ACE Inhibitor–Related Angioedema

Are Your Patients at Risk?

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Welcome to the Pharmacovigilance Forum. Each column in this new series will discuss noteworthy topics related to adverse drug reactions (ADRs), including drug-induced disease, that are occurring in the clinical realm. Every medication has the potential to cause disease, but clinicians are often slow to recognize drug therapy as an etiological factor. Therefore, I will strive to raise awareness and educate while encouraging clinicians to report ADRs through the proper channels.

For this inaugural column, the topic is angiotensin converting enzyme (ACE) inhibitor–related angioedema.

The First ACE Inhibitor

In the 1970s, Sir John Robert Vane, a professor of experimental pharmacology at the Institute for Basic Medical Sciences at the Royal College of Surgeons in England, and a Brazilian postdoctoral student, Sergio Ferreira, PhD, were experimenting with hypertension and bradykinin-potentiating factor (BPF).[1] This extract from the venom of the Brazilian viper *Bothrops jararaca,* BPF, was tested and found to be a potent inhibitor of angiotensin-converting enzyme (ACE). Dr. Vane was a consultant to E. R. Squibb (now Bristol-Myers Squibb) and was subsequently awarded the Nobel Prize in 1982 for his work with prostaglandins.

David Cushman, PhD, and Miguel A. Ondetti, employees of E. R. Squibb, succeeded in turning the viper snake venom peptide (which initially required injection for action) into an oral dosage form in the mid-to-late 1970s ... and, well, the rest is history.[2] With their discovery, the two were recognized by their peers as heroes of chemistry.

The first ACE inhibitor, captopril (Capoten, Apothecon/Bristol-Myers Squibb), was approved by the FDA in 1981.[3] Ten ACE inhibitors are currently available in the U.S. for treating hypertension, and all are available as generic drugs: benazepril (Lotensin, Novartis), captopril, enalapril (Vasotec, Merck/Biovail/Valeant), fosinopril (Monopril, Bristol-Myers Squibb), lisinopril (e.g., Zestril, AstraZeneca; Prinivil, Merck), moexipril (e.g., Univasc, Schwarz/UCB), perindopril (Aceon, Servier/Solvay/Xoma), quinapril (Accupril, Pfizer), ramipril (Altace, Monarch/King), and trandolapril (e.g., Mavik, Abbott).[4]

In addition, most ACE inhibitors are approved to treat heart failure (captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril, and trandolapril), and some are used to prevent nephropathy.[5]

Pathophysiology

Angioedema is characterized by a localized, noninflammatory, nonpruritic, and well-demarcated, nonpitting swelling that occurs as large erythematous areas in the skin and subcutaneous tissues.[6] It can involve any area of the body, including the lips, tongue, face, glottis, oropharynx, periorbital or perioral regions, intestines, genitals, extremities, and peripheral tissues.[6,7] It is usually a benign condition, but it can cause respiratory distress and death if severe laryngeal edema occurs.[8,9]

The common mechanism appears to be activation of the complement system or activation of other proinflammatory cytokines, such as prostaglandins and histamine, which may trigger rapid vasodilatation and edema.[10] Angioedema can be either hereditary or acquired (e.g., medication-related). One of the most common causes of drug-related angioedema is from ACE inhibitor treatment. Other medications less often associated with angioedema include angiotensin-receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), bupropion (e.g., Zyban and Wellbutrin, GlaxoSmithKline), beta-lactam antibiotics, statins, and proton pump inhibitors.[10]

Incidence and Treatment

I have been following ACE inhibitor–related angioedema as an ADR since the early 1990s, when only six agents from this class were available. As was (and still is) the case, the incidence of angioedema reported in the labeling for ACE inhibitors is in the range of "only" 0.1% to 0.7%.[11] Monitoring patients for this ADR is important, because although angioedema is rare, it may be life-threatening, leading to respiratory arrest and death.[8,12,13] Further, if angioedema is not initially recognized, it may lead to extensive and expensive workups before it is identified as a cause.[12,14]

Most often, these reactions are mild and can be managed by discontinuing the drug and by prescribing oral antihistamines.[6] Other than the higher risk among African-American patients, there are no known predisposing factors for the development of ACE inhibitor–related angioedema.[11,15] The reaction does not appear to be related to the dose, to a specific ACE inhibitor, or to concurrent medications. C1-esterase inhibitor protein deficiency or seasonal allergies, or both, may also be risk factors.[15]

Most reactions occur within the first week or month of initial therapy and often within hours of the initial dose.[16] However, some cases may occur years after therapy has begun.[12,17] No diagnostic test is available that specifically identifies those at risk. If the patient is identified as being at risk, the ACE inhibitor should be discontinued and should not be readministered.

I find it surprising that there continue to be published reports, some serious, of ACE inhibitor–related angioedema in the medical literature. Some health care professionals have even called it a silent epidemic—silent because among the millions of individuals who take ACE

inhibitors for hypertension, heart failure, or nephropathy, a handful of patients develop life-threatening reactions.[12,18] These patients are often admitted to intensive-care units (ICUs), whereas others with less severe presentations are often treated and released from emergency departments (EDs). Although no therapies are recommended *per se*, if there is any potential for airway obstruction, appropriate therapy such as subcutaneous (SQ) epinephrine injection 1:1000 (0.3 mL to 0.5 mL) should be promptly administered.[19] Other recommended treatments include antihistamines and steroids, even though none have been prospectively studied.[10]

In the hospital setting, we still see a fair amount of patients with angioedema probably related to the use of ACE inhibitors. Some patients might also be having mild reactions and present to their primary care provider or specialists in the outpatient setting. The following patients were seen in our institution over the preceding 6 months.

Case Studies

Case 1

An 85-year-old female patient was being treated with lisinopril 20 mg for hypertension (it was not known for how long). Her additional past medical history was significant for asthma and atrial fibrillation. Besides lisinopril, she was receiving daily warfarin (Coumadin, Bristol-Myers Squibb) 2.5 mg and oral digoxin (Lanoxin, GlaxoSmithKline) 0.125 mg every 48 hours.

The patient had recently been admitted to a local medical center for management of hypertension. She stayed for 1 week, and the lisinopril dose was increased from 10 mg to 20 mg daily. Just before arriving at the ED, she had noticed right-sided facial swelling, followed by a swollen lip. This occurred within 30 minutes of taking the lisinopril dose. She was also experiencing wheezing, shortness of breath, and coughing, which she attributed to her asthma. Emergency medical services (EMS) was called. She was treated with three SQ doses of epinephrine 0.3 mg immediately and was given supplemental oxygen.

She was transported to the ED, where she received intravenous (IV) diphenhydramine (e.g., Benadryl, McNeil) 50 mg. Following treatment, she had neck discomfort without any shortness of breath.

The patient was given IV methylprednisolone 125 mg and a nebulizer treatment of ipratropium 0.5 mg/albuterol 0.083% (e.g., Combivent, Boehringer Ingelheim; DuoNeb, Dey). Her symptoms completely resolved, and she was admitted to the ICU for airway monitoring. In the ICU she was given IV dexamethasone 10 mg every 8 hours, IV diphenhydramine 25 mg every 8 hours, and IV famotidine (Pepcid, Merck) 40 mg daily. The ACE inhibitor was withheld, and the patient was told to never take it again. She was hydrated with dextrose 5% in water and normal saline at a rate of 75 mL/hour and underwent a swallowing study, which she passed.

Tryptase and C1 esterase levels were tested. The patient was switched to oral prednisone 60 mg daily. On day 2, her throat symptoms were resolving and her oxygen saturation was 97%. Renal function was normal, and she had no further shortness of breath or wheezing. She was walking, and her home medications were started.

On day 3, the lip swelling was much improved compared with day 2. Because she was markedly improved without shortness of breath or stridor and had no tongue edema or posterior pharyngeal swelling, she was later discharged. She was advised to follow up with her primary care doctor within the week.

Case 2

An 80-year-old woman was taking an unknown dose of lisinopril for hypertension. She arrived in the ED with gradual tongue swelling. Her history did not reveal consumption of any unusual foods or recent medication changes. It was not known how long she had been receiving lisinopril. No shortness of breath or voice changes were noted.

Lisinopril was stopped, and she was treated with IV methylprednisolone 125 mg and IV diphenhydramine 50 mg, along with IV famotidine 20 mg. She was observed over several hours, and her airway remained patent.

Later that day, the patient was discharged and was counseled to discontinue lisinopril and not to take any ACE inhibitors. She was to follow up with her primary care doctor within the week.

Case 3

A 70-year-old man arrived at the ED with a past medical history significant for type-2 diabetes mellitus, hypertension, gout, and coronary artery disease. His lips and tongue were swollen. He had been taking ramipril 2.5 mg daily for 1 month. Ramipril was stopped, and he received IV methylprednisolone 125 mg and IV diphenhydramine 50 mg, with improvement. He was admitted to the ICU for monitoring and continued with IV methylprednisolone and diphenhydramine around the clock. He had no respiratory distress but did have some difficulty swallowing. Tryptase and C4 levels were normal. He also had a low level of C1 esterase inhibitor.

On day 3, the patient was switched to oral prednisone with a taper to continue upon discharge. He was told to avoid ACE inhibitors and ARBs.

Case 4

A 67-year-old woman was being treated for hypertension with fosinopril 20 mg. Her past medical history was also significant for type-2 diabetes, coronary artery disease, two previous myocardial infarctions, a cerebrovascular accident 30 years before, and multiple episodes of angioedema from different foods and sulfonamides. She was brought to the ED via ambulance having symptoms of generalized itching, swelling of the lips and tongue, and stridor. She had eaten lunch with a new sauce while at work and subsequently experienced generalized itching, shortness of breath, and tongue and eye swelling. She did not have her epinephrine auto-injector (e.g., EpiPen, Mylan/Pfizer/Meridian) with her.

Symptoms worsened, and the patient called EMS. She was treated with SQ epinephrine 0.3 mg, IV methylprednisolone 125 mg, and IV diphenhydramine 50 mg. At the ED, she received another 0.3 mg of epinephrine SQ, IV famotidine 40 mg, and nebulized ipratropium 0.5 mg/albuterol 0.083%. IV methylprednisolone 60 mg was continued every 6 hours, diphenhydramine was changed to 50 mg orally every 8 hours, and oral famotidine was continued as 40 mg twice daily.

An allergist was consulted, and fosinopril was discontinued. The patient improved overnight and was transferred to a medical floor on a prednisone taper. She was discharged on day 2 and was advised to follow up with her primary care doctor and an allergy specialist.

In this patient, fosinopril, a food allergy, or both, might have caused the reaction. Sometimes the cause is not always clear, and a re-challenge is not always feasible because of potential risks.

Potential ARB Cross-Reactivity

There have been reports of cross-reactivity between ACE inhibitors and ARBs; however, the incidence of such a reaction has not been reported.[15,20] The question of whether to prescribe an ARB if a patient has experienced angioedema after taking ACE inhibitors remains controversial. However, if ARB treatment is instituted, extreme caution should be used. Patients should be advised to stop taking the ARB immediately if a reaction occurs. Oral antihistamines are recommended. If the ADR is more severe, a call should be placed to 911.[6]

Reporting Adverse Drug Reactions

All ADRs should be reported to MedWatch at 1-888-INFO-FDA, 1-888-463-6332, or online. The FDA 3500 Voluntary Adverse Event Report Form can be easily accessed online for reporting ADRs at www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm.

The FDA is interested in serious reports that include any of the following patient outcomes: death; life-threatening condition; initial hospitalization; prolonged hospitalization; disability or permanent damage; congenital anomalies or birth defects; and other serious conditions for which medical or surgical intervention is needed to prevent one of the aforementioned outcomes.

The FDA is also interested in any unlabeled ADRs for new drugs (e.g., usually those approved within the previous 2 years).

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