hospital and placed on maintenance doses of diphenhydramine and methylprednisolone. All of her signs and symptoms improved; the patient was fairly comfortable in 24 hours and asymptomatic in 96 hours. Diphenhydramine and methylprednisolone were then discontinued abruptly, administration of a previously prescribed arthritis medicine was resumed, and there was no recurrence of symptoms.

The patient insisted that she had almost never missed a dose of her enalapril.

Discussion

Most of the reported cases of angioedema affecting the tongue and glottis have occurred shortly after the patient

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Table 1. Classification of Angioedema

- Hereditary
  - Type 1: deficiency of C1 esterase inhibitor
  - Type 2: functional abnormality of C1 esterase inhibitor
- Acquired
  - Unopposed complement activation
    - Lymphoma: abnormal antibodies activate complement system
    - Autoantibodies to C1 esterase inhibitor
  - Substance-induced
    - IgE mediated
      - Many drug allergies
      - Many contact allergies
      - Many food allergies
      - Hymenoptera stings
      - Infections
    - Non-IgE mediated
      - Cyclooxygenase inhibition
        - Aspirin
        - Other nonsteroidal anti-inflammatory drugs
      - Angiotensin-converting enzyme inhibition
  - Systemic lupus erythematosis
  - Hypereosinophilia
  - Physical causes
    - Some contact reactions
    - Cholinergic
      - Heat
      - Exercise
      - Emotional stimulation
    - Solar
    - Vibratory
    - Cold
  - Idiopathic

**Adapted from Greaves and Lawlor.*[14]

began using the ACE inhibitor.[5–7] For example, in one series of 19 cases, the times of onset ranged from 6 hours to 28 days after the patient took the first dose, with a median of 3 days.[5] However, a number of reports of late onset of angioedema have now been published.[8–12] One report documents severe respiratory obstruction due to angioedema that occurred more than 3 years after the start of enalapril use.[13] It has been estimated that the risk of angioedema is 14 times greater in the first week of ACE inhibitor therapy than it is in subsequent weeks.[3] Since the patient in the present report took her medicine faithfully, it appears that the lateness of the onset of angioedema was not due to noncompliance with prescribed therapy. This case is reported in order to draw attention to the possibility of such late reactions and to their potential severity.

Angioedema can occur from a variety of causes (Table 1). Allergic angioedema frequently occurs as a part of the immunoglobulin E–mediated reaction to a drug, often in conjunction with urticaria. The angioedema related to ACE inhibitors does not appear to be mediated by this type of hypersensitivity reaction. No antibodies to ACE inhibitors are detectable in these patients.[15] Rather, the ACE inhibitors enhance the response to bradykinin.[16–18] This accounts for the usual onset of symptoms within a week of the start of ACE-inhibitor therapy, a period of time shorter than that required for the immune system to produce an amnestic response. It is possible that there is a relationship to hereditary angioedema, a condition in which deficient C1 inhibition renders a person unusually sensitive to bradykinin.[19] In one study, none of the six patients with ACE-inhibitor–related angioedema possessed the biochemical abnormality of hereditary angioedema,[7] while in another study all four patients had a history of idiopathic angioedema.[20] This possible relationship has not been adequately clarified. Until it is better understood, a history of hereditary angioedema or of idiopathic angioedema might be seen as a relative contraindication to the use of ACE inhibitors.

It is important to note that some patients have mild symptoms of ACE-inhibitor–related angioedema for months before a severe reaction brings the problem to a physician's attention.[8,13] Therefore, if every patient taking an ACE inhibitor were routinely questioned concerning symptoms of angioedema, some severe reactions might be avoided.

The potential severity of this adverse effect mandates that the physician be mindful of it. Patients who are candidates for the initiation of therapy with ACE inhibitors should be questioned concerning a history of idiopathic angioedema and hereditary angioedema. Patients returning for follow-up visits should be questioned concerning the occurrence of episodes of swelling of the tongue, throat, face, or neck. The present author concurs with other authors that virtually any occurrence of ACE-inhibitor–related angioedema should lead the physician to stop the drug.[3,12,13] It is hoped that some severe reactions could be forestalled by surveillance for symptoms at routine follow-up visits. Such surveillance, however, would not have prevented the episode reported here.

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