Angiotensin-converting Enzyme Inhibitor and Other Drug-associated Angioedema

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KEYWORDS

• Angioedema • ACE inhibitor • Bradykinin • NSAID • Leukotriene • Drug
• Medication

KEY POINTS

- Drug-induced angioedema should be characterized as being either allergic (histamine mediated) or nonallergic mechanism based, because this guides therapeutic decision making.
- Nonsteroidal antiinflammatory drugs can cause angioedema in a susceptible host via shifts in the synthesis of prostaglandins and leukotrienes.
- A growing number of drugs cause angioedema by inhibiting pathways involved in the degradation of bradykinin and substance P.
- B_2 receptor antagonism and kallikrein inhibition have not been as successful in the treatment of drug-induced bradykinin-mediated angioedema as in hereditary angioedema.

INTRODUCTION

Angioedema is characterized by localized deep dermal, subcutaneous, and/or mucosal edema resulting from increased vasodilatation and vascular permeability. Nonsteroidal antiinflammatory drugs (NSAIDs), β-lactam antibiotics, non–β lactam antibiotics, and angiotensin-converting enzyme (ACE) inhibitors are the most common classes of drugs that cause angioedema.[1–3] Drug-induced angioedema is best categorized as allergic or nonallergic. The most common form of allergic angioedema is caused by immunoglobulin (Ig)-E–mediated degranulation of mast cells and release of histamine (type I hypersensitivity) in response to a drug and this is the most common

Disclosure: The authors have nothing to disclose.

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Immunol Allergy Clin N Am 37 (2017) 483–495
http://dx.doi.org/10.1016/j.iac.2017.04.006
immunology.theclinics.com

cause of angioedema caused by β-lactam and other antibiotics.[1] Nonallergic forms of angioedema result as a consequence of the underlying mechanism of the drug. NSAIDs may cause hypersensitivity reactions but angioedema results more commonly because of the diversion of arachidonic acid metabolism from the cyclooxygenase (COX) pathway to the leukotriene pathway. ACE inhibitor–associated angioedema results from decreased degradation of kinins and other vasoactive peptides; there is a growing list of drugs that affect these pathways.

Clinically it is important to distinguish between allergic and nonallergic forms of drug-induced angioedema because the response to therapy differs dramatically. Allergic forms of drug-induced angioedema respond to antihistamines, glucocorticosteroids, and epinephrine, whereas nonallergic forms do not. The presence of pruritus or urticaria in a patient without a prior history of urticaria suggests an allergic form of drug-induced angioedema. For completeness, **Table 1** provides a list of drugs that cause histamine-mediated angioedema (see Busse PJ, Smith T: Histaminergic Angioedema, in this issue). This article focuses primarily on nonallergic forms of drug-induced angioedema.

ANGIOEDEMA ASSOCIATED WITH NONSTEROIDAL ANTIINFLAMMATORY DRUG USE

The European Academy of Allergy and Clinical Immunology Task Force on NSAID Hypersensitivity proposed classifying immediate-type NSAID reactions into 5 categories, 3 of which can present with angioedema.[4]

Table 1
Drugs that cause histamine-medicated angioedema and their reported mechanisms of mast cell degranulation

IgE Mediated	Direct Mast Cell Degranulation, Via G-Protein–coupled Receptors or Other Means	Drug Causes Histamine-mediated Angioedema Only Rarely, or Mechanism is Not Understood
Antimicrobials: Penicillins,[51] cephalosporins,[52] Carbapenems,[51] fluoroquinolones,[53] sulfonamides,[54] vancomycin,[55] macrolides[56] Chemotherapeutics: Platinum-based agents,[57] paclitaxel,[58] cetuximab (via galactose-alpha-1, 3-galactose allergy)[59] Procedural medications: Radiographic contrast,[60] opiates,[61] neuromuscular blocking agents,[62] NSAIDs[63] Gastrointestinal medications: Proton pump inhibitors,[64] polyethylene glycol[65]	Antimicrobials: Fluoroquinolones,[66] sulfonamides[67] (especially in patients with human immunodeficiency virus), vancomycin[a] (associated with worsening of angioedema only)[3,55] Chemotherapeutics: Paclitaxel[a,68] Procedural medications: Radiographic contrast,[a,69] opiates,[a,70] neuromuscular blocking agents[a,66]	Antimicrobials: Daptomycin,[71] clindamycin,[72] chloramphenicol[73] Antituberculosis agents: Rifampicin,[74] streptomycin,[75] ethambutol,[76] isoniazid[77] Immune suppressants: Tacrolimus,[78] sirolimus[79] Psychiatric medications: selective serotonin reuptake inhibitors[80] Procedural medications: Hyaluronidase[81]

[a] For medications with more than 1 reported mechanism, what seems to be the most common mechanism for reactions is indicated when that information is available.