Angiotensin-converting enzyme inhibitor–associated angioedema treated with c1-esterase inhibitor: A case report and review of the literature

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ABSTRACT

Case Report: *A 59-year old man currently on >5 years of angiotensin-converting enzyme inhibitor (ACEI) therapy presented to the emergency department with angioedema of the tongue and difficulty swallowing. After receiving conventional therapy of antihistamine, steroids, and epinephrine, the patient's condition continued to deteriorate, with imminent intubation. The patient was treated with a C1-esterase inhibitor (C1-INH) and experienced rapid resolution of symptoms, which avoided airway complications.*

Discussion: *Although no therapy has been approved for the treatment of ACEI–associated angioedema (AAE), the conventional therapy (antihistamine, steroids, and epinephrine) often proves ineffective in this bradykinin-mediated angioedema. There are drugs approved and used for hereditary angioedema that may be effective in the acute phase of ACEI-AAE that may prevent the need for further interventions, such as intubation and tracheotomy. These drugs include icatibant, ecallantide, fresh frozen plasma, and C1-INH.*

Conclusion: *The literature and clinical evidence indicate C1-INH can be effectively used in the treatment of ACEI-AAE to halt the progression of the condition, prevent airway compromise and the need for intervention, and lead to rapid resolution of symptoms.*

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No current therapy or drug has been approved for the treatment of angiotensin-converting enzyme inhibitor (ACEI) associated angioedema (AAE). Despite conventional therapy and management of angioedema, this condition can progress and require further intervention. This is a case report of a patient for whom conventional therapy failed. He was treated with C1-esterase inhibitor (C1-INH) and experienced rapid resolution of his condition. We reviewed the literature and various off-label treatments that were reported to be effective in the management of this condition.

METHODS

We performed a PubMed search for bradykinin-mediated angioedema and treatment (C1-INH) to include hereditary angioedema (HAE), and, specifically, ACEI associated or induced angioedema (AAE). We described the case and treatment with outcome. We also discussed and provided an overview of the pathophysiology of ACEI-AAE and the current literature on treatments and clinical presentation. No institutional review board approval was required.

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Case Presentation

A 59-year-old African American man presented to the emergency department with unilateral left-sided tongue swelling, difficulty swallowing, and throat tightness. The patient reported that his tongue had significantly swollen over the course of an hour. The patient had no dyspnea, abdominal pain, nausea, vomiting, or syncope, or any cutaneous symptoms (rash or hives). He also had no history of angioedema. The patient did not have any food or latex allergies. He also did not have any recent insect stings or a family history of angioedema. His current medications were hydrocodone for rheumatoid arthritis pain, metformin, exenatide, and insulin glargine for his diabetes mellitus, and a daily aspirin. The patient was also taking Lotrel (amlodipine besylate and benazepril; Lupin Pharmaceuticals, Inc., Baltimore, MD), a calcium channel blocker/ACEI, for his hypertension on a daily basis for the past 5 years.

In the emergency department, the patient was rapidly evaluated; intravenous (IV) access was obtained, and he underwent management for histamine-mediated angioedema. He received methylprednisolone 125 mg IV, diphenhydramine 25 mg IV, and epinephrine 1 μg IV (normally dosed intramuscularly; however, he

was given an IV because IV access was already obtained) without improvement in symptoms. Fifteen minutes after the initial treatment; the patient received an additional 9 μg of epinephrine IV without response. Thirty-five minutes after treatment was initiated, the patient's condition continued to decline, and airway collapse was imminent. The patient was dosed with ranitidine 150 mg IV and C1-INH (Berinert [CSL Behring GmbH, Marburg, Germany], 3000 U, 20 U/kg IV). A response was noted 15 minutes after the dose of the C1-INH, with reduction of swelling and resolution of dysphagia. The patient was admitted to the medical intensive care unit for observation overnight and for evaluation by an otolaryngology specialist. The patient's complement levels were drawn and revealed no abnormalities in C4 level (35 mg/dL) and C1-INH functionality (105% mean normal).

The diagnosis of ACEI-AAE was confirmed based on his history, patient profile, and normal complement levels and functionality. The patient was discharged the following day without complication, with a scheduled follow-up with the allergy department. At the time of diagnosis of ACEI-AAE, the patient was instructed to discontinue and avoid future use of all ACEIs. He was transitioned to valsartan/hydrochlorothiazide (160 mg/25 mg) for blood pressure control. At 1-year follow-up, the patient remained without recurrence of angioedema, and his blood pressure remained well controlled on the combination medication.

DISCUSSION

This patient's presentation is not uncommon. Overall, the risk of developing ACEI-AAE is relatively low, at 0.1 to 0.7% of recipients.[1–3] However, given the large number of people (35–40 million individuals in 2001)[4] in the United States who take an ACEI for various indications (*i.e.*, hypertension, myocardial infarction, heart failure with systolic dysfunction, diabetes, and chronic kidney disease),[5] ACEI-AAE is the leading cause of drug-induced angioedema in the United States. It accounts for 25 to 40% of all emergency department visits for angioedema each year.[4]

The time frame for the presentation of ACEI-AAE varies widely. ACEI-AAE may occur at any time, from commencing therapy to years after treatment.[1,2] In our case, the reaction occurred after 5 years of ACEI therapy. In a large retrospective study, two-thirds of angioedema episodes occurred within the first 3 months of therapy[2]; however, there have been multiple case reports that documented episodes of ACEI-AAE after years of stable therapy, as with our patient.[1,2,5–7]

ACEI-AAE, as with other types of angioedema, is characterized as an asymmetric, nonpitting swelling of the subcutaneous or submucosal tissues, which most commonly affects nondependent areas. In ACEI-AAE, the typical areas of involvement include the lips, tongue, face, and intestines (which is often characterized by episodic abdominal pain). There is an absence of itching or urticaria in ACEI-AAE because the presence of urticaria merits suspicion of multiple other etiologies.[7,8] ACEI-AAE is typically episodic and often follows a fairly predictable time course. In the case described, the swelling developed over several hours, which is deemed typical because ACEI-AAE develops over minutes to hours, followed by a peak in symptoms, and resolution over the next 24 to 72 hours. However, complete resolution can be unpredictable and may take days, despite ACEI discontinuation.[4,7] Typically, the reported duration is 2–5 days and resolves spontaneously and requires no intervention.

The role of bradykinin in ACEI-AAE is well accepted. Bradykinin is an inflammatory vasoactive peptide that leads to increased capillary permeability and acts as a potent vasodilator. ACEIs block the effects of the angiotensin-converting enzyme (ACE) (also known as kininase II), which impacts the renin-angiotensin-aldosterone pathway and diminishes the degradation of bradykinin. The liver produces angiotensinogen, which is converted to angiotensin I in the kidney by renin. Angiotensin I is metabolized in the lungs by ACE to produce angiotensin II. Angiotensin II causes vasoconstriction through stimulation of angiotensin I and II receptor.

Although ACE is the primary peptidase involved in the degradation of bradykinin (these effects are blocked by ACEI), angiotensin II also participates in the inactivation of bradykinin.[9] Thus, ACEI further leads to increased levels of bradykinin by decreasing the production of angiotensin II. This leads to elevated levels of bradykinin, which also causes the release of nitric oxide and prostaglandins, which results in vasodilatation and hypotension.[9] Elevated levels of plasma bradykinin activity have been demonstrated in patients with ACEI angioedema.[10] The high levels of bradykinin stimulate vasodilation and increase vascular permeability of the postcapillary venules and allow for plasma extravasation into the submucosal tissue, which leads to angioedema.[6,11]

Although the majority of patients who take an ACEI will never experience ACEI-AAE, there are various risk factors that have been identified with an increased likelihood of such reactions. Our patient possessed risk factors, including African American ethnicity and daily aspirin use. Other risk factors to consider in patients with angioedema include the following: a history of previous episodes of angioedema, age >65 years, aspirin and other nonsteroidal anti-inflammatory use, female sex, smoking, seasonal allergies, mechanistic target of rapamycin inhibitor use, a transplantation, and an underlying C1-inhibitor deficiency (hereditary

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or acquired).[1,4,10,12,13] There seems to be a reduced risk of angioedema due to ACEIs in people with diabetes.[1]

The primary treatment of ACEI-AAE is first and foremost discontinuation of the inciting drug and management of the airway. The angioedema typically spontaneously resolves within 24–72 hours. Patients who experienced angioedema attributed to an ACEI should never resume treatment by this class of medication. In addition to discontinuation of the inciting drug and management of the airway, most angioedema attacks should be initially treated as a histamine-mediated condition because the majority of angioedema cases are histamine mediated.[14]

The treatment includes antihistamines, glucocorticoids, and epinephrine. Although these medications are the first-line treatment for angioedema, they are considered ineffective or minimally effective in treating bradykinin-mediated angioedema.[3,8] In this case and multiple other reported cases, this therapy aimed at histamine-mediated angioedema was ineffective. Without any medication approved for ACEI-AAE,[14] the next course of management is debatable yet critical when the symptoms of ACEI-AAE continue to progress and threaten the airway. There have been studies and reports that support the use of various drugs in treating bradykinin angioedema symptoms and preventing airway intubation. These drugs include synthetic bradykinin B_2-receptor agonists, kallikrein inhibitors, fresh frozen plasma (FFP), and complement-1 esterase inhibitors (C1-INH).

Icatibant, a synthetic bradykinin B_2-receptor antagonist, is approved for the acute treatment of HAE attacks and has been shown to be effective for the treatment of ACEI-AAE. This drug seems to be the most efficacious in the first few hours of the angioedema attack while the swelling is progressing. The efficacy of icatibant was demonstrated in a randomized trial of 27 adults who presented to the emergency department with angioedema of the upper autodigestive tract while taking an ACEI.[15] All the subjects randomized to icatibant experienced initial relief in ~2 hours and complete resolution of angioedema in a median time of 8 hours. In comparison, those who received standard therapy (steroids, antihistamines, and epinephrine) had resolution in a median of 27.1 hours, with three patients who required rescue therapy (30 mg of icatibant and 500 mg prednisolone) and with one underwent tracheotomy.[15]

Ecallantide (DX-88; Dyax Corp., Cambridge, MA) is a recombinant 60 amino-acid protein that specifically inhibits plasma kallikrein. This inhibition prevents the breakdown of high-molecular-weight kininogen to bradykinin, which, in turn, leads to the downregulation of high-molecular-weight kininogen (the precursor of bradykinin),[11,16] which, in turn, halts the accumulation of bradykinin. Two randomized controlled trials (RCT)[16,17] were performed to compare efficacy of standard therapy with ecallantide versus standard therapy with placebo, however, with mixed results. The first RCT[16] involved 50 adults assigned to receive either ecallantide (30 mg) or placebo (in addition to standard therapy with glucocorticoids and antihistamines). The patients were required to have presented within 12 hours of symptom onset and to have worsening symptoms or failure to improve during 2 hours of initial observation. The primary end point was eligibility for discharge within 4 hours of treatment. Discharge criteria were met within 4 hours in 31 versus 21% of subjects who received ecallantide and placebo, respectively (95% confidence interval, −14 to 34%). Although the confidence intervals overlapped, which demonstrated no effect, the study did demonstrate that ecallantide is safe to use and may increase the proportion of patients who meet early discharge criteria by ~10%.[16]

A second RCT[17] was performed in which 76 adults with angioedema on current ACEI therapy presented for emergency care within 12 hours of symptom onset; 86% received standard therapy (glucocorticoid, antihistamine, epinephrine) and either ecallantide (at doses of 10 mg, 30 mg, or 60 mg) or placebo. The mean time from symptom onset to treatment was 7.2 hours, and 72% of patients who received placebo improved during that time. The primary end point was defined as eligibility for discharge from the emergency department within 6 hours of receiving treatment in both groups. No difference was found between the groups.[17]

FFP (solvent detergent-treated plasma or FFP) has also been shown to be effective in various case reports. FFP works in bradykinin-mediated angioedema by supplying C1-INH and ACE to catabolize the accumulated levels of bradykinin.[18] Case reports described administration of FFP, which led to rapid improvement of ACEI-AAE without further recurrence of symptoms.[19] In addition, a recent retrospective cohort study demonstrated that control patients, who were not treated, were more frequently intubated in the emergency department and required more extended intensive care unit admissions (60 versus 35%, $p = 0.05$; 3.5 versus 1.5 days, $p < 0.001$, respectively).[18]

Another option for the treatment of ACEI-AAE is the use of purified C1-INH (Berinert). C1-INH functions through the inactivation of plasma kallikrein and factor XIIa (Hageman factor), which is thought to modulate vascular permeability by preventing the generation of bradykinin, a potent mediator of vascular permeability,[20] which, thus, counteracts the accumulation of bradykinin caused by the ACEI.[8,11] This was demonstrated to be effective for ACEI-AAE in various case reports, with resolution of symptoms 20 minutes to 2 hours after dosing.[21–24] However, there has not been a

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placebo controlled trial to prove this. One case series[8] of 10 patients with ACEI-AAE who were treated with an average of 1000 U of C1-INH demonstrated symptom improvement at a mean time of 88 minutes and complete resolution of symptoms at 10.1 hours without the need for further interventions. This was contrasted with 47 historical patients who underwent conventional therapy (antihistamines and steroids), with a mean time of complete resolution of symptoms at 33.1 hours (three patients with tracheotomy and two who were intubated secondary to symptom progression and worsening).[8] This improvement after C1-INH infusion was demonstrated despite underdosing the patients. Current proposed dosing is 20 U/kg (approved dose for types 1 and 2 HAE), which would have increased the average dose to 1500 U. As noted in our case, the patient was treated with 3000 U at a dosing of 20 U/kg and experienced improvement of symptoms within 15 minutes of administration.

CONCLUSION

Although the risk of ACEI-AAE is relatively low, the occurrence accounts for up to 40% of emergency department visits for angioedema.[4,6] However, no drug therapy has been approved for the acute management of ACEI-AAE.[8,14] The current recommended management for allergic and/or histaminergic angioedema is ineffective for bradykinin-induced angioedema and is rarely able to prevent progression of the swelling and angioedema. There are drugs used for HAE that may be effective in the acute phase of ACEI-AAE and may prevent the need for further interventions, such as intubation and tracheotomy.[8] These drugs include icatibant, ecallantide, FFP, and C1-INH. Our case reports adds to the body of literature and clinical evidence that C1-INH may be effectively used in the treatment of ACEI-AAE to halt the progression of the condition, prevent airway compromise and the need for intervention, and lead to rapid resolution of symptoms.

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