Fatal Angioedema Associated with Enalapril
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A 37-year-old female with a history of hypertension for 5 years was brought to the emergency room with swelling of the tongue and neck after the second dose of enalapril. After administration of hydrocortisone by her physician, she went to the emergency room. Her dyspnea and dysarthria were relieved. However, she experienced recurrence of the symptoms followed by respiratory arrest. She suffered severe anoxic brain damage and died three days later. Although angioedema is a rare occurrence with the use of enalapril, it is potentially life threatening. (Internal Medicine 32: 308-310, 1993)

Key words: hypertension, swelling of tongue and neck, narrowing of trachea, anoxic brain damage

Introduction
Angiotensin-converting enzyme (ACE) inhibitors have been widely used as effective anti-hypertensive agents, and more recently used for the treatment of congestive heart failure (1). Although generally well tolerated, numerous side effects have been reported (2-4). Headache, dizziness, fatigue, diarrhea, skin rash, cough and nausea are the more common (1 to 5%) side effects. The less frequent (1% or less) side effects are nephrotic syndrome, azotemia, pancytopenia and angioedema.

We report a case of fatal angioedema of the laryngeal regions that occurred in a patient who was recently administered the ACE inhibitor, enalapril, for treatment of hypertension.

Case Report
A 37-year-old female presented with swelling of the tongue and neck and dysarthria at the emergency room. Her past history and family history revealed no allergic diathesis. She had been prescribed calcium antagonist and diuretics for approximately 5 years for the treatment of essential hypertension. Because her blood pressure was poorly controlled recently, her physician had changed the drug to enalapril. She took the first 5-mg dose of enalapril in the evening. When she awoke the next morning approximately 8 hours later, she noticed swelling of her tongue and neck, but she did not feel any difficulty in breathing. So she took the second dose. A few hours later, swelling of the tongue and neck increased markedly and she complained of slight dyspnea and dysarthria, and then visited the office of her doctor. After administration of 2000 mg hydrocortisone and 5 mg chlorpheniramine maleate, she was referred to us.

Her dyspnea had been relieved when she was presented to the emergency room. Her consciousness was clear. Her tongue was markedly swollen and protruded, so she could not close her mouth (Fig. 1). Her anterior neck was also markedly swollen (Fig. 2). No other areas of the body were affected by this reaction. On physical examination, her blood pressure was 198/100 mmHg, pulse 100/min, respiration 28/min, and body temperature 37.4°C. Electrocardiogram and chest roentgenogram showed no remarkable changes. Laboratory tests were unremarkable except leukocytosis (8,900/mm³). Computed tomographic scan showed swelling of the soft tissues from the upper pharynx to sub-vocal cords, tongue and vocal cords (Fig. 3). It also showed swelling of the mucosa of the trachea and the soft tissue around it, and narrowing of the trachea in other slices. We considered the condition of the patient to be relatively stable, therefore no additional doses of hydrocortisone nor chlorpheniramine maleate were administered.

Approximately two hours after admission, the patient’s condition rapidly deteriorated with severe respiratory distress and stridor. Intravenous adrenaline was immediately administered. Despite this treatment, respiratory arrest followed. Oral endotracheal intubation was attempted but was unsuccessful due to severe laryngeal edema. Subsequently a needle cricothyroidotomy was performed, and was followed by a tracheotomy. The
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Fig. 1. The tongue was markedly swollen and protruded, and the patient could not close her mouth.

Fig. 2. Anterior aspect of the neck was also markedly swollen.

Fig. 3. Computed tomographic scan showed the swelling of the soft tissues from the upper pharynx to sub-vocal cords, tongue and vocal cords. It also showed the narrowing of the trachea in other slices.

total anoxic period was 8 minutes, and hemodynamic deterioration ensued with development of ventricular fibrillation. Eventually, her hemodynamics were stabilized by positive inotropic agents, but severe anoxic brain damage persisted. On the third day of hospitalization, brain death was diagnosed and declared. A request for a post mortem examination was refused.

Discussion

The term angioedema denotes a well-demarcated, non-pitting edema that occurs as large erythematous areas in the skin, mucosa and subcutaneous tissues (3). It most commonly involves the face, lips and glosso-pharyngeal areas. In some instances it may cause respiratory distress, caused primarily by laryngeal edema. Hereditary and acquired types have been described (3). Hereditary angioedema is rare, with acquired or idiopathic angioedema being more common. It is associated with many precipitating factors, such as foods, insect stings, infections, transfusions and a variety of drugs.

The mechanism of angioedema associated with ACE inhibitors remains unclarified, but it is assumed that a biochemical phenomenon, not an immunologic mechanism, mediated through the kallikrein-kinin system plays a role (5). ACE inhibitors are known to decrease the metabolism of bradykinin; increased levels of tissue bradykinin, which is a potent vasodilator that also increases vascular permeability, are thought to be the cause of angioedema.

The incidence of angioedema associated with the use of ACE inhibitors has been estimated to be from 0.1 to 0.2% (2–4). Angioedema occurs at the initiation of the drug therapy. Although the majority of cases were reported to occur within the first week of therapy, especially within the first few doses (6), Hedner et al reported cases in which angioedema occurred after over three months and three years on ACE inhibitors (7). In the present case, severe symptoms recurred after
adequate initial treatment and the patient died eventually. The decreased blood levels of hydrocortisone and chloropheniramine maleate might contribute to the recurrence of symptoms, but the development of relapse might also be contributory. The development of relapse was reported by Giannoccaro, who stated that it is plausible that the long half-life of enalapril (approximately 11 hours) leads to the relapse (8). In the present case, the second or third doses of hydrocortisone and chloropheniramine maleate should have been administered to prevent the recurrence of symptoms, and further, intubation should have been immediately performed.

It is essential to be aware of the adverse reactions of ACE inhibitors, especially angioedema which can be fatal. Patients must be instructed to seek medical attention immediately when signs of angioedema have occurred. Once angioedema has occurred in patients taking ACE inhibitors, the following measures are needed; discontinue the drug; administer steroids and antihistamines; observe the patient carefully for a possible relapse. We emphasize the need for early intubation or tracheotomy if signs of airway obstruction are present, before angioedema is severe enough to hinder the procedures.

References