

ACE Inhibitor–Induced Angioedema

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Abstract Much has been written about hereditary angioedema (HAE) in recent literature; however, the prevalence of angiotensin-converting enzyme inhibitor–induced angioedema (ACEiIA) far exceeds that of HAE. Similarly, multiple therapies have been developed for HAE, yet no definitive therapy is available for ACEiIA. In this article, we discuss the mechanism, prevalence, pathophysiology, and management of ACEiIA, with focus on newer therapies recently approved for HAE and how they may be effective for ACEiIA.

Keywords Angioedema · ACEi–induced angioedema · Hereditary angioedema · Angiotensin-converting enzyme inhibitor · Icatibant · Ecallantide

Introduction

Angioedema is a self-limiting, localized swelling of the skin and/or mucosal membrane resulting from extravasation of fluid into the interstitium. It can be acute or chronic, is usually transient, but is often recurrent. It usually involves surfaces that have loose connective tissue such as the face, lips, mouth, throat, larynx, and

uvula; however, occasionally, bowel mucosa and visceral organs may be involved. Angioedema can be differentiated from other causes of edema as it is seen in nondependent areas and is asymmetric in distribution, with onset in minutes. Angioedema may be associated with other allergic symptoms as well. Most cases of angioedema are self-limiting, nonetheless, reaction can be severe and even life threatening, especially if it involves the swelling of the tongue, glottis, and/or larynx [1]. If it involves only layers of visceral organs, especially the gastrointestinal tract, it causes anorexia, nausea, vomiting, and abdominal pain. In the absence of visible edema, angioedema may go undiagnosed for years. Most edema associated with angiotensin-converting enzyme inhibitor (ACEi) involves the skin and upper airway, but edema from ACEi should be included in differential diagnosis of abdominal pain with findings on imaging of ascites, bowel dilatation, and lumen attenuation [2].

Angioedema Varies by Mechanism

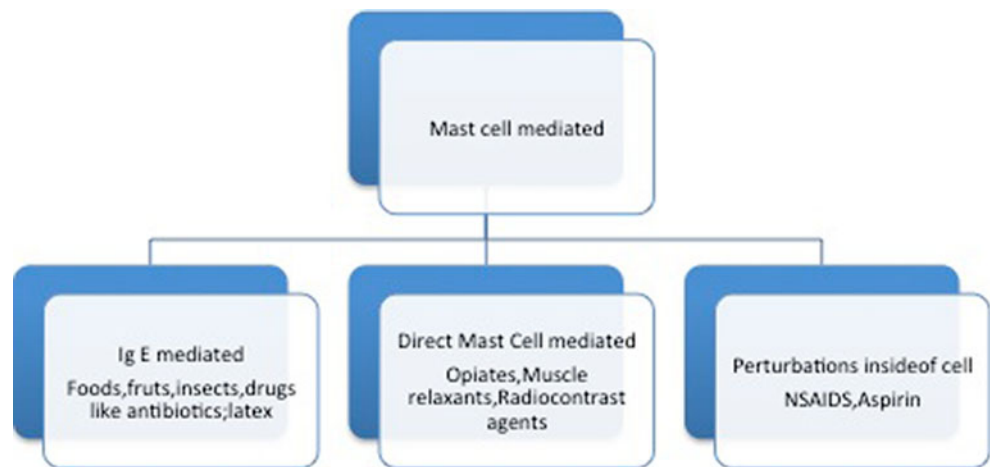
Figure 1 illustrates the various types of histamine-induced angioedema [3••]. This includes most idiopathic angioedema, which is often associated with urticaria or anaphylaxis. Allergic types of angioedema, such as drug, insect, or food induced, are also histamine induced. Bradykinin also causes angioedema and is the cause of angioedema seen in hereditary angioedema (HAE), ACEi-induced angioedema (ACEiIA), acquired bradykinin-induced angioedema with deficiency of C1 inhibitor, and hereditary angioedema with normal C1 inhibitor (Fig. 2).

Angioedema has become a dominant allergic disorder that results in hospitalization in the United States [4]. The angioedema hospitalization rate was 3.3 per 100,000 in 1998 and rose to 4.0 per 100,000 in 2005. A large

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Fig. 1 Mechanisms of angioedema: histamine mediated (via mast cell)



percentage of these cases are secondary to ACEi. Death due to angioedema usually results from the respiratory tract causing laryngeal swelling and inflammation, ultimately leading to asphyxiation.

Until recently, therapy had been supportive only, with the main emphasis on preserving the airway. New and novel therapies available in the treatment of angioedema may provide benefit if used appropriately. Just as newer drugs have revolutionized the prophylactic therapy in HAE [5], the expectation is that in the future, some of these medications will be used for ACEiIA as well.

Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema

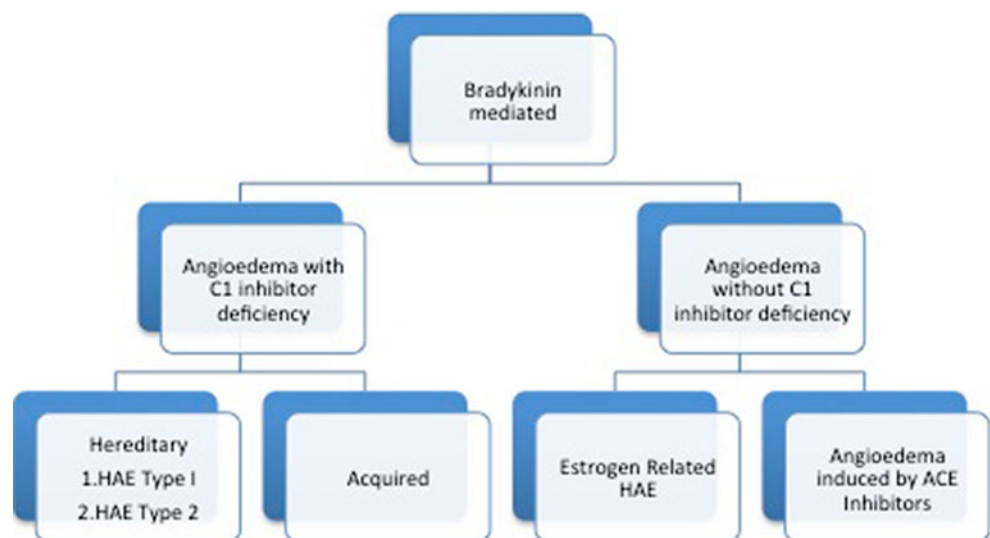
Hypertension is a highly prevalent disease, as one in every three adults in the United States has it [6]. ACEi are among the most common and most effective medications

used for the treatment of hypertension, and with more than 30% of antihypertensive drug prescriptions being written for ACEi [7], it is reasonable to assume that ACEi therapy is prevalent in the US population. In addition, ACEi are used extensively in the treatment of diabetes mellitus and congestive heart failure, both of which are common chronic diseases.

Characteristics

Angioedema from ACEi is uncommon, occurring in approximately 0.1–2.2% of patients treated with ACEi [8•], with a higher incidence in women and African Americans [1, 9, 10]. Banerji et al. [11] determined that although ACEiIA was rarely fatal, it accounted for one third of angioedema treated in the emergency department. In addition, patients often required inpatient hospitalization and intensive care treatment for management of respiratory compromise and upper airway angioedema [11].

Fig. 2 Differential diagnosis of bradykinin-mediated angioedema. ACE, angiotensin-converting enzyme; HAE, hereditary angioedema. (Based on text from Caballero et al. [3••])



ACEiIA can occur any time during therapy. Even after years of therapy, angioedema may develop in a previously angioedema-free individual. Most cases were found to happen in the first week of therapy, and up to 25% had angioedema within the first month of therapy [12]. The exact reason for the occurrence of angioedema after months to years of uneventful therapy is not known. Some of the known associations have been described. C1 inhibitor deficiency is a risk factor for developing ACEiIA. Unknown are the number of patients with HAE who are asymptomatic until prescribed ACEi and then have their first attack. Other risk factors for ACEiIA include age older than 65, female gender, smoking, aspirin/NSAID use, seasonal allergies, and history of ACEi-induced cough [13•, 14]. In addition, ACEi dose, frequency, and concomitant therapy with cholesterol-lowering medications such as statins and mammalian target of rapamycin (mTOR) inhibitors (eg, everolimus/sirolimus) also have been identified as predisposing risk factors [15]. The individual duration of action of ACEi is not a determinant in the incidence of the associated angioedema, as this is a class effect. Of importance is that the mechanism explained below for ACEiIA disputes that angiotensin receptor blockers (ARBs) should not cause angioedema as with ACEi.

Pathophysiology

Angiotensinogen is synthesized by the liver and enters into the bloodstream, where it is cleaved by renin and secreted by the kidneys to form angiotensin I. ACE, present in the lung, catalyzes the conversion of angiotensin I to angiotensin II. The same enzyme, also known as kininase II or dipeptidyl-carboxypeptidase I, degrades bradykinin (Fig. 3). The formation of angiotensin II sets off a cascade of effects in various organs, including the brain, heart, kidneys, and vasculature, that includes an increase in blood pressure.

Inhibition of ACE by ACEi results in diminished production of angiotensin II. The decreased plasma levels of angiotensin II lead to decreased vasopressor activity, decreased aldosterone secretion, and the beneficial hemodynamic effects seen with ACEi use. The inhibition also prevents the degradation of bradykinin and other kinins [16]. Increased bradykinin in the system in turn activates tyrosine kinase, Janus kinase-activated pathways [17], and protein kinase pathway [18], leading to release of predominantly nitrous oxide and prostaglandins and resulting in subsequent vasodilatation.

Presently, two bradykinin receptors have been identified: BKR1 and BKR2. Unlike HAE, in ACEiIA, the high plasma bradykinin concentrations are not accompanied by the presence in plasma of cleavage products of high molecular weight kininogen (the precursor of bradykinin) [19]. In HAE, the lack of C1 inhibitor results in excess metabolism of

complement, the activation of the contact system, to include factor XII, plasmin, and to a lesser degree factor XI. Kallikrein is activated and causes the overproduction of bradykinin. Thus, it is overproduction of bradykinin in HAE, not the lack of metabolism of bradykinin as with ACEiIA, that causes the angioedema. Secondary to this difference, it would be unlikely that C1 inhibitor would be effective in reversing or preventing the angioedema associated with ACEi.

Of note, even though the mechanism of action of ACEi remains similar in all treated patients, less than 1% of the treated population experience angioedema. Several triggers have been proposed. HAE may unmask ACEi-associated angioedema, as both ultimately increase bradykinin [20]. An association exists between low plasma activity of aminopeptidase P and previous episodes of angioedema. Because aminopeptidase P plays a major part in plasma bradykinin catabolism when ACE is inhibited, the lower plasma concentrations of aminopeptidase P, as seen in patients who previously had ACEi-associated angioedema, could indicate a predisposition for development of angioedema in some patients treated with ACEi [19, 21]. Transplant patients have been found to be more susceptible to angioedema. This may be attributable to the effects of immunosuppressants on dipeptidyl peptidase-4 activity, causing it to decrease [22]. The combination of multiple genetic and environmental factors that affect the degradation and action of vasoactive peptides during ACE inhibition likely contribute to ACEi-associated angioedema pathogenesis [23].

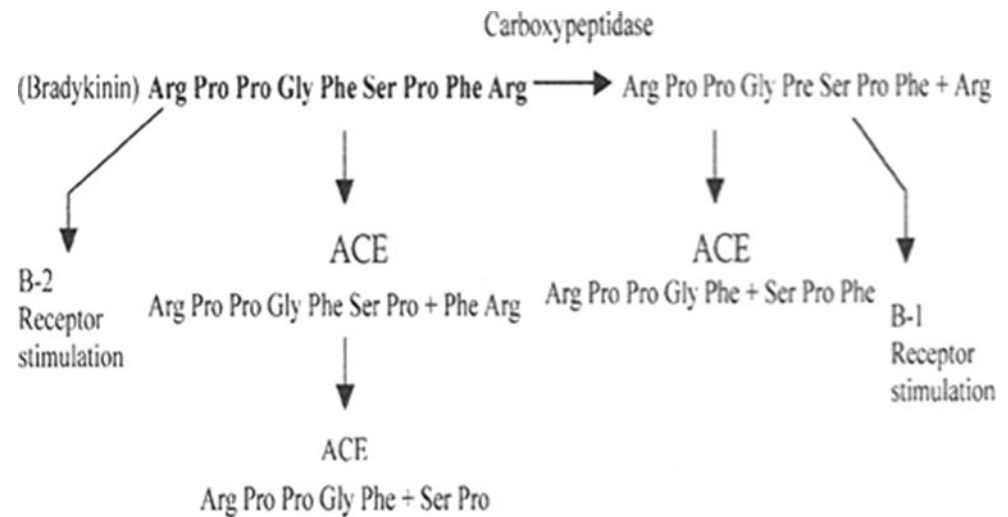
Diagnosis

Physical examination is the key to diagnosis of angioedema. However, angioedema resulting from ACEi use can be distinguished from HAE and acquired angioedema only by history, C1 inhibitor levels, and complement assays. Most patients who develop ACEiIA have normal C1 inhibitor levels and function. However, ACEi trigger attacks when taken by individuals with HAE [24]. A complete laboratory work-up for patients with ACEiIA must include C1 inhibitor function and protein levels, C4 levels, and C1q levels, especially in patients who have angioedema after stopping ACEi or who have a history of angioedema preceding ACEi use. At the present time, there are no unique physical or laboratory tests to confirm the diagnosis, and history of ACEi use and resolution of angioedema after stopping therapy is the only way to confirm the diagnosis.

Differential Diagnosis

Angioedema may present in association with urticaria. This is especially true for histamine-induced angioedema.

Fig. 3 Bradykinin metabolism by angiotensin-converting enzyme (ACE). (Used with permission from Allen Kaplan, MD)



Bradykinin-induced angioedema, including ACEiIA, is not associated with urticaria. Occasionally, angioedema may be difficult to diagnose, and the following differentials should be kept in mind [25]:

- Parasitic infections: filariasis, strongyloides, C. trichinosis
- Melkersen-Rosenthal syndrome
- Solid facial acne causing swelling
- Hypertrophic branchial myopathy
- Myxedema
- Superior vena cava syndrome
- Dermatomyositis
- Scleroderma
- Amyloidosis
- HAE with decreased C1 inhibitor levels
- Acquired angioedema associated with decrease C1 inhibitor levels

Fig. 4 The renin-angiotensin (AT)-bradykinin (BK) system and sites of drug action. ACE, angiotensin-converting enzyme. (From Hurst and Empson [30]; with permission from *The New Zealand Medical Journal*)

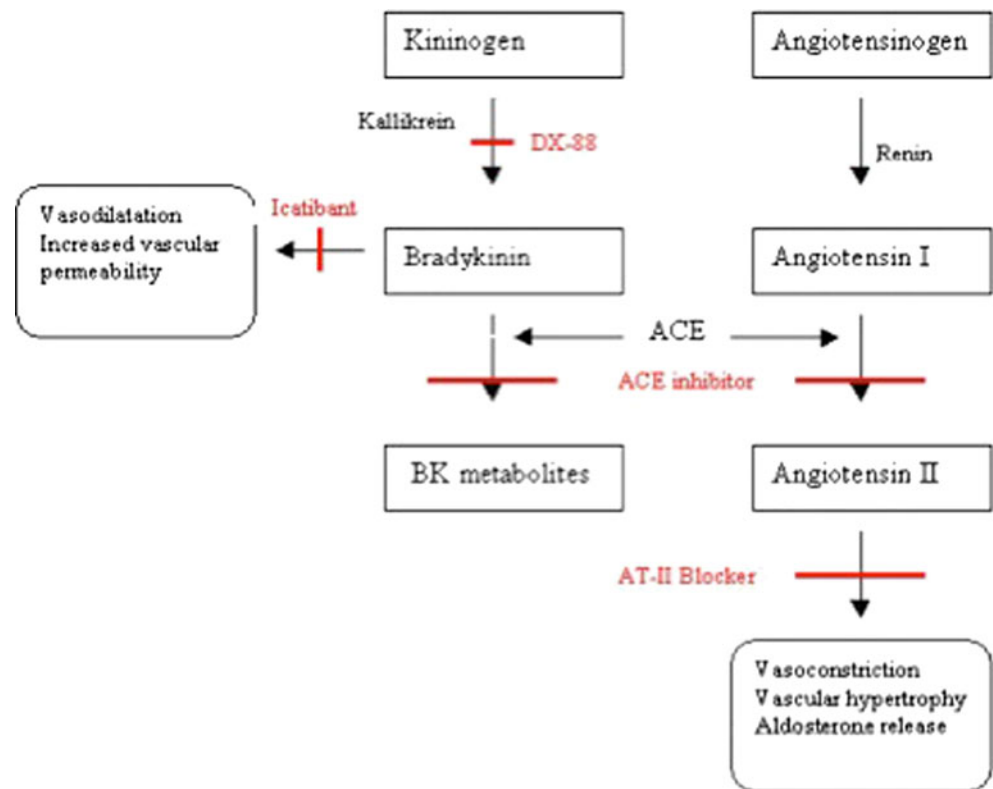
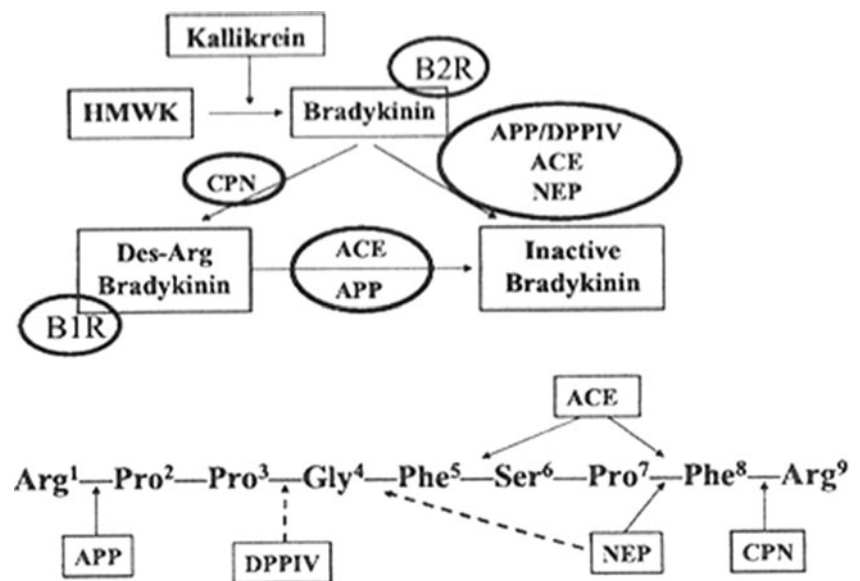


Fig. 5 The mechanism of generation of bradykinin and the effects of icatibant and ecallantide. Icatibant is a competitive inhibitor of the bradykinin 2 receptor (B2R). Ecallantide inhibits the activation of kallikrein and as such decreases bradykinin production. ACE, angiotensin-converting enzyme; APP, aminopeptidase P; B1R, bradykinin 1 receptor; CPN, carboxypeptidase N; DPPIV, dipeptidyl peptidase-4; HMWK, high molecular weight kallikrein; NEP, neutral endopeptidase (Used with permission from Allen Kaplan, MD)



- HAE associated with normal C1 inhibitor levels
- Histamine-induced angioedema (idiopathic, allergic, drug induced)

Management

Discontinuation of the drug is the first step in treating ACEiIA. The signs and symptoms usually resolve 24–48 h after discontinuation of medication but may last longer in some cases. Assessing the patency of the airway is an essential first step. If any airway compromise exists, then lifesaving procedures such as intubation and mechanical ventilation should be performed promptly if indicated. Medications such as antihistamines, anticholinergics, and corticosteroids are unlikely to be effective but are often used. Similarly, epinephrine is unlikely to be effective, but in severe cases, especially with airway compromise, use is warranted. Plasma contains ACE (kininase II), and it is postulated that administration of fresh frozen plasma (FFP) leads to the breakdown of accumulated bradykinin with subsequent resolution of angioedema. FFP was associated with the resolution of resistant, life-threatening angioedema due to an ACEi in case reports, but these data are limited, and the use of FFP for ACEiIA is not based on any high-grade evidence [26]. Bas et al. [27••] used the bradykinin B2 receptor antagonist icatibant in eight patients with ACEiIA. This was followed by a complete, rapid recovery in all eight patients, and they did not require any invasive procedures such as intubation or tracheostomy. Icatibant may provide a more targeted therapy for ACEiIA in the future [27••].

Purified C1 inhibitor therapy is being used successfully in the treatment and prevention of HAE [28]. Use in ACEiIA is unclear, as the concentration of C1 inhibitor in

ACEiIA is normal. Nonetheless, C1 inhibitor has been used successfully in a case report [29]; however, as noted above, the mechanism of action of C1 inhibitor makes it unlikely that the resolution in the case reports were cause and effect. Use of C1 inhibitor for prevention of angioedema in HAE patients who require ACEi for cardiomyopathy, albuminuria, hypertension, or diabetes mellitus may be successful. Using an ARB instead may be more prudent, as it provides similar benefit without the risk of angioedema associated with ACEi. Ecallantide, a kallikrein receptor blocker approved for HAE, may have some benefit by inhibiting production of bradykinin; however, ACEiIA is likely caused by the persistence of bradykinin due to the lack of metabolism, and therefore, the authors are not enthused with the potential benefit of ecallantide in ACEiIA (Figs. 4 and 5).

Once angioedema has occurred, further use of any ACEi is contraindicated. Limited evidence suggests that for patients who develop angioedema when taking an ACEi, the risk of development of angioedema with the use of an ARB is 0–9.2%. This should not necessarily deter prescribing ARBs for patients with ACEiIA who have hypertension, albuminuria, cardiomyopathy, congestive heart failure or diabetes mellitus, as the mechanism of angioedema with ACEi differs from that expected from ARBs [12, 21].

Conclusions

Due to the widespread use of ACEi in practice, the occurrence of ACEiIA is not uncommon. Prompt diagnosis is essential to initiate appropriate treatment. Traditional therapies used for histamine-induced angioedema are ineffective. Discontinuation of the offending agent, maintaining patency

of the airway, and supportive therapy are the mainstays of management of this condition. Medications recently released for HAE, to include icatibant and possibly ecallantide, may be effective therapies for ACEiIA. Randomized controlled trials are needed to study the usefulness of these medications before they can be used in clinical practice for ACEiIA.

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Dr. Vasekar reported no potential conflicts of interest relevant to this article.

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- Of major importance

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