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CLINICAL VIGNETTE

A Case Report of ACE Inhibitor Induced Angioedema and Review of Management Options

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Introduction

Angiotensin Converting Enzyme (ACE) inhibitor induced angioedema is a rare but life threatening complication of a common hypertensive therapy. This popular class of anti-HTN medications is commonly used because of the favorable profile that ACE inhibitors have in regards to patients with a history of heart failure and their effects on curbing the deleterious remodeling of the heart. Understanding the pathophysiology of ACE inhibitor induced angioedema and how it differentiates itself from other types of angioedema or swelling can be critical in instituting appropriate treatment modalities.

Case Report

A 55-year-old obese male presents to the emergency room at a county hospital with tongue swelling and sensation of throat closing. Symptoms began that morning about two hours before and quickly progressed. His history is significant for CAD with drug-eluting stent to right coronary artery 15 months ago, Atrial Fibrillation, HTN, history of CHF, recent echo displaying an ejection fraction of 25%, Asthma/COPD, and ETOH abuse. Interestingly, patient had a previous episode of angioedema 15 months ago while taking an ACE inhibitor, which was discontinued. By patient report and for unclear reasons, he restarted the benazepril and had been taking the medication for the last 5 months per his doctor's orders. There had been no adverse medication related events in the interim.

Anesthesiology and Head and Neck were immediately consulted. On physical exam, he was in a tripod position on a 100% non-rebreather mask. He was drooling, dyspneic, dysphonic, and only able to open his mouth minimally. He had obvious macroglossia with tongue protrusion precluding visualization of the soft and hard palate. His submental space had firm non-fluctuant swelling. Vital signs were 212/126, HR 84, RR 18, and spO₂ 93%.

The patient received IV diphenhydramine, famotidine, and methylprednisolone. Fresh frozen plasma was ordered. There was debate on the efficacy of epinephrine and its potential contribution to myocardial oxygen demand. Nebulized racemic

epinephrine was administered and IM epinephrine was also given. Emergency crico-thyroidotomy tray was available at bedside.

An operating room setup was initiated and a quick non-invasive view with a nasal fiberoptic scope showed soft palate edema, visualization of the oropharynx with enlargement of the base of tongue, a non-enlarged epiglottis, and a large pooling of secretions, and inability to visualize vocal folds. Fresh frozen plasma was subsequently transfused, and the patient was transferred to the operating room. By time of arrival, he had improvement of airway swelling and decreased respiratory distress. A successful awake tracheotomy was performed, and the patient was transferred to intensive care unit for postoperative monitoring. His postoperative course was uneventful with airway swelling returning to normal 48 hours after the initial event.

Discussion

Ace inhibitors represent nearly 30% of anti-hypertensive medications prescribed in the United States. They are used both as a single agent and in combination therapy. Evidence supports the use of ACE inhibitors particularly in patients with history of myocardial infarction and depressed systolic function. Studies demonstrate increased survival and decreased morbidity and mortality from cardiovascular events.¹ ACE inhibitors are also beneficial in patients with proteinuric kidney disease, reducing proteinuria in patients with or without diabetes, and is commonly used for its renal protective effects.²

ACE inhibitor therapy does not come without problems. ACE inhibitor induced angioedema is a rare but life-threatening complication of this antihypertensive therapy. Incidence is rare, estimated between 0.1 to 2.2%.³ However, 30-40% of all angioedema emergency room visits are attributable to ACE inhibitor induced angioedema and are the leading drug-induced cause of angioedema.⁴

Classic treatment of angioedema includes steroids, epinephrine, and antihistamines. However, specifically in ACE inhibitor induced angioedema, there is little evidence of efficacy despite their use. Correctly identifying the pathology can be confusing but may be critical in instituting the correct therapy.

First, the presence or absence of urticarial should be determined. Urticaria is characterized by raised pink pruritic, edematous lesions that are up to a few centimeters in diameter. The pruritus indicates a disorder of histamine etiology,⁵ which is not classic for ACE inhibitor induced angioedema. Standard antihistamine and treatments should be instituted.⁶

Angioedema is defined by non-pruritic swelling of the subcutaneous tissue or mucosa and may be due to histamine or bradykinin pathology. Histamine related angioedema, such as allergic angioedema, should also be treated with typical antihistamines and epinephrine.

The bradykinin pathway consists of prekallikrein, which is converted to kallikrein, and then cleaves high molecular weight kinogen ultimately to release bradykinin. Hereditary and acquired angioedema are types of bradykinin mediated angioedema, caused by factor C1 inhibitor deficiency or dysfunction, which results in amplified kallikrein synthesis and conversion to ultimately more bradykinin activity.

In contrast, ACE inhibitor induced angioedema occurs when angiotensin converting enzyme blocks the degradation of bradykinin and to some degree substance P. The increase in bradykinin and substance P activity cause increased tissue permeability and vasodilation, leading to tissue swelling and edema.⁷ ACE inhibitor induced angioedema often affects the face and airway. Airway compromise occurs in up to ten percent of patients with occasionally associated mortality.⁸ A visceral component can also present with nausea, vomiting, diarrhea, and abdominal cramping and can affect the mucosa of the entire intestinal tract.⁹

Treatment of angioedema depends on understanding the etiology of the angioedema, as well as treatment availability at the institution. Regardless of the etiology of airway compromise, airway management including careful monitoring and possible invasive measures to secure patient airway can be critical. Intubation or emergent surgical airway may be indicated. Discontinuation of inciting agent is crucial. Although symptoms of ACE inhibitor induced angioedema should subside 48 to 72 hours after symptoms present, the medication should never be restarted due to the unpredictability of recurrent episodes. One study found that even with discontinuation of ACE inhibitors after angioedema episode, there were frequent recurrences.¹⁰

Most studies suggest antihistamine therapy is unlikely to produce benefit in ACE inhibitor induced angioedema.¹¹ One

study did however demonstrate decreased intubation times and ventilator dependence on a pool of patients that received antihistamine therapy.¹² Although not considered mainstay, there may be little downside to antihistamine treatment. We await analysis of risks and benefits of antihistamine treatments particularly with epinephrine. Antihistamines may be useful, especially when etiology of airway swelling is unclear.

Since ACE inhibitor induced angioedema is felt to be caused by disorder of the bradykinin pathway, newer medications have been demonstrated to provide benefit in this life-threatening condition. Icatibant is a selective Bradykinin B2 antagonist. At an average cost of \$10,000 for the 30 mg, 3ml subcutaneous injection,¹³ it may be cost prohibitive. This drug is already used to treat hereditary angioedema and has similar improvement with a single dose, compared with standard steroid, antihistamine therapy.¹⁴

Purified C1 concentrate has benefit in ACE inhibitor induced angioedema in isolated cases.^{15,16} Purified C1 concentrate is a human plasma derived, purified, pasteurized, lyophilized concentrate of the protein C1 esterase inhibitor supplied as a freeze-dried powder for reconstitution for intravenous administration. The recommended initial dose is 20 units per kg body weight by intravenous injection, costing about \$5,000 per dose for a normal-sized adult.¹⁷

For institutions with financial constraints or logistical barriers to stocking these expensive life saving medications, fresh frozen plasma has been used and shown benefit in ACE inhibitor induced angioedema, documented in case reports.¹⁸ It is theorized that increased kininase II activity from fresh frozen plasma transfusions assists in the breakdown of bradykinin.¹⁹ Typically 2 units of plasma are transfused with an average cost \$60/unit.²⁰

Ecallantide, which has been used also to treat hereditary angioedema, has not consistently worked for ACE inhibitor induced angioedema. Ecallantide inhibits conversion of high molecular weight kinogen to bradykinin. Cost is about \$13,000 for a dose of three 10 mg 1 ml subcutaneous injections.²¹ Since ACE inhibitor induced angioedema is a disorder that inhibits bradykinin breakdown and not related to the synthesis of bradykinin, it might be logical that ecallantide does not specifically address the primary problem. Some studies demonstrate some benefit, though ecallantide is not generally recommended for ACE inhibitor induced angioedema, versus suspected hereditary angioedema.²²

Summary

ACE inhibitor induced angioedema is a rare complication of common anti-hypertensive therapy. This potentially life threatening emergency needs to be identified and differentiated from other similar conditions. In addition to addressing the

immediate airway concerns, proper therapy should be initiated. If true ACE inhibitor induced angioedema is present, typical treatments for histamine related angioedema such as steroids, anti-histamines, and epinephrine may not be effective. If readily available at your institution, icatibant should be administered if the condition is deemed life threatening as it directly blocks the action of bradykinin. Purified C1 concentrate may also be effective. Fresh frozen plasma can also be given if these products are not readily available with some historical efficacy and lower cost than these newer medications. When the clinical picture is confusing, it may be appropriate to treat this critical condition with measures that act upon different pathways for multiple etiologies.

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