EM CASE OF THE WEEK

BROWARD HEALTH

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January 8, 2023 I Vol 16 I Issue 1

ACE Inhibitor-Induced Angioedema

A 50-year-old African American female with a past medical history of hypertension well controlled with Lisinopril, presented to the ED with difficulty swallowing and throat pain persisting for the past 2 hours. She woke up at 4:00am with dry, itching sensation in her throat, which resolved with drinking water. At 10:00 am, she started experiencing dry throat and feeling like "something swollen back there". She was unable to swallow due to the discomfort since that time. She denied similar prior episodes, any known allergies, fevers, chills, rhinorrhea, cough or dyspnea.

Vitals signs are significant for blood pressure 168/99 mmHg, otherwise within normal limits. On physical exam, patient has an edematous and swollen posterior pharynx and uvula. No overlying erythema is appreciated in the throat. She is spitting out copious amounts of saliva and is unable to swallow without extreme discomfort and the persistent feeling of "something in the back of my throat". There is no lymphadenopathy in the head and neck. She is anxious appearing and visibly uncomfortable, but in no acute respiratory distress.

Which of the following is the most appropriate initial treatment for this patient's condition?

A. Immediate intubation

B. Intramuscular Epinephrine, Oxygen and IV fluids

C. Immediate discontinuation of Lisinopril, Diphenhydramine 50mg and IV Methylprednisolone 60mg.

D. Immediate ENT consult

E. Icatibant

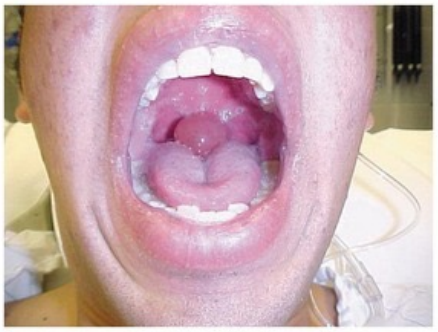

Figure 1. Angioedema is defined as self-limited, localized swelling of the dermis, subcutaneous and/or submucosal tissues caused by fluid leakage into the interstitium. Most commonly occurs in the face, lips, tongue, or upper airway. [1,5]

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Discussion

The correct answer is C, immediate discontinuation of Lisinopril, Diphenhydramine 50mg and IV Methylprednisolone 60mg.

ACE inhibitors are the leading cause of drug induced angioedema in the US. They induce angioedema in 0.1 to 0.7 percent of recipients, and there is a constant risk of angioedema occurrence over the duration of medication use. There is a five times greater risk in people of African descent.

ACE inhibitor therapy causes bradykinin levels to become elevated due to impaired metabolism, leading to release of nitric oxide and prostaglandins. Increased bradykinin levels stimulate vasodilation, hypotension and increased vascular permeability in the post capillary venules, allowing for plasma extravasation into the submucosal tissues.

Clinical Manifestations

Patients with angioedema present with asymmetric, non-pitting, non-dependent swelling of the lips, tongue, upper airway, or face. Laryngeal involvement with dyspnea and inspiratory stridor predicts a potential life-threatening reaction.

Histamine-mediated angioedema is often associated with urticaria, bronchospasm, hypotension, and pruritus. Onset of the reaction occurs within 30 minutes to 2 hours of the exposure. Resolution occurs over 12 to 24 hours.

Bradykinin-mediated angioedema (such as ACE inhibitor-induced angioedema) is associated with laryngeal edema (stridor, dyspnea, dysphonia), extremity or truncal edema, and may manifest with GI symptoms such as colicky abdominal pain, nausea, and vomiting. It is not associated with urticaria and pruritus.

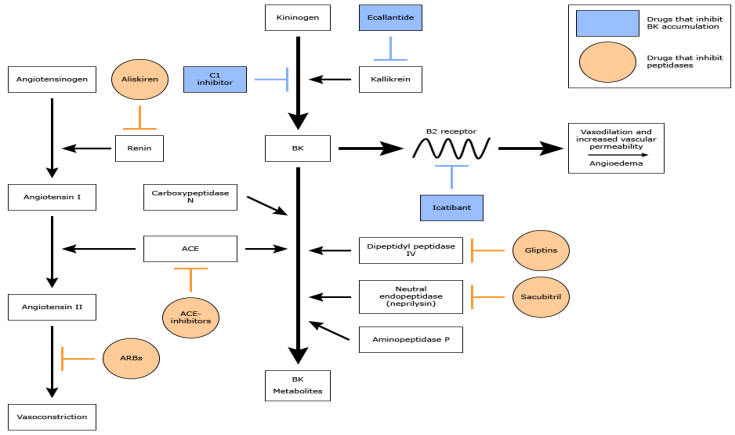

Figure 2. The RAAS and bradykinin degradation pathway

Onset develops over hours following the trigger or exposure. Resolution occurs over the following 24 to 72 hours. Over half of the cases of ACE inhibitor-induced angioedema occurs during the first week of exposure to ACE inhibitors. However, cases can occur at any time during treatment, from hours to years after initiation of the drug.

Diagnosis

Diagnosis of ACE inhibitor-induced angioedema is made clinically, based on the above-mentioned physical exam findings and patient history of ACE inhibitor use. Diagnosis is confirmed with discontinuation of ACE inhibitors and no further episodes of angioedema. There are no definitive labs to diagnose ACE inhibitor-induced angioedema. A CBC, CMP, ESR/CRP are indicated in all patients with isolated angioedema. A serum level of C4 complement protein is indicated if there is suspicion of a bradykinin-mediated angioedema. A low C4 should prompt follow up labs including C1 inhibitor function and protein levels and C1q levels. CT scan of the neck may be indicated, if fear of respiratory compromise, or if another cause of swelling is suspected. CT abdomen is indicated if angioedema involving the bowel wall is suspected.

Treatment

Airway Monitoring – If the mouth or throat is involved, the airway should be evaluated and repeatedly monitored until swelling is resolving. Intubation and mechanical ventilation may be required if there is evidence of airway compromise

Discontinuation of ACE inhibitor – Symptoms tend to self-resolve within 42 to 72 hours. However, if ACE inhibitors are continued, there is an increased rate of angioedema recurrence and subsequent attacks may become more severe or life threatening. Patients have a lifelong contraindication to ACE inhibitors.

Allergic Angioedema – H1 antihistamines (cetirizine up to 20mg BID or Diphenhydramine 25 to 50mg QD for 1-3 days) and Glucocorticoids (Methylprednisolone 60 to 80mg IV initially, then transitioned to oral and tapered over 5-7 days or Prednisone 20 to 40mg PO QD tapered over 5-7 days). If Anaphylaxis is suspected, treatment with IM Epinephrine, IV fluids and oxygen.

Therapies of Unproven Efficacy – In hereditary angioedema (a bradykinin-mediated angioedema) and potentially in ACE inhibitor-induced angioedema, abortive therapies such as Icatibant (a synthetic bradykinin B2 receptor antagonist), C1 inhibitor concentrate (inhibits kallikrein), TXA 1g PO or IV, Ecallantide 30 to 60 mg (inhibitor of kallikrein) and FFP (contains ACE) may be used.

Take Home Points

- There are many causes of angioedema, including mast cell-mediated (histamine mediated secondary to allergic reactions and NSAIDs) and bradykinin-mediated angioedema (due to ACE inhibitor use or enzyme deficiencies). Approximately 20-40% of all cases in the ED are due to ACE inhibitor use.
- The diagnosis of ACE inhibitor-induced angioedema is based upon clinical presentation of asymmetric, non-pitting, non-dependent swelling of the lips, tongue, upper airway, or face. Symptom onset is acute, over hours and may present at any time during medication use.
- Mainstay of treatment for ACE inhibitor-induced angioedema is airway monitoring, and immediate discontinuation of ACE inhibitors. For potential allergic angioedema and in the acute setting of ACE inhibitor angioedema, H1 antihistamines and glucocorticoids are indicated. If anaphylaxis is suspected, treat with IM Epinephrine, IV fluids and oxygen. Other potential abortive treatments of unproven efficacy for ACE inhibitor-induced angioedema include Icatibant, C1 inhibitor concentrate, TXA, Ecallantide and FFP.

About the Author

This month's case was written by Lauren Polan-Couillard. Lauren is a 4th year medical student from the American University of the Caribbean School of Medicine. She did her emergency medicine rotation at Broward Health North in May 2022. Lauren plans on pursuing a career in Emergency Medicine after graduation.

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