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Immunol Allergy Clin N Am
26 (2006) 725–737

IMMUNOLOGY
AND ALLERGY
CLINICS
OF NORTH AMERICA

Angiotensin-Converting Enzyme Inhibitor-Associated Angioedema

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Angiotensin-converting enzyme (ACE, kininase II) inhibitors reduce mortality in patients who have hypertension, congestive heart failure, and diabetic nephropathy and in patients who are at high risk for cardiovascular events [1–4]. ACE inhibitor–associated angioedema is a rare, potentially life-threatening side effect of treatment with ACE inhibitors. Reactions range from mild swelling of the tongue, lips, other areas of the face, hands, feet, or bowel to life-threatening airway compromise. Given that 35 to 40 million people worldwide are currently taking ACE inhibitors, the number of people at risk for this side effect is substantial.

Clinical features of angiotensin-converting enzyme inhibitor–associated angioedema

Angioedema is characterized by self-limited, nonpitting edema of vascular origin. The most common sites of involvement in ACE inhibitor–associated angioedema are the lips, tongue, and face (Fig. 1) [5–7]. Pruritis and urticaria, seen in hypersensitivity reactions, typically do not accompany ACE inhibitor–associated angioedema. Rarely, ACE inhibitor–associated angioedema may involve the bowel wall [8]. In such cases, patients present with nausea and vomiting, abdominal pain, diarrhea, or ascites associated with ACE inhibitor use. The diagnosis may be confirmed by the

This work was supported by NIH Grants HL079184 and HL076133 and National Center for Research Resources Grant RR-00095.

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doi:10.1016/j.iac.2006.08.001

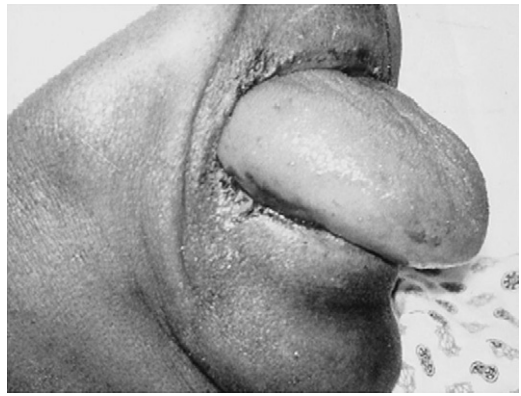

Fig. 1. Photograph illustrating a case of ACE inhibitor–associated angioedema. (*From* Agah R, Bandi V, Guntupalli KK. Angioedema: the role of ACE inhibitors and factors associated with poor clinical outcome. Intensive Care Med 1997;23(7):795; with permission.)

identification of bowel edema on CT scan and resolution of symptoms with discontinuation of ACE inhibitor use; however, failure to suspect ACE inhibitor–associated angioedema can lead to surgical procedures. A unique form of hemioral angioedema has been associated with tissue-type plasminogen activator administration in stroke patients who are taking an ACE inhibitor [9].

The incidence of ACE inhibitor–associated angioedema is highest during the first month of treatment. Slater and colleagues [10] reported a 14-fold higher incidence of angioedema during the first week of treatment compared with subsequent exposure, and Kostis and colleagues [7] observed that the incidence of angioedema was ninefold higher in the first month of ACE inhibitor use. Although the risk for angioedema per exposure is greatest in the first month of treatment with an ACE inhibitor, the majority of cases occur after 1 month of treatment, and as many as 27% of cases present more than 6 months after initiation of ACE inhibitor therapy [11,12]. The range of treatment duration before angioedema onset was 1 day to 10 years in one series [13].

Early recognition and discontinuation of the ACE inhibitor remain the primary therapy for ACE inhibitor–associated angioedema. To date, no other specific treatment for ACE inhibitor–associated angioedema has been tested in clinical trials. Nielsen and Gramstad [14] reported that administration of complement 1 inhibitor (C1-INH) concentrate decreased symptoms in a patient who had ACE inhibitor–associated angioedema. Administration of fresh frozen plasma has also been effective in the treatment of resistant cases [15]. Although bradykinin receptor antagonism has proved effective in shortening the duration of hereditary angioedema [16], clinical trials of bradykinin receptor antagonism in ACE inhibitor–associated angioedema are lacking. Primary supportive therapy includes management of the airway, with a minority of cases requiring intubation or

cricothyroidotomy. Although many physicians treat patients with antihistamines, steroids, and, in more severe cases, epinephrine, no clinical trial has addressed the efficacy of these treatments in ACE inhibitor–associated angioedema. Patients presenting with angioedema should be tested for C1 inhibitor function as well as C4, C3, and C1q antigens to exclude the possibility of hereditary angioedema or acquired C1-INH deficiency.

The adverse event of angioedema is a class effect of ACE inhibitors, so patients who have experienced angioedema while taking one ACE inhibitor may not be treated with another. Because it may be desirable to substitute another drug that interrupts the renin-angiotensin system for an ACE inhibitor in patients who have experienced angioedema, Cicardi and colleagues [6] addressed the safety of administering an angiotensin receptor blocker (ARB) to patients who have previously experienced ACE inhibitor–associated angioedema. This study suggests that it is generally safe to treat individuals who have a history of ACE inhibitor–associated angioedema with an ARB. Unlike ACE inhibitors, ARBs do not potentiate the vasodilator response to the vasoactive peptide bradykinin [17]. However, studies in animals suggest that ARBs may increase bradykinin by means of the actions of angiotensin II at the unblocked angiotensin II type 2 receptor [18]. In addition, circulating bradykinin concentrations may be increased in individuals who are taking an ARB [19]. Although case reports suggest that patients taking ARBs occasionally experience angioedema, the rate of angioedema in patients taking ARBs is not increased over that observed in the general public, and it is significantly lower than the rate of angioedema observed during ACE inhibition [20].

Epidemiology of angiotensin-converting enzyme inhibitor–associated angioedema

The reported incidence of ACE inhibitor–associated angioedema varies from 0.1% to 0.7%, calculated from postmarketing surveillance or epidemiologic studies, to as great as 2.8% to 6% when ascertained prospectively in clinical trials [10,21,22]. Black Americans have an incidence of ACE inhibitor–associated angioedema that is four to five times that of white Americans [7,12,23]. Smoking, increasing age, and female gender are also associated with increased risk for ACE inhibitor–associated angioedema, whereas diabetics appear to be protected from ACE inhibitor–associated angioedema (Table 1) [7,22,24]. A history of ACE inhibitor–associated cough increases the risk for ACE inhibitor–associated angioedema [24]. However, patterns of racial differences in the incidence of ACE inhibitor–associated cough and ACE inhibitor–associated angioedema do not suggest a tight link between cough and angioedema. For example, Asians frequently develop cough but are not at increased risk for angioedema [24,25]. At least one group has reported an increased rate of ACE inhibitor–associated angioedema among immunocompromised cardiac and renal transplant patients [26].

Table 1
Risk factors associated with angioedema in the Omapatrilat Cardiovascular Treatment versus Enalapril (OCTAVE) study

Risk factor	Odds ratio (95% CI)	*P* value
African American race	2.97 (2.24, 3.92)	<.0001
Current smoker	2.49 (1.86, 3.34)	<.0001
Female gender	1.49 (1.16, 1.91)	.002
Seasonal allergies	1.52 (1.12, 2.06)	.008
Former smoker	1.47 (1.09, 1.99)	.013
History of diabetes	0.58 (0.38, 0.90)	.014

Data from Bristol Myers Squibb Co., New York, NY.

Mechanisms of angiotensin-converting enzyme inhibitor–associated angioedema

The mechanism or mechanisms of ACE inhibitor–associated angioedema remain to be elucidated, but the clinical presentation of ACE inhibitor–associated angioedema may provide clues to its causation. As noted earlier, ACE inhibitor–associated angioedema frequently occurs after prolonged exposure; furthermore, it may remit spontaneously and recur after prolonged time intervals [27]. This pattern excludes a typical allergic or immediate hypersensitivity mechanism and suggests that some concurrent event or exposure must precipitate angioedema in an individual who is taking an ACE inhibitor. In this regard, ACE inhibitor–associated angioedema resembles hereditary angioedema, or C1 esterase inhibitor deficiency, in which patients also report recurrent episodes.

ACE inactivates bradykinin, and studies using bradykinin receptor antagonists demonstrate that endogenous bradykinin contributes to the hypotensive effects of ACE inhibitors [28]. Activation of the kallikrein-kinin system, with consumption of kininogen, has been demonstrated in patients who have hereditary angioedema [29]. In addition, genetic bradykinin receptor deficiency attenuates edema in C1 esterase–deficient mice [30]. Bradykinin B_1 and B_2 receptors are expressed in the tongue, laryngeal areas, and parotid gland [31]. Administration of the bradykinin receptor antagonist Icatabant (HOE 140, JE 049) decreases the severity of hereditary angioedema in Phase II trials [16].

Although the role of the kallikrein-kinin system in the pathogenesis of hereditary angioedema is established, definitive data implicating bradykinin in ACE inhibitor–associated angioedema are sparse. Nussberger and coworkers [32] reported that circulating bradykinin concentrations were increased in both patients who had hereditary angioedema and in one patient who had ACE inhibitor–associated angioedema; however, bradykinin concentrations in control subjects taking ACE inhibitors without angioedema [33] were not reported in this study. In addition, although high molecular weight kininogen is consumed in hereditary forms of angioedema,

there is no increased cleavage of kininogen in ACE inhibitor–associated angioedema [33]. This observation is compatible with the hypothesis that, to the extent that bradykinin plays a role in ACE inhibitor–associated angioedema, impaired metabolism, rather than increased generation, contributes to this adverse event.

Animal models of angioedema

In addition to bradykinin, substance P is another peptide substrate of ACE that causes vasodilation and increased vascular permeability. Both bradykinin and substance P produce tracheal edema in animals [34,35]. For example, Emanueli and coworkers [34] demonstrated that acute administration of captopril or enalapril caused extravasation of Evans blue dye in the trachea, stomach, duodenum, and pancreas of mice. Pretreatment with either the bradykinin B_2 receptor antagonist HOE 140 or the substance P (tachykinin) neurokinin I (NK1) receptor antagonist SR 140,333 significantly decreased ACE inhibitor–induced plasma extravasation. Genetic disruption of the B_2 receptor also prevented ACE inhibitor–induced edema. Taken together, these data suggest that ACE inhibition causes edema by increasing tissue bradykinin, which in turn can stimulate substance P release from nerve fibers, leading to enhanced vascular permeability and leakage of plasma protein into the interstitial space [36,37]. It follows that enzymes involved in the degradation of either bradykinin or substance P may be involved in the pathogenesis of ACE inhibitor–associated angioedema in specific populations.

Angiotensin-converting enzyme inhibitors and the degradation of vasoactive peptides

Fig. 2 shows the enzymatic pathways involved in the degradation of the ACE substrates bradykinin and substance P. Bradykinin is degraded primarily by ACE (Enzyme Classification [EC] 3.4.15.1); however, during ACE inhibition, other enzymes, including neutral endopeptidase (NEP-24.11, EC 3.4.24.11), aminopeptidase P (APP, EC 3.4.11.9), and kininase I (carboxypeptidase N, EC 3.4.17.3), assume greater importance in the metabolism of bradykinin [38]. Cleavage of bradykinin by kininase I yields the active metabolite des-Arg^9-bradykinin, which is inactivated primarily by APP.

To determine whether impaired metabolism of kinins contributes to the pathogenesis of angioedema in the presence of ACE inhibition, Blais and colleagues [39] characterized the ex vivo metabolism of bradykinin in the sera of patients who had a history of ACE inhibitor–associated angioedema. In the absence of ACE inhibition, kininase I played a minor role in degradation of bradykinin. During ACE inhibition, the relative contribution of kininase I to the degradation of bradykinin increased to a greater extent in individuals who had a history of angioedema compared with normal controls. This finding of enhanced degradation of bradykinin by means of kininase I during ACE inhibition in the sera of individuals who have ACE

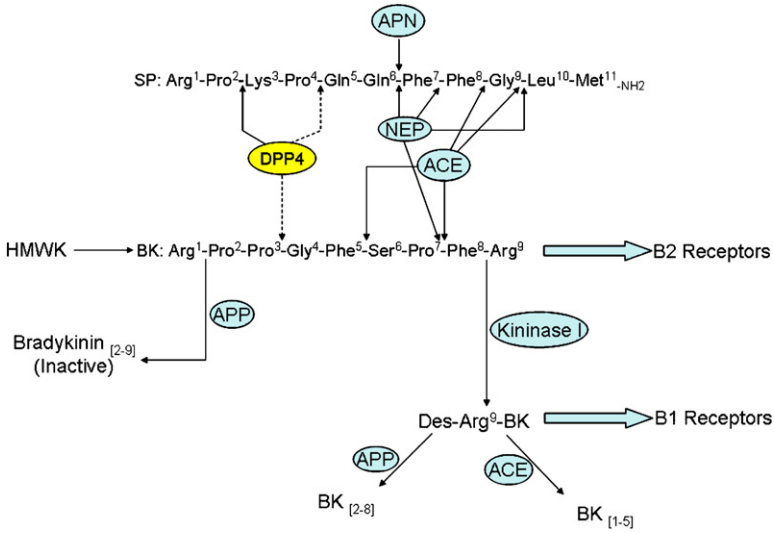

Fig. 2. Degradation of bradykinin, des-Arg^9-bradykinin, and substance P. APN, aminopeptidase N or M; APP, aminopeptidase P; BK, bradykinin; DPP4, dipeptidyl peptidase IV; HMWK, high molecular weight kininogen; NEP, neutral endopeptidase; SP, substance P.

inhibitor–associated angioedema suggests that such individuals may have a defect in a non-ACE, non–kininase I pathway of kinin degradation.

Aminopeptidase P deficiency and adverse events associated with angiotensin-converting enzyme inhibition

During ACE inhibition, the contribution of APP to the degradation of bradykinin also increases [40,41]. Thus, during ACE inhibition, deficient APP activity could lead to enhanced degradation of bradykinin by means of kininase I, as well as to accumulation of bradykinin and des-Arg^9-bradykinin. Adam and coworkers [42] have reported decreased APP activity in sera from 39 patients (20 male, 19 female; 16 $\pm$10 nmol/min/mL) who had a history of ACE inhibitor–associated angioedema compared with 39 age- and gender-matched hypertensive controls (23 $\pm$10 nmol/min/mL; $P = .003$). No difference was found between groups in kininase I activity in the absence of ACE inhibition.

The investigators further characterized the metabolism of bradykinin and des-Arg^9-bradykinin following stimulation of the formation of bradykinin ex vivo by incubation of plasma with glass beads. In the presence of ACE inhibition (enalaprilat 130 nM), there was a slight but significant ($P = .022$) decrease in the catabolism of bradykinin in patients who had a history of angioedema (Fig. 3), compared with controls. However, there was no difference between angioedema patients and controls in maximal bradykinin concentration or area under the curve (AUC). In contrast, both maximal

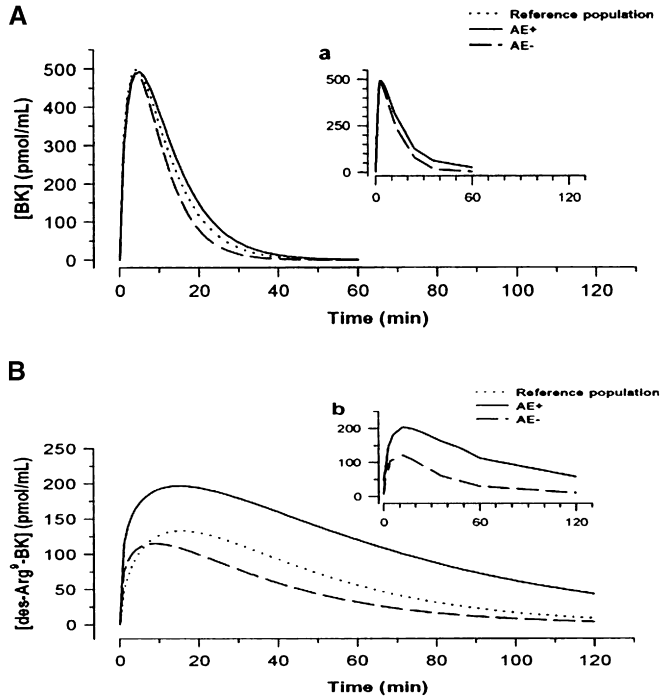

Fig. 3. Model-fitted profiles of the formation of bradykinin (BK) (*A*) and des-Arg^9-bradykinin (des-Arg^9-BK) (*B*) in individuals who have a history of angioedema (AE+, *solid lines*) and controls (AE−, *dashed lines*) after activation of the contact system in the presence of enalaprilat with glass beads. Dotted lines are for a reference population. Superscript graphs show measured values. (*From* Molinaro G, Cugno M, Perez M, et al. Angiotensin-converting enzyme inhibitor–associated angioedema is characterized by a slower degradation of des-arginine(9)-bradykinin. J Pharmacol Exp Ther 2002;303(1):234; with permission.)

des-Arg^9-bradykinin concentration and the AUC for des-Arg^9-bradykinin were significantly increased in patients who had angioedema, as was the half-life of degradation. These data confirm that des-Arg^9-bradykinin formation by kininase I is increased in the sera of patients who have angioedema (again, suggesting a defect in other degradative pathways of bradykinin) and raise the possibility that des-Arg^9-bradykinin degradation is decreased.

Despite these intriguing data, decreased APP activity does not account entirely for the pathophysiology of ACE inhibitor–associated angioedema. One third of the individuals with a history of ACE inhibitor–associated angioedema who were studied by Adam and co-workers [42] had normal APP activity. In addition, the frequency of decreased APP activity in the population (18%) exceeds the incidence of angioedema in ACE inhibitor–exposed patients [43]. Moreover, the investigators have not found a decrease in APP activity or des-Arg^9-bradykinin metabolism in black individuals who have

a history of ACE inhibitor–associated angioedema [39,44]. Taken together, these data suggest that other pathways may play a role in ACE inhibitor–associated angioedema.

Dipeptidyl peptidase IV and angiotensin-converting enzyme inhibitor–associated angioedema

In addition to increasing vascular permeability directly by means of its B_2 receptor, bradykinin stimulates the release of substance P, which causes increased vascular permeability by acting at the NK_1 receptor [37]. ACE also degrades substance P; however, in the setting of ACE inhibition, dipeptidyl peptidase IV (DPPIV/CD26; EC 3.4.14.5) sequentially degrades substance P to substance P 5-11, which lacks vasoactive function and is susceptible to further degradation by aminopeptidase N (APN/CD13, 3.4.11.2) [45]. LeFebvre and colleagues reported decreased DPPIV activity in a small number of patients who had a history of ACE inhibitor–associated angioedema [46]. The group has recently confirmed this finding in a larger group of patients (abstract). Interestingly, clinical risk factors for angioedema, including increasing age and smoking [24], were associated with decreased DPPIV antigen concentrations in this study.

Pharmacogenetics of angiotensin-converting enzyme inhibitor–associated angioedema

In contrast to hereditary angioedema, in which mutations in the C1 esterase gene have been identified, ACE inhibitor–associated angioedema results, by definition, after an environmental exposure and must involve gene–environment interactions. The heritability of ACE inhibitor–associated angioedema has not been formally established. However, ethnic differences in the frequency of angioedema provide presumptive evidence that genetic factors play a role.

Efforts to identify genetic factors predisposing to ACE inhibitor–associated angioedema have focused on enzymes involved in the degradation of bradykinin and substance P. For example, based on data indicating that APP activity is decreased in patients who have angioedema, Duan and colleagues [44] performed quantitative trait locus analysis to determine the genetic factors regulating APP activity in eight pedigrees in which at least one family member had developed an anaphylactoid reaction during hemodialysis (six families), angioedema (one family), or both (one family) (Fig. 4). Human APP exists in two forms, a glycosylphosphatidylinositol (GPI) anchored membrane form (hmAPP) and a cytosolic form (hcAPP). The gene encoding hmAPP (*XPNPEP2*, MIM 300,145) localizes to chromosome Xq26.1 [47], whereas the gene encoding hcAPP (*XPNPEPL*, MIM 602,443) localizes to 10q25.1 [48]. Duan and colleagues [44] found that variation in the *XPNPEP2* gene accounted for 34% of the heritability of plasma APP activity. There was no linkage with the hcAPP gene, suggesting

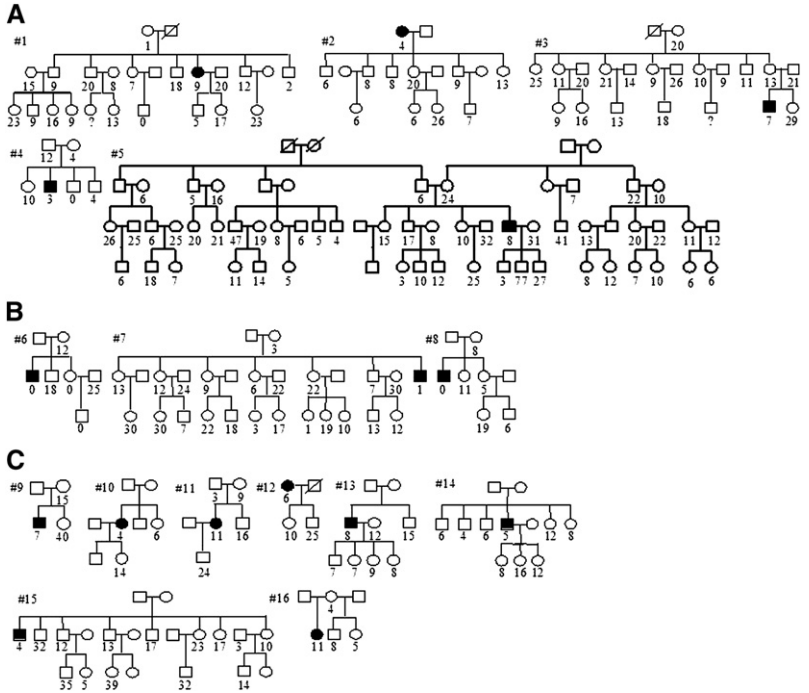

Fig. 4. Pedigrees including a proband (*shaded*) with hemodialysis-induced anaphylactoid reaction during ACE inhibitor use. The proband in family 8 had angioedema; the proband in family 3 had both an anaphylactoid reaction during hemodialysis and angioedema. Numbers indicate individual APP activities. □ male with no history of angioedema or anaphylactoid reaction; ■ male affected by angioedema and/or anaphylactoid reaction; ○ female with no history of angioedema or anaphylactoid reaction; ● female affected by angioedema and/or anaphylactoid reaction. (*From* Duan QL, Nikpoor B, Dube MP, et al. A variant in XPNPEP2 is associated with angioedema induced by angiotensin I–converting enzyme inhibitors. Am J Hum Genet 2005;77(4):619; with permission.)

that hmAPP is the primary contributor to plasma APP activity. The investigators identified a single nucleotide polymorphism (C-2399A) that associated with plasma APP activity, such that the A allele was associated with lower APP activity. An association between the C-2399A genotype and APP activity as well as angioedema was confirmed in unrelated white ACE inhibitor–associated angioedema cases and controls. In addition, the investigators identified a 175bp genomic deletion (g.2953-3127) that resulted in a truncated mAPP protein in one family with a proband who had both angioedema and an anaphylactoid reaction to hemodialysis. The mutant protein lacked both predicted active sites and the GPI anchor.

Despite this interesting finding that variation in the gene encoding mAPP predicted APP activity in families who had a history of anaphylactoid reactions, the applicability of these findings to prediction of those who are at

greatest risk for ACE inhibitor–associated angioedema is not certain. Although individuals who have anaphylactoid reactions may experience angioedema, these reactions are typically characterized by hypotension, which is not a feature of ACE inhibitor–associated angioedema. In addition, mutations in an X-linked gene are not likely to account for the majority of cases of angioedema, given that angioedema affects women more often than men.

Brown and coworkers have recently studied the relationship between polymorphisms in the gene encoding DPPIV and ACE inhibitor–associated angioedema. Human DPPIV is located on chromosome 2 locus 2q24.3 and contains 26 exons [49]. Using single-strand conformational polymorphism, the authors identified 17 polymorphisms in the gene. One of these, a synonymous single nucleotide polymorphism T24C, correlated with DPPIV antigen and activity concentrations in white individuals, suggesting that it is in linkage disequilibrium with an as yet unidentified functional polymorphism. Whether the frequency of the allele associated with lower DPPIV antigen concentrations is increased in individuals who have a history of ACE inhibitor–associated angioedema is under investigation.

Future directions

Ultimately, verification of a role for bradykinin, substance P, or any other vasoactive peptide substrate of ACE in the pathogenesis of ACE inhibitor–associated angioedema will require clinical studies assessing the effect of specific peptide receptor antagonists on the resolution of angioedema. Such studies are difficult to conduct because of the remitting and relapsing pattern of ACE inhibitor–associated angioedema. Drugs that inhibit DPPIV are currently under development for the treatment of diabetes, and clinical studies using these drugs may serve to clarify the role of DPPIV in the pathogenesis of ACE inhibitor–associated angioedema. Finally, the development of animal models of ACE inhibitor–associated angioedema would greatly enhance our ability to study the causation of this adverse drug effect.

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