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CASES OF NOTE

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Angiotensin-Converting Enzyme Inhibitor Angioedema

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ABSTRACT
Angioedema from angiotensin-converting enzyme inhibitors (ACEIs) is a potential, emergent, and frightening problem that presents to the emergency department. This article focuses on angioedema caused by using ACEIs. The presentation, pathology, diagnostic testing, treatment, and patient education of angioedema are explored. This article explores using fresh frozen plasma as an initial approach to the treatment of ACEI angioedema. **Key words:** ACEI angioedema, ACEI treatment, angioedema, FFP, fresh frozen plasma

RECOMMENDED first-line therapies for management of hypertensive-cardiovascular disease include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (Guyer & Banerji, 2018). The Eighth Joint National Committee (JNC8) recommends an ACEI as one of the four classes of medicines for use in hypertensive patients. An ACEI is normally used in patients with chronic kidney disease. ACEIs are not recommended for people of African descent unless chronic kidney disease is present (Page, 2014). ACEIs make up 35% of all antihypertensive medications prescribed, with an estimated 40 million users worldwide (Guyer & Banerji, 2018). A rare, but potentially life-threatening, side effect associated with ACEI use is angioedema. In a longitudinal study over 8 years by Banerji, Blumenthal, Lai, and Zhou (2017) found that out of 134,945 patients prescribed ACEI, only 888 patients (0.7%) experienced angioedema. Compared with White patients, the rate of angioedema was five times greater among people of African descent. ACEIs are not recommended for people of African descent unless chronic kidney disease is present (Page, 2014). Although it is not clear why ACEI angioedema occurs at a higher rate among African Americans, there is a greater probability of a lower renin profile, which causes increased side effects with antihypertensive medications (Williams, Nicholas, Vaziri, & Norris, 2014). This article explores the diagnosis and treatment of a patient who presented with ACEI angioedema years after

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being prescribed an ACEI and highlights the importance of patient education related to this type of severe medication-related side effect.

CASE STUDY

A 47-year-old African American man suddenly became short of breath when speaking long sentences and developed facial edema as well as edema to his ankles. In an attempt to relieve his symptoms, he took 25 mg of diphenhydramine orally, with no improved outcome. After 4 hr of progressively worsening symptoms, he sought care at the emergency department.

On examination, the patient was anxious and short of breath after speaking long sentences. He presented with periorbital edema and angioedema of the lips and lower face. Pitting edema +1 to his ankles and feet was also observed. The patient reported no prior episodes of this type of angioedema. His blood pressure was 160/86 mmHg, pulse 104 per minute and regular, and respirations 19 per minute, with an oxygen saturation of 92% on room air. The patient was afebrile (98.7 °F), and no abnormal skin findings were noted.

The patient reported no drug allergies. He reported an allergy to latex but denied any recent exposure to latex. The patient was obese (weight 222 lb, height 75 in., and ideal body weight 84.5 kg) and has a history of congestive heart failure, chronic atrial fibrillation, and hypertension. His prescribed medications included buffered aspirin (Bufferin) 81 mg daily, digoxin (Lanoxin) 0.25 mg daily, furosemide (Lasix) 20 mg twice daily, and lisinopril (Zestril) 5 mg daily. The patient reported that his primary physician recently changed his furosemide from once a day to twice a day due to increased swelling of his ankles. He reported taking lisinopril (Zestril) for 5 years.

The patient was consequently diagnosed with ACEI angioedema of the tongue and lips by ruling out differential causes by history, laboratory test results, assessment, and use of ACEI. Following the diagnosis of ACEI angioedema, the patient was administered fresh frozen plasma (FFP). Symptoms decreased quickly following FFP administration. The patient was monitored for 3 hr after completion of FFP administration. The patient was instructed to discontinue lisinopril and was prescribed amlodipine (Norvasc) 5 mg daily. Once swelling subsided, he was prepared to be discharged from the emergency department. The patient was informed that angioedema could recur. Discharge instructions included specific signs and symptoms indicative of angioedema that would require immediate return to the emergency department.

Discussion

A study conducted by Ishoo, Shah, Grillone, Stram, and Fuleihan (1999) revealed that 36 out of 80 hospitalized angioedema cases were due to side effects of an ACEI. ACEI angioedema often results without obvious cause. Signs and symptoms typically occur within 1 month of beginning the medication; however, this condition can develop at any time during the course of using an ACEI (Guyer & Banerji, 2018).

Laboratory Testing and Diagnosis

Currently, there is no specific diagnostic test to identify ACEI angioedema. Diagnosis is performed primarily by ruling out other conditions associated with angioedema. Ludwig's angina can be life-threatening and should be ruled out for all cases of angioedema (Amey, Waidyasekara, & Kollengode, 2013). Other differential diagnoses related to angioedema include anaphylaxis, Type 1 hypersensitivity/allergens, infection, hereditary angioedema, and acquired C1 esterase inhibitor deficiency, and ACEI angioedema. Anaphylaxis is due to the release of large amounts of histamines. Symptoms consist of wheezing, hypotension, erythema, and multiorgan disruption. Reactions to allergens may present with upper airway swelling and no other systemic symptoms. Infection is typically accompanied by fever, redness, or increased

warmth at an injury site. Hereditary and C1 esterase deficiency angioedema involves recurrent episodes of angioedema that last 2–5 days without treatment and abnormal C4 protein levels in patients who do not use ACEI or nonsteroidal anti-inflammatory drugs (Cicardi & Zuraw, 2018).

Meanwhile, ACEI angioedema typically presents with focal swelling that is often asymmetric, edema of the lips and tongue, and nonpitting edema to the face (Guyer & Banerji, 2018). ACEI angioedema is painless and swelling may progress over hours (Sica & Black, 2002). Skin lesions, itching, and fever are uncommon with ACEI angioedema (Guyer & Banerji, 2018). Patients who present with angioedema should have standard laboratory test results and liver function tests, C-reactive protein/erythrocyte sedimentation rate, and complement C4 protein levels to help rule in and out causes (Zuraw, 2017). During an ACEI angioedema episode, C4 protein levels will remain the same. An increased or decreased C4 protein level may provide clues to the provider to recognize different bradykinin-mediated angioedema causes (Guyer & Banerji, 2018). In addition, ultrasonography or computed tomography may show small bowel wall edema, ascites, or incomplete obstruction and these findings can facilitate treatment decisions based on the buildup of bradykinin (Zuraw, 2017). Finally, an echocardiogram can help identify transient myocardial dysfunction, sometimes observed with ACEI angioedema (Sica & Black, 2002).

Pathophysiology

ACEI medications are used to reduce high blood pressure by slowing the conversion of angiotensin I to angiotensin II, which causes the blood vessels to enlarge. Angiotensin I is produced in the liver and then distributed into the bloodstream. Angiotensin-converting enzyme, also known as kininase II, is metabolized in the lungs where it converts angiotensin I to angiotensin II. The primary function of angiotensin II is to cause tissues and muscles around blood vessels to contract, which promotes narrowing of the vessels and can result in high blood pressure (Ogbru, 2017). Angiotensin II is also responsible for inactivating bradykinin (Guyer & Banerji, 2018). ACEI can result in up to 10-fold increases in bradykinin levels due to the slowed conversion of angiotensin I to angiotensin II. The tongue then begins to swell due to a rise of plasma extravasation in the submucosal tissue caused by high levels of bradykinin, resulting in increased vascular permeability (Guyer & Banerji, 2018).

Treatment

Initial treatment of ACEI angioedema should include monitoring vital signs every 15 min, electrocardiogram, venous access, and laboratory testing. The patient must be monitored for airway maintenance, and the care team should be prepared to perform intubation using nasotracheal, fiber-optic, or video laryngoscopic techniques (Wood, Choromanski, & Orlewicz, 2013). Corticosteroids, antihistamines, and epinephrine may be used to help rule out anaphylaxis but will have little to no effect on ACEI angioedema (Salem & Alchakaki, 2016). Patients who have confirmed ACEI angioedema with C1 esterase inhibitor deficiency and no allergen-induced angioedema should not receive antihistamines, corticosteroids, or epinephrine due to the lack of benefit (Lang et al., 2012).

ACEI use may result in swelling in any part of the body, but swelling around the face can be life-threatening (Guyer & Banerji, 2018). In moderate to severe cases of ACEI angioedema with respiratory distress or failure, 2–4 units of FFP may be administered. FFP contains kininase II, identical to the angiotensin-converting enzyme, and will degrade the elevated levels of bradykinin that are causing the angioedema. Once bradykinin levels begin to decline, vascular permeability decreases and plasma extravasation occurs (Chaava et al., 2017). ACEI angioedema typically decreases within 2 hr after the initiation of FFP (Chaava et al., 2017). FFP is associated

with a 1% chance of side effects. Side effects of FFP include a headache, nausea, pruritus, and urticaria (epocrates, 2018).

The Ishoo classification system is used to monitor the upper airway. Patients with Stage I (facial rash and edema) and Stage II (soft palate edema) can be managed as outpatient (Moellman, Bernstein, & Lindsell, 2014). Most patients are discharged from the emergency department if swelling of the tongue and larynx decreases and no other airway compromise is present. Most observation times range from 2–6 hr (Bernstein, Cremonesi, Hoffmann, & Hollingsworth, 2017). Patients with Stage III (lingual edema), Stage IV (laryngeal edema), or swelling of three airway sites or (i.e., lips, tongue, mouth, soft palate, or larynx) should be admitted for a minimum of 24 hr of observation (Moellman et al., 2014).

Following a diagnosis of ACEI angioedema, ACEI medications should be discontinued. Gastrointestinal upset can continue for several weeks after discontinuing ACEI. Once a reaction to an ACEI occurs, the patient should never receive this category of medication again and ACEI should be listed as an allergy in the patient's medical record.

Prior to discharge, patients should be educated regarding the importance of returning to the emergency department if swelling or other symptoms reoccur. Patients who have had a reaction to ACEI and discontinued the medication have a 46% chance of recurrence of angioedema. Most recurrent episodes occur within the first month after medication discontinuation. Patients should return to the emergency department if difficulty breathing or airway swelling occurs.

Following discharge, patients should schedule a follow-up with a primary physician, allergist, or immunologist within a week. Recurrent tissue swelling may occur for months after initial treatment but should eventually resolve (Guyer & Banerji, 2018). The patient should be referred to an allergy specialist if swelling continues after the first few months (Guyer & Banerji, 2018). Most patients have a high success rate for recovering from ACEI angioedema.

CONCLUSION

ACEI medications are a leading cause of drug-induced angioedema. ACEI angioedema is caused by an accumulation of bradykinin and affects the lips, tongue, and face, occurring anywhere from months to years after starting the medication. A patient should seek medical attention as soon as facial swelling begins. There is no diagnostic test specific for ACEI angioedema and other potential causes of angioedema should be ruled out (Guyer & Banerji, 2018). Emergency treatment of angioedema includes airway management, administration of FFP, and discontinuation of ACEI.

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