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Case study

Angiotensin-converting enzyme inhibitor-induced angioedema may not be a class-related event

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ABSTRACT

Angioedema is a rare but potentially life threatening condition commonly associated with angiotensin-converting enzyme inhibitors (ACEIs). The incidence is approximately 0.1–0.2% and may occur within the first week to several years of taking an ACEI. We present a case of a 37-year-old African American male who was uneventfully taking a drug combination of quinapril and hydrochlorothiazide. When his medication was changed to lisinopril he developed an acute swelling of his lower lip and chin on fifth dose. The angioedema subsided within 24 hours after discontinuation of lisinopril. Therefore, this suggests that future treatment with ACEIs, as well as angiotensin receptor blockers (ARBs), is not recommended in this type of patient.

Keywords: angioedema, angiotensin-converting enzyme inhibitors, lisinopril, hypertension, African American

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INTRODUCTION

Angioedema presents as an acute, painless, nonpruritic and well-circumscribed edema of subcutaneous and submucosal tissues that usually resolves in 24 to 48 hours.¹ This condition is well documented and is a potential lethal complication commonly associated with ACEI. Since the extensive use of this class of medication for hypertension,² congestive heart failure,³ chronic renal failure,⁴ diabetes⁵ and acute myocardial infarction,⁶ the incidence of angioedema has been reported to be 1–2 cases per 1000 patients.⁷ This may occur within the first week to several years after first taking an ACEI.⁸

CASE REPORT

A 37-year-old African American male with a history of hypertension presented to the emergency room complaining of a swollen lower lip and chin when he arose in the morning. He denied shortness of breath, wheezing or voice changes. He was being treated with a combination of quinapril/hydrochlorothiazide (Accuretic®) for three years without adverse effects. Subsequently, he was switched to the same combination of quinapril/hydrochlorothiazide with a different brand (Quinaretic®) for 7 months, also without adverse effects. He discontinued all medications for three months and then he started lisinopril (20 mg/day) 5 days prior to developing angioedema. Five years previously, he had an acute allergic reaction with swelling of his lower lip, chin and mild dyspnea three hours after eating an avocado. This allergic reaction resolved spontaneously within 20 minutes. Currently, he denies recent contact with insects, consumption of foods such as avocado, nuts, shellfish, milk, eggs, illicit drug use, over the counter medications or herbal remedies. His family history was significant for hypertension.

On examination in the emergency room he appeared anxious but in no acute distress. His vital signs were temperature 37.1°C, pulse oximetry 98% on room air, blood pressure 120/89 mmHg, pulse 90/min and regular and respirations 18/min and non-labored. He was noted to have significant non-pitting edema of his lower lip and chin with a normal tongue and clear oropharynx. Heart rhythm was regular and without murmurs, rubs or gallops. His lungs were clear to auscultation and percussion, abdomen was benign. Extremities were negative for cyanosis or peripheral edema. There was no evidence of skin rash, urticaria or petechia. The remainder of physical exam was unremarkable. Laboratory tests showed normal CBC, Chemistry 8, liver function, thyroid function, ANA, and complement levels (C1q, C2, C4, CH50, and C1 esterase inhibitor).

In the emergency room he was treated intravenously with methylprednisolone (Solu-Medrol) 125 mg, diphenhydramine (Benadryl) 25 mg, famotidine (Pepcid) 20 mg and 0.9% normal saline at 50 ml/h. Lisinopril was discontinued and he was admitted to a general medical floor for observation and respiratory monitoring. He was started on loproressor for blood pressure control. By the next morning his symptoms were completely resolved. He did well and was discharged home with tapering doses of methylprednisolone (Medrol) and diphenhydramine as needed for itching, rash or swelling. He was instructed to avoid taking ACEIs as well as ARBs, and was advised to follow up with his primary care physician within one week.

CASE DISCUSSION

Angioedema is a clinical diagnosis. The overall incidence of angiotensin converting enzyme inhibitor-associated angioedema has been reported to be 1–2 cases per 1000 persons.⁷ African Americans have an incidence rate four times higher than White (Caucasian?) Americans.^{7,9}

The etiology of angioedema is multifactorial; it can be hereditary or acquired and caused by allergies or reactions to drugs. Our patient presented with acute onset of non-pitting edema of the lower lip and chin without an obvious trigger except for starting lisinopril five days prior. There was no history of exposure to common allergens such as food or over the counter medications. Thus, an acute allergic reaction was unlikely. The Congenital C1 Esterase Inhibitor (C1-INH) deficiency, or Hereditary Angioedema (HAE), is a rare autosomal dominant disease due to either a decreased synthesis of normal C1-INH or a functional absence of the C1-INH. There are two forms of acquired deficiency of C1 esterase inhibitor; the more common one is associated with lymphoproliferative disease or other malignancies^{10,11} while the uncommon one is caused by autoantibodies against C1-INH.^{12,11} The deficiency of C1-INH in these patients results from consumption of C1-INH due to an excessive complement activation.^{10,11} The mechanism of this type of angioedema is due to an activation of the kallikrein-kinin system leading to overproduction of bradykinin (BK), the main mediator of vascular permeability.¹³

Our patient had normal complement component levels (C1q, C2, C4, CH50, and C1 esterase inhibitor), normal antinuclear antibody, normal white blood cell counts, and a negative family history of angioedema. Therefore, hereditary angioedema and acquired C1 esterase inhibitor deficiency were excluded in our patient. Considering he was taking only lisinopril and his symptoms were resolved in 24 hours after discontinuation, we retrospectively established the diagnosis of ACEI-related angioedema.

Since only a minority of patients taking an ACEI develops angioedema, the presence of known triggering factors such as trauma,¹⁴ and head and neck surgery¹⁵ may cause this rare entity to be expressed. Angioedema may also develop in the absence of any identifiable predisposing factors.

The pathophysiology of this entity remains unclear and, although many vasoactive peptides were involved, the main mediator is BK.¹⁶ ACEI inhibits the catalysis of angiotensin I to angiotensin II and the degradation of BK, resulting in elevated systemic and tissue levels of BK.^{16,8} Therefore, the BK interacts with the BK-2 receptors on endothelial cells increasing vascular permeability, releasing nitric oxide and increasing C-GMP. The BK also stimulates the release of substance-P which contributes to an additional vascular permeability by acting at NK1 receptors.¹⁷ Additionally, other BK or substance-P metabolizing enzymes like carboxypeptidase N,¹⁸ aminopeptidase P,¹⁹ neutral endopeptidase,²⁰ and dipeptidyl peptidase IV²¹ may be involved in the pathogenesis of ACE inhibitor-associated angioedema in predisposed patients.

Individuals who had prior episodes of ACEI-associated angioedema develop a higher recurrent rate and serious morbidity when re-treated with ACEI²² therefore, their use is not recommended. Although there are scattered reported cases of ARB-associated angioedema with the risk of airway compromise, the unknown risk of cross reactivity, and the higher occurrence in African American population, ARBs are not a safe alternative in this class of patient.^{23,24,25} Gibbs *et al.*²⁶ suggest that the use of an ACEI in this population should be avoided as a first line agent unless the patient is a hypertensive diabetic or has impaired left ventricle systolic function.

The successful management in the majority of patients with ACEI-related angioedema is ensuring airway patency, withdrawing the causative agent, and providing supportive care. In the case of pharyngo-laryngeal angioedema, the administration of corticosteroids, antihistamines, and nebulized or injected epinephrine have been used, although their role is controversial.²⁷ In the case of a progressive pharyngo-laryngeal angioedema, an immediate intervention such as intubation or tracheotomy may become necessary.²⁷

CONCLUSION

We conclude two important points from this case and the literature review. First, ACEI-related angioedema is more common and may be more severe in African American patients. Therefore, the use of ACEIs as first line therapy in this ethnic group should only be chosen in a proper clinical setting. Second, after a long non-eventful period of using a drug combination of an ACEI and a thiazide diuretic, our patient has developed angioedema shortly after introducing a different ACEI. Thus, patients could develop angioedema to one ACE inhibitor and not the other, regardless of the time frame. Therefore, ACE inhibitors should be avoided in such patients.

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