

# Drug-Induced Angioedema

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## ABSTRACT

Drug-induced angioedema may be mediated by immunologic or nonimmune mechanisms. Histamine is the major vasoactive peptide responsible for angioedema due to immunoglobulin E (IgE)-mediated hypersensitivity to drugs. Angioedema caused by angiotensin-converting enzyme inhibitor (ACEI) use is not an immune-mediated reaction but rather due to accumulation of the vasoactive peptide bradykinin. While IgE-mediated reactions respond to antihistamines and corticosteroids, angioedema due to ACEIs is resistant to treatment with these agents. Epinephrine is effective in relieving IgE-mediated drug reactions but has limited clinical utility in angioedema due to ACEIs. Laryngeal swelling is a common manifestation of ACEI-induced angioedema and, left untreated, can lead to asphyxiation and possibly death. Management of drug-induced angioedema involves prompt recognition of the cause of angioedema, securing the upper airway, discontinuation of the offending drug, and initiation of appropriate therapy. (*J Angioedema*. 2011;1(2):14-22)

## INTRODUCTION

Adverse reactions to drugs can be divided into those that are immunologic and those that are mediated by nonimmune mechanisms. This article focuses on drug-induced angioedema without urticaria that occurs as an isolated cutaneous symptom or sign and is not accompanied by other organ abnormality. Particular emphasis is placed on angioedema due to angiotensin-converting enzyme inhibitors (ACEIs), a common cause of angioedema cases presenting acutely in emergency rooms throughout the United States.<sup>1</sup>

## IMMUNE-MEDIATED REACTIONS TO DRUGS

Classification of immunologic drug reactions is based on an augmented version of the original Gell and Coombs classification that distinguishes reactions as type I, II, III, or IV.<sup>2</sup> Type Ia reactions are mediated by the immunoglobulin E (IgE) antibody and include drug-induced urticaria, angioedema, asthma, and anaphylaxis. The allergic late-phase reactions responsible for the cellular infiltrate associated with "allergy" are classified as type Ib. Type II reactions involve antibodies (usually IgG, but occasionally IgM or IgA) directed against a cell or tissue type, such

as anti-basement membrane or anti-red blood cell antibodies, and are not associated with angioedema. Type III reactions are due to immune complex deposition in tissues. The prototype is serum sickness, which manifests as fever, arthralgia (occasionally arthritis), lymphadenopathy, and urticaria. Urticaria associated with type III reactions may be associated with angioedema. Type IV reactions are cell-mediated immune reactions and may be classified into 4 subgroups based on the predominant T cell type involved (lymphocytes [helper-inducer or cytotoxic], eosinophils, or neutrophils). Each of these type IV subgroups has a prototypical clinical manifestation. Type IVa reactions involve Th1 cells that activate macrophages. Although a pure type IVa reaction has not been described, the inflammation associated with contact dermatitis has a type IVa component.<sup>3</sup> Type IVb reactions involve Th2 cells, which secrete cytokines that promote B cell production of IgE and IgG4, macrophage deactivation, and mast cell and eosinophil responses. An example of a type IVb-mediated response is drug-induced hypersensitivity syndrome, or drug rash with eosinophilia and systemic symptoms (DRESS).<sup>3</sup> Type IVc reactions involve cytotoxic T cells, which can migrate to inflamed tissue and kill or induce apoptosis in resident

cells. Several types of drug-induced delayed hypersensitivity reactions are type IVc reactions, including contact dermatitis, maculopapular and bullous eruptions, drug-induced hepatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.<sup>3</sup> Finally, type IVd reactions involve neutrophils; a typical example is generalized exanthematous pustulosis.<sup>2,3</sup> Type Ia, type III, and some type IV reactions may be associated with drug-induced angioedema.

### **Type I Allergic Reactions**

Type I allergic reactions can theoretically occur in response to any drug, although some medications are clearly more immunogenic than others. Moreover, the degree to which different drugs are utilized varies greatly, and this influences the frequency of the reactions seen. Although allergy in the population at large has a clear familial predisposition with manifestations that include atopic dermatitis, extrinsic asthma, and allergic rhinitis, drug-induced allergy does not share this allergic phenotype. Thus, families with allergy as defined above have only a slightly increased incidence of IgE-mediated reaction to drugs compared to families that are otherwise devoid of atopic manifestations.

Once IgE antibody to a drug has been synthesized (requiring the usual antigen-presenting cells, CD4+ T lymphocytes, and B cell switching from IgG to IgE production), the IgE binds to mast cells throughout the body, but reactivity with skin mast cells, in particular, is required to present as urticaria or angioedema. Urticaria and angioedema can occur separately or together, the difference being the depth of the skin at which the reactions occur.<sup>4</sup> Degranulation of more superficial mast cells surrounding the superficial venous plexus is associated with urticaria, while degranulation of mast cells in the deep dermis and subcutaneous tissue is associated with angioedema.<sup>5</sup>

Histamine is the major vasoactive peptide responsible for angioedema due to IgE-mediated hypersensitivity to drugs.<sup>4</sup> It dissociates from its heparin-dependent granule binding sites once in contact with interstitial fluid. Since most cutaneous mast cells are of the TC type (ie, containing both tryptase and chymase), there is simultaneous release of the enzymes tryptase, chymase,

and carboxypeptidase along with low-molecular-weight peptides and proteoglycans, such as heparin. This reaction may occur between 30 seconds and 2 minutes after the binding of drug to cell-surface IgE antibody, whereas the synthesis and secretion of leukotrienes and platelet-activating factor (PAF) occur between 2 minutes and 10 minutes after binding; synthesis and release of cytokines and chemokines may occur hours later. The latter events contribute to the allergic late-phase response (a type Ib reaction), which may then contribute to the persistence of individual lesions. However, data are lacking with regard to this distinction when angioedema is an issue. Fleeting urticarial lesions, as seen with dermatographism or cholinergic urticaria, have no associated late phase, whereas individual hives lasting 12 to 24 hours, as can occur with a drug reaction, undoubtedly have a late-phase component contributing to the inflammatory response. However, the duration of angioedema may be prolonged due to slow absorption of interstitial fluid, and there is little cellular infiltration observed on biopsy.

Drugs that commonly cause IgE-mediated hypersensitivity include antibiotics, medications for seizure disorders, muscle relaxants used during anesthesia, and antineoplastic agents.<sup>6</sup> Angioedema may occur in the absence of urticaria in this setting, but most patients have concomitant acute urticaria.

## **NON-IMMUNE-MEDIATED REACTIONS TO DRUGS**

### **Angioedema Due to ACEIs**

Angioedema due to ACEIs accounts for about one third of acute angioedema cases presenting to emergency rooms in the United States.<sup>1</sup> ACEIs are used to treat hypertension, for afterload reduction in congestive heart failure, and to prevent acute malignant hypertension (renal crisis) as a manifestation of systemic sclerosis (scleroderma). The overall incidence of ACEI-induced angioedema has been estimated to be between 0.1% and 2%, and it is 5 times more common in African Americans than among whites.<sup>7,8</sup> The reaction commonly occurs early in the course of therapy, a few weeks to 4 months after beginning treatment; 50% of cases occur within the first week of treatment.<sup>8,9</sup> However, ACEI-induced angioedema can occasionally occur several years after the start of ACEI therapy.

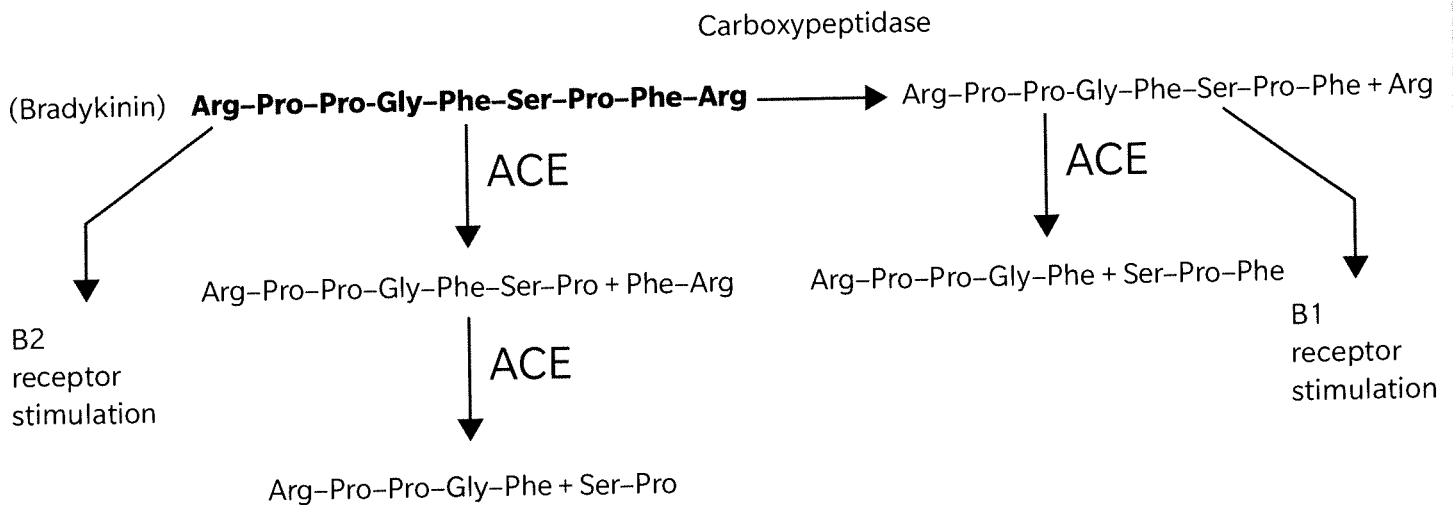
It is important to recognize this possibility because continued use of drugs in this category can lead to increasingly severe attacks and possibly death. Among the manifestations of ACEI-induced angioedema are laryngeal edema and massive tongue or pharyngeal swelling, which can lead to an inability to handle oral secretions, aspiration, or even asphyxiation. Up to 20% of reported cases are life-threatening.<sup>10</sup>

*Pathogenesis*

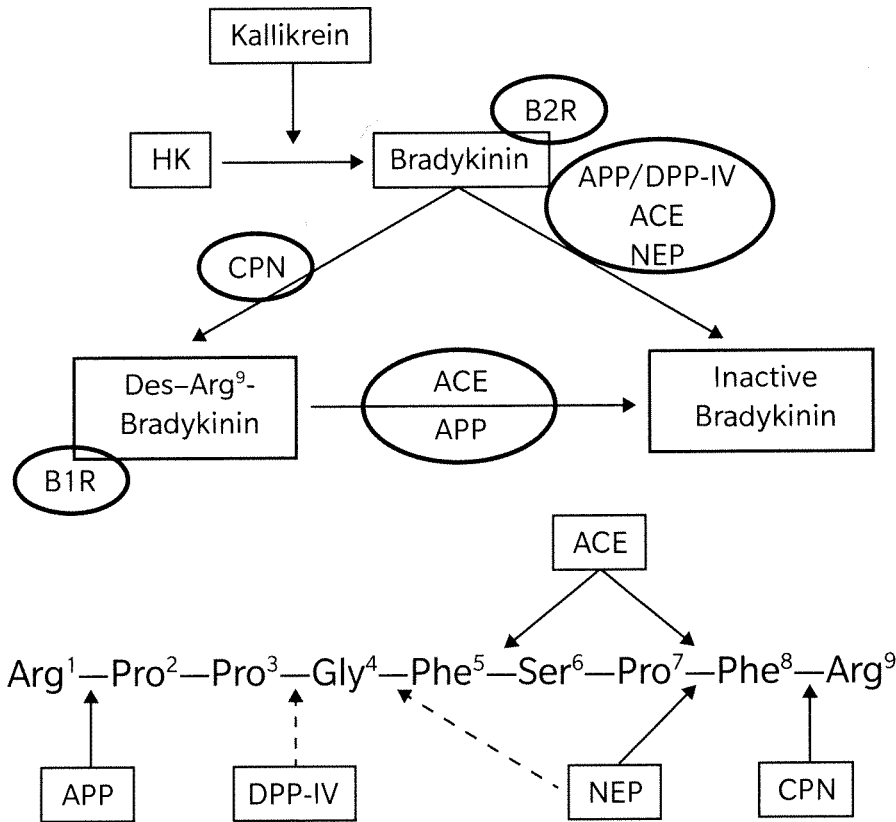
The pathogenesis of swelling due to ACEIs involves increased levels of the vasoactive peptide bradykinin.<sup>11</sup> Thus, the clinical presentation is reminiscent of that seen with hereditary or acquired C1 inhibitor deficiency, in which bradykinin is the primary mediator of swelling.<sup>12</sup> The functions of ACE are depicted in **Figure 1**. The primary substrate of ACE is the decapeptide angiotensin I, from which it cleaves the C-terminal dipeptide His-Leu to generate the octapeptide angiotensin II.<sup>13</sup> ACE is also present in plasma. Here, it was originally designated as kininase II<sup>14</sup> because it inactivates the nonapeptide bradykinin by cleaving the C-terminal Phe-Arg, eliminating bradykinin's ability to interact with either B2 or B1 receptors. A second cleavage removes Ser-Pro, leaving the pentapeptide Arg-Pro-Pro-Gly-Phe.<sup>15</sup> ACE inhibition, therefore, decreases concentrations

of the potent vasoconstrictor angiotensin II, which is beneficial for lowering blood pressure or reducing peripheral resistance to facilitate cardiac output. At the same time, ACE inhibition decreases the degradation of bradykinin, resulting in increased blood levels, which can induce angioedema.

ACE is known as a dipeptidase, but less appreciated is its function as a tripeptidase in bradykinin metabolism.<sup>15</sup> In a plasma system, the major kininase (ie, kininase I) is carboxypeptidase N,<sup>16</sup> which removes the C-terminal Arg from bradykinin. This does not eliminate kinin-like activity, but it does markedly reduce its binding to the B2 endothelial cell receptor, which is constitutively expressed. Instead, the product des-Arg<sup>9</sup>-bradykinin binds to the B1 receptor,<sup>17,18</sup> which is induced in inflammatory states by cytokines such as interleukin-1β.<sup>19</sup> Stimulation of B1 receptors by des-Arg<sup>9</sup>-bradykinin leads to vasodilation and increased vascular permeability, similar to that seen with bradykinin stimulation of B2 receptors.<sup>20</sup> ACE can then inactivate des-Arg<sup>9</sup>-bradykinin to release Ser-Pro-Phe (tripeptidase activity)<sup>15</sup> since the Pro-Phe bond can no longer be cleaved when the C-terminal Arg is not present. Thus, it is possible that inhibition of this tripeptidase



**Figure 1.** Metabolism of bradykinin. Bradykinin, a nonapeptide, is digested by angiotensin-converting enzyme (ACE) to release Phe-Arg and then Ser-Pro. These products have no interactions with kinin receptors. Carboxypeptidases N, M, or U remove C-terminal Arg, leaving an octapeptide (des-Arg<sup>9</sup>-bradykinin) that interacts with bradykinin B1 receptors. ACE degrades des-Arg<sup>9</sup>-bradykinin to a pentapeptide and a tripeptide.



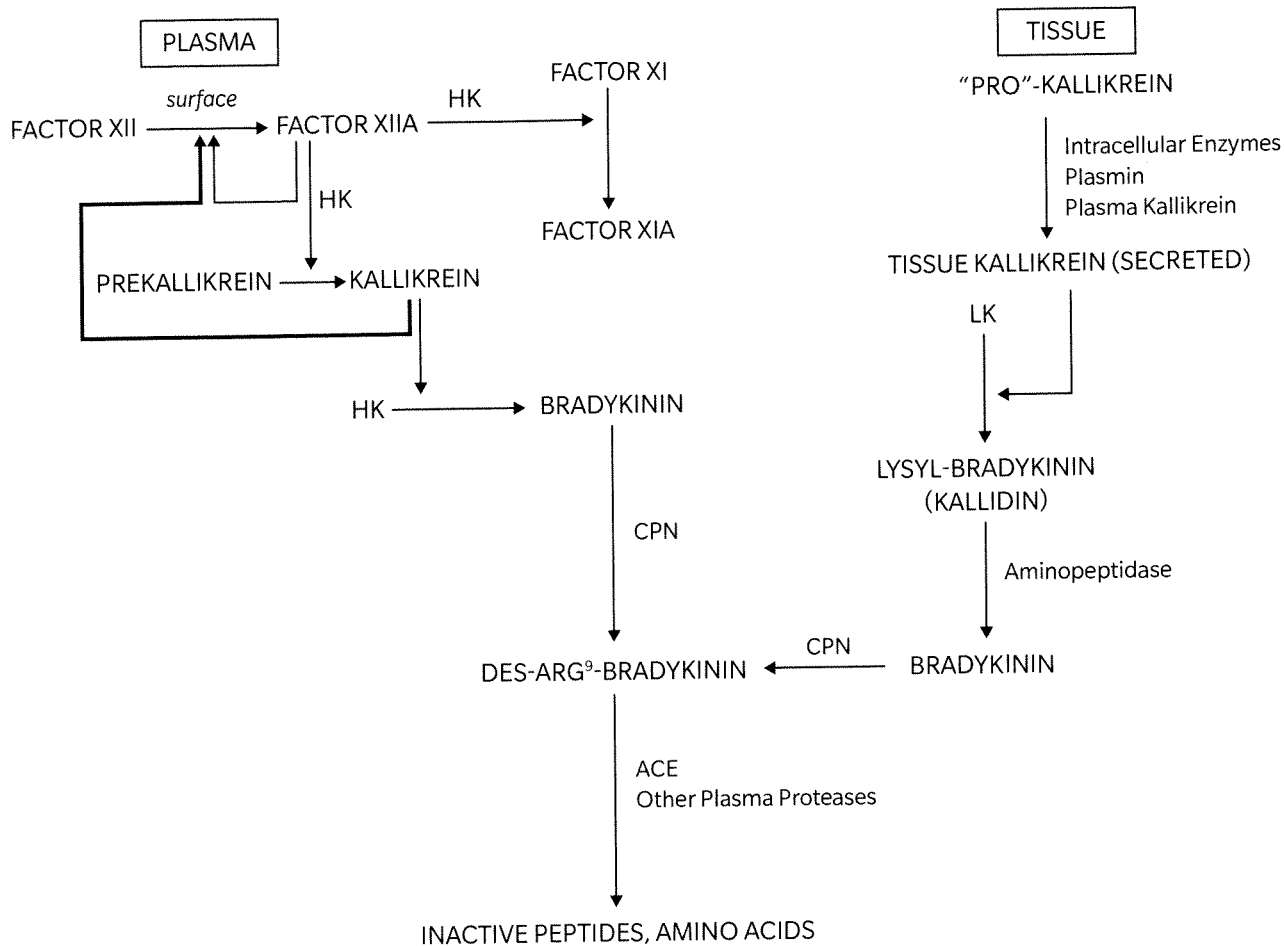
**Figure 2.** Enzymatic bond cleavage of bradykinin by tissue and plasma kininases. Carboxypeptidases M and U also cleave the C-terminal Arg of bradykinin. B2R = bradykinin B2 receptor; HK = high-molecular-weight kininogen; CPN = carboxypeptidase N; APP = aminopeptidase P; DPP-IV = dipeptidylpeptidase IV; NEP = neutral endopeptidase; B1R = bradykinin B1 receptor.

activity by an ACEI could also lead to accumulation of des-Arg<sup>9</sup>-bradykinin,<sup>21</sup> but for this to contribute to angioedema would require upregulation of B1 receptors. The most important site of bradykinin degradation *in vivo* is the pulmonary vasculature (ie, pulmonary vascular endothelial cells), rather than plasma, and here, ACE appears to be the primary kininase.<sup>22,23</sup> Pulmonary vascular endothelial cells also express carboxypeptidase M at the cell surface, which is a different gene product from carboxypeptidase N but functionally the same.<sup>24</sup>

In the presence of drug-induced ACE inhibition, degradation of bradykinin is dependent on carboxypeptidases such as carboxypeptidases M and N and additional enzymes, including aminopeptidase P (APP), neutral endopeptidase (NEP), and dipeptidylpeptidase IV (DPP-IV). Thus, the blood and tissue levels of these enzymes may be particularly

important in the prevention of angioedema when ACE has been inactivated. The sites of cleavage by each of these enzymes are shown in **Figure 2**. There is evidence to suggest that African Americans have polymorphisms in the genes that code for APP and/or NEP, resulting in lower blood levels of these enzymes and predisposing those patients taking ACEIs to ACEI-induced angioedema.<sup>25</sup> In fact, African Americans have increased cutaneous sensitivity to injected bradykinin even in the absence of medication.<sup>26</sup> Furthermore, inhibition of either DPP-IV<sup>27</sup> or NEP<sup>28</sup> in conjunction with ACE inhibition increases the risk of angioedema even further.

Bradykinin levels cannot increase unless it is also being continuously produced. Although the mechanisms by which bradykinin is generated are well understood, their individual contributions to maintenance of normal



**Figure 3.** Kinin formation and degradation. Pathways for the production of bradykinin include the plasma (factor XII-dependent) intrinsic pathway and the extrinsic pathway dependent on tissue kallikrein. HK = high-molecular-weight kininogen; CPN = carboxypeptidase N; ACE = angiotensin-converting enzyme; LK = low-molecular-weight kininogen

bradykinin levels are unknown. These pathways are depicted in **Figure 3** and include the extrinsic pathway dependent on the release of kinin-forming enzymes from cells (tissue) and the intrinsic or factor XII-dependent pathway for bradykinin formation in the blood. The extrinsic pathway involves release of tissue kallikrein,<sup>29</sup> a 30-kD enzyme that digests a low-molecular-weight form of kininogen (LK) to release lysyl-bradykinin, from which the plasma aminopeptidase P rapidly removes the N-terminal lysine to yield bradykinin.<sup>15</sup> The intrinsic pathway involves activation of factor XII, conversion of plasma prekallikrein to kallikrein, and digestion of a high-molecular-weight form of kininogen (HK) by kallikrein to release bradykinin.<sup>30</sup> Baseline bradykinin level in humans is approximately 10

pg/mL. In a rodent system, deficiency of factor XII decreases baseline bradykinin by one half,<sup>31</sup> indicating that the intrinsic pathway is contributing to the maintenance of that level. The extrinsic pathway may also contribute to plasma bradykinin baseline levels, but one very recent observation suggests a second possible contribution by the intrinsic pathway, namely, the ability of prekallikrein (rather than kallikrein) to digest HK to release bradykinin.<sup>32</sup> This reaction is normally blocked by plasma C1 inhibitor,<sup>32</sup> but traces of activity may persist since inhibition is rarely 100%. It should be noted that tissue kallikrein and plasma prekallikrein are encoded by completely different genes and that the difference between LK and HK is due to alternative splicing<sup>33</sup> so that they share the same

N-terminal half plus bradykinin and the next 9 amino acids. Thereafter, they are synthesized employing different C-terminal domains.<sup>34</sup>

### *Clinical Manifestations*

The clinical features of ACEI-induced angioedema are similar to those of C1 inhibitor deficiency, where overproduction of bradykinin<sup>35</sup> rather than diminished degradation is the cause of angioedema. Although it has not been proven unequivocally that bradykinin is the mediator of swelling in ACEI-induced angioedema, as it has for C1 inhibitor deficiency, there is no evidence to date that accumulation of other peptides that are also metabolized by ACE has any role in causing angioedema.

Clinical manifestations of ACEI-induced angioedema include peripheral, orofacial, and gastrointestinal edema. Peripheral angioedema can affect the hands, feet, and genitalia.<sup>12</sup> Orofacial angioedema can include the face, lips, tongue, pharynx, larynx, and subglottic area. When orofacial swelling is severe, the ability to handle oral secretions may be compromised. Early laryngeal edema may manifest as hoarseness and progress to inspiratory stridor. Gastrointestinal attacks are due to bowel wall edema and manifest as severe abdominal pain and vomiting, occasionally associated with diarrhea.<sup>12</sup> Attacks of angioedema can last 2 to 4 days.

### **Angioedema Due to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

Angioedema caused by NSAIDs is another example of nonallergic, drug-induced angioedema. Urticaria is commonly associated with angioedema caused by these agents but is not necessarily present. NSAIDs are typically inhibitors of cyclooxygenase-1 (COX-1) or both COX-1 and COX-2.<sup>36</sup> Inhibition of COX-1 blocks formation of prostaglandin G<sub>2</sub> and H<sub>2</sub> intermediates, and arachidonic acid metabolism is shunted through the 5-lipoxygenase pathway with enhanced formation of cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>) and other highly vasoactive hydroxy fatty acids. Although mast cell degranulation is associated with aspirin-induced urticaria or angioedema, the mechanism linking COX products and mast cell activation is not clearly delineated.

The reactions can be very acute, occurring within minutes of ingestion or injection of an NSAID. Sensitive patients need to avoid all drugs within this class. Susceptible patients will generally tolerate those drugs that selectively inhibit COX-2.<sup>37</sup> The COX-2 antagonists are generally well tolerated. Acetaminophen, a weak COX-1 inhibitor, is tolerated by many patients, although occasional exceptions are seen,<sup>38</sup> particularly at high doses.

### **TREATMENT OF DRUG-INDUCED ANGIOEDEMA**

Allergic angioedema can occur very rapidly (within minutes) or several hours after exposure to a drug and can occur alone, with urticaria, or as part of a more generalized anaphylactic reaction. If the respiratory tract is involved (eg, laryngeal edema), securing the airway is the first priority and may require intubation or, rarely, a tracheostomy to administer oxygen. An intravenous line is placed and intramuscular epinephrine administered to reduce the swelling. A dose of 0.3 mg (0.3 mL at 1:1000 dilution) is typically administered and can be repeated after 20 minutes. Intramuscular or intravenous diphenhydramine (50 mg) is helpful and intravenous methylprednisolone (40-60 mg) may prevent relapse.<sup>39</sup> Peripheral angioedema can be treated with high-dose antihistamines (eg, cetirizine 10 mg qid or diphenhydramine 25-50 mg qid) for a few days until the swelling has reabsorbed. A single dose of epinephrine can be used to abort angioedema that is increasing rapidly, particularly if the tongue is swelling rapidly, vision is significantly compromised, or the face is significantly disfigured. The drug responsible for the reaction needs to be identified and, when multiple possibilities exist, all drugs should be stopped if possible. A switch to a non-cross-reacting agent can be made empirically when continued treatment is needed, or after a definitive identification has been made (eg, by skin test).<sup>40</sup>

When the cause of angioedema is not evident, epinephrine, diphenhydramine, and corticosteroids are usually administered empirically. In the case of ACEI-induced symptoms, a positive response to these agents should not be expected. ACEI-induced angioedema (like all angioedema types mediated by bradykinin) is completely resistant to treatment with antihistamines or corticosteroids. Although often administered, epinephrine is much less reliable in this

context than it is in histamine-mediated angioedema. Rapidly accelerating angioedema affecting the tongue, pharynx, and larynx is often observed in ACEI-induced angioedema, and one must be prepared to intubate the patient or perform a tracheostomy even after epinephrine has been administered. There is no specific therapy for peripheral angioedema due to ACEIs, and symptoms of gastrointestinal edema can be treated with intravenous (IV) fluids and analgesics. New approaches for hereditary angioedema include infusion of C1 inhibitor,<sup>41,42</sup> which inactivates enzymes involved in bradykinin formation; administration of ecallantide<sup>43,44</sup> by subcutaneous injection to inactivate plasma kallikrein; or administration of icatibant, a reversible bradykinin B2 receptor antagonist.<sup>45,46</sup> Any of these treatments could theoretically be effective for ACEI-induced angioedema, but the studies required for FDA approval have not been completed. Patients who experience ACEI-induced angioedema may be safely treated with other antihypertensive agents such as beta-blockers, calcium channel blockers, or diuretics. ACEIs do, however, have cardioprotective effects shared by angiotensin II receptor blockers (ARBs), which, in many circumstances (eg, heart failure, diabetes), would be a preferred alternative.

The incidence of angioedema due to ARBs is low<sup>47</sup> ( $\leq 10\%$  of that of ACEI-induced angioedema), but it is possible that those who have had an adverse reaction to an ACEI are predisposed to ARB-induced angioedema. Although ARBs do not affect bradykinin metabolism directly, they may raise bradykinin levels<sup>48</sup> by downregulating ACE levels<sup>49</sup> or sensitizing B2 receptors to the effects of bradykinin<sup>50</sup> through effects on angiotensin II type 2 (AT<sub>2</sub>) receptors<sup>51,52</sup> (angiotensin's hypertensive effect is due to interaction with AT<sub>1</sub> receptors, which are blocked by ARBs). One study suggests that activation of a cellular kininogenase (with kallikrein-like activity) by stimulation of AT<sub>1</sub> receptors may generate bradykinin through cleavage of kininogen.<sup>51</sup> Additional mechanisms that are being explored include the possibility that AT<sub>2</sub>-receptor stimulation causes endothelial cell secretion of HSP 90<sup>53</sup> or prolylcarboxypeptidase,<sup>54</sup> either of which can generate bradykinin by interacting with the plasma prekallikrein-HK complex. Although there are reports of

significant angioedema after switching to an ARB from an ACEI,<sup>55</sup> most studies indicate that the switch to an ARB is safe and that the benefits outweigh any possible risks.<sup>56-58</sup> Idiopathic angioedema should be suspected in any patient who experiences angioedema reactions to both ACEIs and ARBs; such patients may have angioedema independent of any drug exposure.

NSAID-induced angioedema is treated acutely in the same manner as allergic angioedema, which has been described above. All drugs that act by inhibiting COX-1 need to be avoided. It should be noted that, in aspirin (acetylsalicylic acid), the acetyl groups are responsible for irreversible inhibition of COX-1, whereas the salicylate moiety is responsible for anti-inflammatory activity. Thus, other salicylates, such as choline salicylate or disalicylates, as well as acetaminophen, are usually tolerated by patients who experience angioedema after NSAID exposure.

## CONCLUSIONS

Angioedema is a common symptom of allergic reactions to drugs, and, although typically accompanied by urticaria and/or other abnormalities, it can occur as a sole manifestation. Treatment involves administration of antihistamines (for acute symptoms), corticosteroids (to prevent protracted or additional later symptoms since they require 5 to 6 hours for an initial effect to be seen), and epinephrine for any accelerating, life-threatening manifestation, including symptoms consistent with anaphylaxis. Drug-induced angioedema in the absence of urticaria can be caused by non-immunologic mechanisms as is seen with angioedema induced by ACEIs and NSAIDs. The mediator of ACEI-induced angioedema is thought to be bradykinin, based on the similarity of symptoms to those of C1-inhibitor deficiency (which is known to be caused by bradykinin) and the fact that other peptides metabolized by ACE have no known role as a cause of angioedema in humans. ACE-induced angioedema disproportionately affects the airway (tongue, pharynx, larynx) versus other sites and is one of the most common causes of acute angioedema presenting to emergency rooms in the United States.

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