Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema

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Angiotensin-converting enzyme (ACE) inhibitors frequently are prescribed for the management of cardiovascular disorders. In addition to their therapeutic potential, ACE inhibitors are associated with numerous adverse effects, some of which may be lethal. Angioedema is an uncommon but serious acute event that may affect any individual taking an ACE inhibitor. This review outlines the advances in our understanding of the pathogenesis, clinical presentation, and management of this medical emergency.

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Angiotensin-converting enzyme (ACE) inhibitors are among the most commonly prescribed drugs in modern medicine with more than 40 million patients using them.[1] Numerous ACE inhibitors are currently available (eg, captopril, benazepril, fosinopril, enalapril, zofenopril, ramipril, quinapril hydrochloride, perindopril erbumine, lisinopril), differing primarily in their duration of action and rate of metabolism.[2] Although ACE inhibitors have numerous benefits, multiple adverse effects have been attributed to their use, the most common being syncope/dizziness (2%–5%), dry cough (0.9%–2.9%), and hypotension (0.7%–1.7%).[3]

Angioedema is a rare yet potentially life-threatening condition that has been linked to the use of different medications including ACE inhibitors. The reported incidence of ACE inhibitor–induced angioedema is between 0.1% and 0.68%[4,5]; however, the cumulative risk for developing angioedema is believed to be higher due to the long-term nature of treatment with ACE inhibitors and the fact that angioedema can occur at any point during therapy.[6]

More than 3 decades after the first description of ACE inhibitor–induced angioedema, more is now understood about its underlying pathophysiology and variable clinical manifestations. In this article, we review the historical context of this phenomenon, proposed molecular mechanisms, and clinical considerations in the diagnosis and management of this potentially fatal entity (Table).

History

Angioedema was first described in the literature by Milton[7] in 1876. The term *angioneurotic angioedema* was coined in 1882 by Quincke.[8] Almost a century later, Wilkin et al[9] characterized the association of angioedema with ACE inhibitor use in 1980 in a case series involving 22 patients who received captopril, which at the time was a newly marketed antihypertensive agent. They also were the first to propose a kinin-mediated mechanism for the phenomenon,[9] a theory that now is widely cited. Since then, angioedema has been reported as a side effect associated with nearly all other agents in the ACE inhibitor family.[10] Given the relative rarity of this reaction and the proven benefits of therapy, ACE inhibitors continue to be widely used in the management of hypertension, heart failure, and diabetic renal insufficiency.

Pathophysiology

The pathophysiology of ACE inhibitor–induced angioedema is best understood in the context of the drug's well-characterized mechanism of action. When ACE activity is competitively inhibited, the result is a decreased rate of conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor.[11] Lower concentrations of angiotensin II result in a reduction in downstream aldosterone secretion, contributing to the blood pressure–lowering effect of ACE inhibitors. Additionally, inhibition of ACE, also

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Key Features of ACE Inhibitor–Induced Angioedema

Historical, Pathophysiological, and Clinical Features

- Can occur at any point in therapy
- Possible with any ACE inhibitor
- Pathogenesis is multifactorial though primarily related to elevated bradykinin
- Most common initial signs are shortness of breath, lip and tongue swelling, and laryngeal edema
- Visceral angioedema may mimic an acute abdomen

Short-term and Long-term Management Strategies

- Immediately discontinue use of ACE inhibitor and maintain airway patency
- Airway compromise may necessitate inpatient hospital management
- Promptly initiate alternative pharmacologic therapy for primary condition
- Counsel first-time angioedema patients about increased risk for angioedema with the use of ARBs

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

known as kininase II, decreases the kininase-mediated degradation of the potent vasodilatory nonapeptide bradykinin. Although bradykinin has been implicated as the major mediator in ACE inhibitor–related angioedema, it is becoming clearer that several other factors contribute to its pathogenesis.

Bradykinin—Elevated bradykinin levels have long been presumed to play a central role in the pathogenesis of ACE inhibitor–related angioedema.[9] Angiotensin-converting enzyme inhibitors limit the degradation of bradykinin, permitting increased levels of this nonapeptide. In turn, bradykinin promotes increased vascular permeability and vasodilation. Angiotensin-converting enzyme inhibitors have been shown to enhance bradykinin's hypotensive effects by approximately 20- to 50-fold.[12] These changes are believed to permit local edema formation.

Interestingly, angiotensin II receptor blockers (ARBs), such as losartan, also have been associated with angioedema, though with less frequency.[13] This class of antihypertensive agents also acts on the renin-angiotensin-aldosterone axis but has no known effects on the kallikrein-kinin system, suggesting additional mechanisms in the pathogenesis of angioedema.[14]

Substance P—Substance P is an important peripheral and central nervous system neurotransmitter that has been implicated in the pathogenesis of angioedema. It also is an inflammatory mediator found in unmyelinated fibers of sensory nerves.[15] Angiotensin-converting enzyme inhibitors have been shown to impede the hydrolysis of substance P, thereby permitting its accumulation.[16,17] Furthermore, it has been observed in mice that bradykinin itself enhances the release of tachykinins, such as substance P, from sensory nerves, which further promotes plasma extravasation.[18]

Decreased activity of aminopeptidase P and dipeptidyl peptidase IV, enzymes that are both involved in substance P degradation, also appears to play a role in some patients.[19] In a pedigree analysis by Duan et al,[20] a single nucleotide polymorphism of the X-linked gene X-prolyl aminopeptidase 2, *XPNPEP2* (the C-2399A variant), was associated with decreased activity of aminopeptidase P and a higher incidence of ACE inhibitor–induced angioedema.

Histamine—Histamine is an important amino acid that is implicated in the wheal and flare of inflammation. Its vasodilatory activity also is potentiated by ACE inhibitors.[9,21] Although agents such as opiates (eg, morphine, codeine) and iodinated contrast media have been shown to cause angioedema by direct histamine release, bradykinins, which increase with ACE inhibitor administration, also can induce histamine release from mast cells.[22] One small human study, however, reported no increases in histamine-induced wheal and flare reactions with the addition of an ACE inhibitor.[23]

Complement System—An interaction between ACE inhibitors and the complement system also has been proposed to play a role in the pathogenesis of ACE inhibitor–related angioedema based on observations made in murine models.[24] It is widely understood that patients with hereditary angioedema (HAE) are deficient in C1 esterase inhibitor (C1-INH).[25,26] Although no known studies to date have identified frankly decreased C1-INH levels in patients with ACE inhibitor–related angioedema, it has been proposed that ACE inhibitors may render select patients functionally deficient in C1-INH, putting them at a higher risk for developing angioedema.[27,28] Moreover, multiple accounts of successful treatment of ACE inhibitor–related angioedema with exogenous C1-INH concentrates further support a role for the complement system in the pathogenesis of this entity.[29,30]

Genetic Association—A genetic predisposition to ACE inhibitor–induced angioedema is likely. One large study described intrafamilial similarities in plasma ACE levels, suggesting heritable patterns of renin-angiotensin-aldosterone axis regulation.[31] Because patients with HAE are more susceptible to developing angioedema while taking an ACE inhibitor, the use of ACE inhibitors should generally be avoided in these patients. In addition, carboxypeptidase N, a metalloenzyme inhibitor of complement components and bradykinin whose deficiency has been associated with angioedema, has been found to be deficient in an autosomal-recessive pattern.[32]

Trauma—External trauma may be an inciting or contributing factor in the pathogenesis of ACE inhibitor–induced angioedema. Local trauma has been reported to trigger angioedema in patients on ACE inhibitors or with a history of HAE.[33,34] It is likely that mechanical injury to skin or mucosal cells results in a release of vasoactive substances that, in conjunction with ACE inhibitor–related bradykinin elevation, promote local edema formation.

Clinical Presentation, Epidemiology, and Risk Factors

Angioedema generally presents as an acute onset of localized edema in the dermal, subcutaneous, and mucosal tissues. Most frequently, angioedema occurs in the head and neck, including the face and perioral and oral tissues.[35] In severe cases, laryngeal edema may develop, leading to potentially fatal airway obstruction. A multicenter study of 220 patients presenting to emergency departments with ACE inhibitor–induced angioedema revealed that the most common presenting signs were shortness of breath, lip and tongue swelling, and laryngeal edema.[36]

Angiotensin-converting enzyme inhibitors have been implicated as causative agents in up to 25% of angioedema cases presenting to emergency departments.[37] Multiple retrospective studies from the 1990s, however, highlighted the relative underdiagnosis of this specific entity in the acute care setting.[38-40] Despite increased awareness of ACE inhibitors as a cause of angioedema, underdiagnosis remains a relevant concern.[41]

One factor that may contribute to the underdiagnosis of an ACE inhibitor–related etiology is that acute-onset angioedema does not always correlate with recent use of an ACE inhibitor. Patients often may present with a long history of ACE inhibitor use with no history of reaction. In these cases, a physician may overlook the drug as a potential etiology; however, it is important to note that ACE inhibitor–induced angioedema can occur any time from within several hours of initial administration to up to 5 years later.[6] On average, an angioedematous episode occurs 14 months after starting an ACE inhibitor. With long-term use, the cumulative 10-year risk for developing ACE inhibitor–induced angioedema is estimated to be as high as 1%.[42]

Multiple risk factors have been associated with ACE inhibitor–induced angioedema, including black skin, female gender, and increasing age.[42,43] Historical risk factors such as HAE or idiopathic angioedema,[44,45] autoantibodies against C1-INH,[46] or excessive emotional stress have been proposed in the literature. Furthermore, iatrogenic risk factors such as recent head/neck surgery[47] as well as the use of local anesthesia,[48] other antihypertensive agents, antibiotic agents, and nonsteroidal anti-inflammatory drugs[46] have been suggested as potential triggers.

ACE Inhibitor–Induced Visceral Angioedema

Peripheral angioedema is commonly associated with ACE inhibitor use. Less frequently, ACE inhibitors can produce visceral angioedema, often mimicking the signs of an acute abdomen. The diagnosis easily may be overlooked, and unless potential drug reactions are considered, patients may be subject to misguided workup and management. In addition to multiple single case reports published on this entity,[49-52] Dobbels et al[53] conducted the largest-known single-center case series that described 7 patients with intermittent acute abdominal pain attributable to the use of ACE inhibitors. The authors concluded that ACE inhibitor–related visceral angioedema likely is much more common than has been indicated in the literature.[53]

Management and Prevention

In cases of suspected ACE inhibitor–induced angioedema, immediate discontinuation of the drug and maintenance of adequate airway function are imperative. Isolated cutaneous edema can progress to laryngeal edema within minutes to hours; thus it is recommended that patients be observed for at least 6 hours in the hospital.[54] Patients with signs of compromised upper airway function (eg, tongue swelling, stridor, drooling, accessory muscle use) are at high risk for respiratory decompensation and may require emergency intubation. Depending on symptom severity, these patients should be admitted to either an intensive care unit or a non–intensive care bed for further monitoring.

Additional supportive measures such as fluid resuscitation may be indicated in hemodynamically unstable patients. Adjunct therapies such as subcutaneous epinephrine injections, intravenous or intramuscular diphenhydramine hydrochloride, and oral or intravenous glucocorticoids also may be initiated;

however, the efficacy of angioedema therapies other than discontinuation of ACE inhibitors has come into question by some clinicians, as no known controlled studies assessing these treatments have been conducted.[55]

Proper alternative treatment of the patient's underlying conditions (eg, hypertension, heart failure) should be promptly initiated and may include regimens such as beta-blockers, calcium channel blockers, hydralazine hydrochloride, nitrates, or ARBs. The use of ARBs also has been associated with the development of angioedema. One systemic review and meta-analysis by Haymore et al[56] found that in 71 patients with a history of ACE inhibitor–induced angioedema, the risk for developing subsequent ARB-related angioedema was between 2% and 17%. This important finding may aid clinicians in their discussions with patients about alternative therapies after an episode of ACE inhibitor–induced angioedema.

On the Horizon

A newer drug that has been approved in both Europe and the United States for the management of hereditary angioedema is icatibant, a synthetic bradykinin B2 receptor antagonist that has shown promise based on a study of patients with ACE inhibitor–induced angioedema. Bas et al[57] administered a single subcutaneous injection of icatibant to 8 patients on presentation to the emergency department. Compared to a historical patient cohort, the severity of illness and speed of recovery were markedly improved in the group treated with icatibant.[57] A number of larger-scale clinical trials to evaluate the efficacy of icatibant in ACE inhibitor–induced angioedema are under way or in planning.[58-60]

Recombinant plasma kallikrein inhibitors and purified and recombinant C1-INH also are newer drugs for the prevention and treatment of HAE.[61] Further investigation is warranted to determine the efficacy of these drugs in the treatment of ACE inhibitor–induced angioedema.

Conclusion

Angiotensin-converting enzyme inhibitors have become key agents in the management of cardiovascular disease; however, a rare but serious adverse effect of these drugs is angioedema, which may afflict susceptible patients at any point during therapy. A careful medical and family history should be taken for any patient who presents with the clinical features of angioedema. The most appropriate initial management of ACE inhibitor–induced angioedema is the discontinuation of the drug and maintenance of adequate ventilation until the edema resolves. As with any medication, a detailed discussion of the benefits and risks for ACE inhibitors should occur between the physician and the patient before administration of the drug, and appropriate alternatives should be considered when a patient is at risk for or has previously experienced angioedema while taking an ACE inhibitor.

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