

Angioedema After Long-Term Use of an Angiotensin-Converting Enzyme Inhibitor

Adriana J. Pavletic, MD

Angioedema is an uncommon adverse effect of angiotensin-converting enzyme (ACE) inhibitors. Its frequency ranges from 0.1 percent in patients on captopril, lisinopril, and quinapril to 0.5 percent in patients on benazepril.¹ Most cases are mild and occur within the first week of treatment.²⁻⁴ Recent reports indicate that late-onset angioedema might be more prevalent than initially thought, and fatal cases have been described.⁵⁻¹¹ Many physicians are not familiar with late-onset angioedema associated with ACE inhibitors, and a delayed diagnosis can have potentially serious consequences.^{5,8-11}

Case Report

A 57-year-old African-American woman with class 3 congestive heart failure caused by severe mitral regurgitation came to the family medicine clinic with "swollen face and lips" of several hours' duration. She denied any breathing or swallowing difficulties. Her medical history was negative for allergies and angioedema. Her medications included lisinopril 20 mg/d, digoxin 0.25 mg/d, furosemide 40 mg/d and cyclobenzaprine 10 mg at night, as needed. She had been taking lisinopril for 6 years without any problems. The patient had been intermittently given cyclobenzaprine for recurrent low-back pain and never experienced any side effects. She had been off cyclobenzaprine for the past few months and had taken one 10-mg tablet the night before her symptoms occurred.

She had edema of her lower face and lips, but no evidence of tongue swelling or respiratory compromise. Because she had recently restarted

cyclobenzaprine, her angioedema was initially believed to be an allergic reaction to this drug, and it was discontinued. She was also given 125 mg of methylprednisolone intramuscularly. Her angioedema did not improve, and she returned to the clinic the following day. She was seen by another physician, who discontinued lisinopril, and her symptoms resolved within 24 hours. After her ACE inhibitor was discontinued, she experienced more symptoms and an increased frequency of palpitations, but she had no change in exercise tolerance. A cardiologist was consulted, who prescribed the angiotensin II receptor antagonist losartan (initially at dosages of 25 mg/d and then 50 mg/d). The patient was advised to report any symptoms or signs of angioedema immediately and to discontinue losartan if they occurred.

No side effects were observed after 18 months of treatment. The patient's condition initially improved with losartan therapy (decreased frequency of palpitations), but her congestive heart failure gradually worsened, manifested as decreasing exercise tolerance. An experimental inotropic drug was added to her regimen in March 1996, 6 months after losartan therapy was initiated. She is currently doing poorly and considering cardiac transplantation.

Discussion

ACE inhibitors are prescribed widely for patients who suffer from hypertension, congestive heart failure, and diabetes. These medications have a favorable side-effect profile and are generally well tolerated. Most physicians are familiar with early-onset angioedema, which occurs within the first weeks of therapy. In 1992 Israili and Hall³ reviewed the literature on cough and angioedema related to ACE inhibitors. Their conclusion was that "angioneurotic edema usually occurs within hours or at most 1 week after starting the ACE inhibitor; however, in one report, it developed after long-term therapy with an ACE inhibitor."

Submitted, revised, March 7, 1997.

From the Department of Family Medicine, University of Nebraska Medical Center, Omaha. Address reprint requests to Adriana J. Pavletic, MD, Department of Family Medicine, University of Nebraska Medical Center, 600 South 42nd St, Omaha, NE 68198-3075.

Although diagnosing early-onset angioedema should not pose a problem, many physicians are not familiar with late-onset angioedema, and it frequently goes unrecognized.^{5,8-11} In only one of nine cases of angioedema associated with ACE inhibitors treated at public hospitals in New Zealand was the patient advised to discontinue the ACE inhibitor.¹¹ In the present case, the diagnosis was also initially missed because of a lack of any temporal relation between the ACE inhibitor and angioedema. Moreover, the cause of the edema was somewhat clouded because the patient restarted cyclobenzaprine the night before her symptoms occurred.

The patient was seen the following day by a family practice resident who, during her recent otolaryngology rotation, had become familiar with late-onset angioedema associated with ACE inhibitor therapy. If she had not read Litman's article on late-onset angioedema,⁴ she would also have thought that the cyclobenzaprine was responsible. Although angioedema is listed as a possible side effect, there is no published medical literature on cyclobenzaprine-associated angioedema. Both the patient and her physician were convinced that the patient's angioedema was due to lisinopril, not cyclobenzaprine, as initially suspected. This belief was confirmed when the patient resumed cyclobenzaprine therapy without any problems.

It is possible that the diagnosis was presumptive, because the patient was not rechallenged with lisinopril. Rechallenging might have been of no diagnostic value given that ACE-inhibitor-associated angioedema is not an allergic reaction. That means that a negative result (ie, no symptoms after rechallenging) does not rule out a cause-effect relation between ACE inhibitor and angioedema, because angioedema can recur at any time after restarting the therapy. In a worst-case scenario rechallenging could have caused a severe, potentially fatal reaction.

Angioedema can be sporadic (also known as idiopathic) or hereditary. The sporadic subtype is the most common, with a 5 to 10 percent lifetime risk for the general population.^{10,12} The hereditary form, which can be either allergic or nonallergic, is much less common, with only 198 patients described in the literature through 1983.² Angioedema can occur with drug ingestion, C1 esterase-inhibitor deficiency, circulating immune

complexes, physical stimuli, or agents that promote histamine release.¹³

ACE-inhibitor-associated angioedema is not an allergic reaction. In most patients the disorder occurs after starting ACE inhibitor therapy or after switching from one ACE inhibitor to another during a period that is too short for specific antibodies to develop.² Additional evidence against an allergic basis for this side effect is that the structurally unrelated ACE inhibitors induce similar reactions.¹⁴ The exact pathophysiologic mechanism of this rare side effect is unknown, but it is believed to be nonimmunogenic and related to increased levels of bradykinins as a result of inhibition of bradykinin degradation.²⁻⁴ Angiotensin-converting enzyme, also known as kinasinase II, degrades bradykinin. Consequently, inhibition of ACE is thought to increase the concentration of bradykinin in tissues.¹² Only a very small number of patients develop this side effect, however, probably because of a combination of poorly understood host and environmental factors.¹² Patients who have a history of sporadic and hereditary angioedema might be at increased risk for this complication and should not be given ACE inhibitors.^{15,16} African-Americans can also be at increased risk.¹⁷

The clinical manifestation is highly variable. Jason⁶ reported a case of a 70-year-old African-American man who had been taking captopril for 2 years when he developed obstructive angioedema over 3.5 hours. Oral intubation was unsuccessful, and a difficult tracheostomy was too late to save the patient. In other instances symptoms are mild and can regress spontaneously while the patient continues the medication, thus erroneously prompting an alternative diagnosis.⁷⁻⁹ If the diagnosis is missed, recurrent and more severe episodes can occur with potentially serious consequences.^{5,9} Litman et al⁵ described 2 cases of life-threatening angioedema associated with enalapril that required tracheostomy. One of the patients, who had experienced four previous episodes of tongue swelling, had been seen by several physicians and given steroids and antihistamines with relief of symptoms. Because of the lack of a temporal relation, the enalapril had never been discontinued.

Finley et al¹⁰ described the case of a patient who sought care from qualified emergency physicians for angioedema 18 times during a 3-year pe-

riod before the correct diagnosis was made. Another case report described a patient who had an 18-month history of recurrent swelling (at least 15 or 20 episodes) involving the left side of her face. This patient was examined by several specialists and underwent many diagnostic tests, including magnetic resonance imaging, before her problem was correctly diagnosed as angioedema associated with an ACE inhibitor.⁸

Unusual cases involving the gastrointestinal tract have been reported.¹⁸⁻²⁰ Jacobs et al¹⁸ described a patient who had recurrent episodes of abdominal pain that was initially diagnosed as Crohn disease. The patient failed to respond to a course of prednisone and sulfasalazine. Her symptoms resolved after discontinuing the enalapril. ACE inhibitors have recently been implicated as a potential cause of acute pancreatitis, with reports of cases associated with lisinopril, captopril, and enalapril.^{21,22} Angioedema of pancreatic tissue can result in obstruction of the ductal system and lead to pancreatitis.^{23,24}

The mainstay of therapy is to stop taking the offending drug. In mild cases such as the one described here, which involved the face and lips without respiratory compromise, discontinuing the drug is usually sufficient. More severe cases involving the tongue or causing respiratory compromise are treated with epinephrine, diphenhydramine, and steroids.²⁻⁴ Occasionally airway protection is necessary and is sometimes difficult to accomplish.²⁻⁷

ACE receptor antagonists lack the bradykinin-potentiating capacity and can be prescribed as alternative therapy for patients who cannot tolerate ACE inhibitors, as implied by Goodfriend et al.²⁵ Angioedema has been reported with losartan, however.²⁶ In the present case, the benefits were believed to outweigh the risks of treatment, and the patient was counseled on the possibility of angioedema. Losartan has not yet been approved for treatment of congestive heart failure, although it is currently being evaluated in patients who previously had angioedema from an ACE inhibitor.¹² Early studies in patients with congestive heart failure suggest that losartan exerts the same hemodynamic effects as do ACE inhibitors, reducing afterload and increasing cardiac output.²⁷

The number of patients who have an adverse reaction to ACE inhibitors will increase, given the growing numbers who are receiving prescrip-

tions for these drugs and the longer duration of the treatment. Accordingly, ACE inhibitors should be considered in the differential diagnosis of unexplained swelling of the face, lips, or tongue or acute or recurrent abdominal complaints in patients who are on ACE inhibitor therapy.

References

1. Drug facts and comparisons. St. Louis, Mo: Facts and Comparisons; 1995:165f.
2. Slater EE, Merrill DD, Guess HA, Roylance PJ, Cooper WD, Inman WH, et al. Clinical profile of angioedema associated with angiotensin-converting enzyme inhibition. *JAMA* 1988;260:967-70.
3. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann Intern Med* 1992;117:234-42.
4. Hedner T, Samuelsson O, Lunde H, Lindholm L, Andren L, Wiholm BE. Angio-oedema in relation to treatment with angiotensin-converting enzyme inhibitors. *BMJ* 1992;304:941-6.
5. Litnan RS, Sher WH, Hausman SA. Life-threatening acute airway obstruction due to enalapril induced angioedema. *Immunol Allergy Pract* 1992;14:21-4.
6. Jason DR. Fatal angioedema associated with captopril. *J Forensic Sci* 1992;37:1418-21.
7. Venable RJ. Angioedema after long-term enalapril use. *J Fam Pract* 1992;34:201-4.
8. Frontera Y, Piccuch JF. Multiple episodes of angioedema associated with lisinopril, an ACE inhibitor. *J Am Dent Assoc* 1995;126:217-20.
9. Chin HL, Buchan DA. Severe angioedema after long-term use of an angiotensin-converting enzyme inhibitor. *Ann Intern Med* 1990;112:312-3.
10. Finley CJ, Silverman MA, Nunez AE. Angiotensin-converting enzyme inhibitor-induced angioedema: still unrecognized. *Am J Emerg Med* 1992;10:550-2.
11. Weiner JM. Failure to recognize the association of life-threatening angio-oedema and angiotensin-converting enzyme inhibitor therapy. *Aust N Z J Med* 1995;25:241-2.
12. O'Mara NB, O'Mara EM Jr. Delayed onset of angioedema with angiotensin-converting enzyme inhibitors: case report and review of literature. *Pharmacotherapy* 1996;16:675-9.
13. Megerian CA, Arnold JE, Berger M. Angioedema: 5 years' experience, with a review of the disorder's presentation and treatment. *Laryngoscope* 1992;102:256-60.
14. Fine RM. The Fine Page: angiotensin-converting enzyme angioedema. *Int J Dermatol* 1993;32:95-6.

15. Shepherd GM. Possible contraindications of angiotensin-converting enzyme inhibitors in patients with hereditary angioedema. *Am J Med* 1990;88:446.
16. Orfan N, Patterson R, Dykewicz MS. Severe angioedema related to ACE inhibitors in patients with a history of idiopathic angioedema. *JAMA* 1990;264:1287-9.
17. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitors associated angioedema. *Clin Pharmacol Ther* 1996;60:8-13.
18. Jacobs RL, Hoberman LJ, Goldstein HM. Angioedema of the small bowel caused by an angiotensin-converting enzyme inhibitor. *Am J Gastroenterol* 1994;89:127-8.
19. Gregory KW, Davis RC. Angioedema of the intestine. *N Engl J Med* 1996;334:1641.
20. Pavletic AJ. Angioedema of the intestine. *N Engl J Med* 1996;335:1534. Letter.
21. Marinella MA, Billi JE. Lisinopril therapy associated with acute pancreatitis. *West J Med* 1995;163:77-8.
22. Standridge JB. Fulminant pancreatitis associated with lisinopril therapy. *South Med J* 1994;87:179-81.
23. Dabaghi S. ACE inhibitors and pancreatitis. *Ann Intern Med* 1991;115:330-1.
24. Marinella MA. Angio-oedema induced by ACE inhibitors. *J Intern Med* 1996;239:371-2.
25. Goodfriend TL, Elliot ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996;334:1649-54.
26. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan. *N Engl J Med* 1995;333:1572.
27. Crozier I, Ikram H, Awan N, Cleland J, Stephen N, Dickstein K, et al. Losartan in heart failure. Hemodynamic effects and tolerability. Losartan Hemodynamic Study Group. *Circulation* 1995;91:691-7.