Cardiovascular and Diabetic Medications That Cause Bradykinin-Mediated Angioedema

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Medication-induced angioedema is a bradykinin-mediated process that results from increased production or decreased degradation of bradykinin. These reactions are documented for several cardiac medications including blockers of the renin-angiotensin-aldosterone system (RAAS). Other cardiovascular and diabetes medications further increase the risk of medication-induced angioedema, particularly with concomitant use of RAAS inhibitors. Dipeptidyl peptidase IV inhibitors are a class of oral diabetic agents that affect bradykinin and substance P degradation and therefore can lead to angioedema. Neprilysin inhibitors are a separate class of cardiac medications, which includes sacubitril, and can lead to drug-induced angioedema especially when used in combination with RAAS inhibitors. This article discusses the proposed mechanisms by which these medications cause angioedema and how medication-induced angioedema differs from mast cell-mediated angioedema. It also details how to recognize medication-induced angioedema and the treatment options available. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:610-5)

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CASE

Mr. C was a 76-year-old man who presented to the emergency department with a chief complaint of "sore throat and shortness of breath." Two hours after he took his morning medications, he felt a "burning" sensation in his posterior pharynx, became short of breath, and noted a change in his ability to talk. Medications included fluoxetine, metoprolol, fosinopril, and pravastatin. He had a history of benign essential hypertension, hyperlipidemia, depression, and coronary artery disease. Otherwise, his medical, surgical, social, and family histories and review of symptoms were noncontributory.

His vital signs were normal except for a pulse oximetry of 85% to 86% on room air. He was noted to have audible stertor (low-pitched snoring or rumbling sound). There was no lip, tongue, uvula, or facial swelling. Lungs were clear. The rest of the physical examination was unremarkable.

Laboratory studies revealed a mild leukocytosis, normal differential, normal C4, and were otherwise normal. Chest x-ray was unremarkable and a computed tomography scan of the neck showed edema of the aryepiglottic folds and lateral hypopharyngeal wall bilaterally, with a reduced airway caliber. Laryngoscopy confirmed moderate edema of the arytenoids and aryepiglottic folds and poor visualization of the vocal cords.

Differential diagnosis included a systemic allergic reaction causing laryngeal edema, severe laryngitis, idiopathic angioedema, angiotensin converting enzyme inhibitor (ACEi)-mediated angioedema, and acquired C1 inhibitor deficiency.

Elective intubation was performed approximately 4 hours after his arrival. He was admitted to the intensive care unit where he received 2 units of fresh frozen plasma, methylprednisolone 125 mg IV every 8 hours, and famotidine 20 mg IV every 12 hours. He remained intubated for 1 week, after which he was weaned off the ventilator. The diagnosis was ACEi-induced angioedema secondary to fosinopril.

OVERVIEW OF ANGIOEDEMA

Angioedema is nonpitting swelling of subcutaneous and submucosal tissues due to vascular dilation and increased permeability of arterioles and venules. Mast-cell histaminergic and bradykinin-mediated etiologies are 2 mechanisms that are described below.

Mast cell-mediated angioedema

Mast cells, when perturbed, release mediators including histamine, tryptase, prostaglandin D2, and leukotriene C4, resulting in subcutaneous and cutaneous edema. Urticaria and pruritus usually accompany mast cell-mediated angioedema. It can be triggered in an allergic individual by foods, drugs, insect stings, and other allergens via IgE mediation and manifests rapidly after allergen exposure. It usually resolves over 24 to 48 hours. In systemic allergic reactions, serum tryptase, a marker of mast cell activation, may be elevated. An elevated tryptase can also be an indication of mast cell activation syndrome, or even mastocytosis, and it is used as a screening tool for these conditions in cases of unexplained anaphylaxis. Tryptase is used clinically by measuring serum levels in patients with angioedema to clarify the mechanism of the reaction.

Idiopathic angioedema is also likely histaminergic in etiology because it responds to antihistamines. Unlike bradykinin-mediated angioedema, which may be life threatening,

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Abbreviations used

ACEi- Angiotensin-converting-enzyme inhibitor
ANP- A-type natriuretic peptide
APP- Aminopeptidase P
ARB- Angiotensin receptor blocker
ARNI- Angiotensin receptor neprilysin inhibitor
AT2- Angiotensin type 2 receptor
B1- Bradykinin type 1 receptor
B2- Bradykinin type 2 receptor
CPN- Carboxypeptidase N
DPP-IV- Dipeptidyl peptidase IV
FFP- Fresh frozen plasma
HAE- Hereditary angioedema
NEP- Neutral endopeptidase (neprilysin)
PARADIGM-HF- Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure
RAAS- Renin-angiotensin-aldosterone system
TRANSCEND- Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease

idiopathic angioedema is usually not life threatening, even when it occurs in the laryngopharynx. However, precaution should still always be taken, as some individuals may have smaller anatomical upper airways, posing a higher potential risk of asphyxiation. It is commonly associated with urticaria.

Treatment for mast cell or histamine-mediated angioedema includes antihistamines, glucocorticoids, and also epinephrine, particularly when it is associated with the signs and symptoms of a systemic allergic reaction.

Bradykinin-mediated angioedema

This paper focuses on bradykinin-mediated angioedema, which results from the overproduction of bradykinin or the inhibition of bradykinin degradation. Mast cells are not the primary culprit, so urticaria and pruritus do not accompany this form of angioedema. The primary areas affected include the face, lips, tongue, and laryngopharynx. Bradykinin-mediated angioedema is unique in that it also may affect the gastrointestinal mucosa, causing bowel wall edema, presenting with abdominal pain, nausea, vomiting, and diarrhea.[1] This occurs in both hereditary and acquired angioedema. The 2 main etiologies of bradykinin-mediated angioedema are C1 inhibitor deficiency, either acquired or hereditary, or medication-mediated, the topic of this article.

Bradykinin and its physiologic roles

Bradykinin is a peptide composed of 9 amino acids and is a potent vasodilator, causing increased capillary permeability. It has 2 receptors, bradykinin type 1 receptor (B1) and bradykinin type 2 receptor (B2), the latter of which is constitutively expressed and participates in bradykinin's vasodilatory role. When bradykinin binds its receptor B2, downstream signaling pathways ultimately release mediators, including nitric oxide and prostaglandins. These potentiate increased vascular permeability and plasma extravasation into submucosal tissues, resulting in angioedema.[2,3] Bradykinin is broken down by ACE, neutral endopeptidase (NEP), aminopeptidase P (APP), carboxypeptidase N (CPN), dipeptidyl peptidase IV (DPP-IV), and kininase I. One of the metabolites of bradykinin, des-Arg9-bradykinin, stimulates the B1 receptor, which is upregulated in inflammatory states and perpetuates the effects of bradykinin.[4] Substance P is an undecapeptide belonging to the "tachykinin" family, but like bradykinin it has vasodilatory effects.[5,6] Figure 1 depicts pathways involved in bradykinin-mediated angioedema and medications that affect these pathways.

MEDICATION-INDUCED BRADYKININ-MEDIATED ANGIOEDEMA

Renin-angiotensin-aldosterone system (RAAS) blocker-induced angioedema

RAAS blockers, most notably ACEi and angiotensin receptor blockers (ARBs), are prescribed worldwide and reduce the morbidity and mortality from hypertension, cardiovascular disease, and diabetes.[7] However, ACEi have an uncommon but important side effect of drug-induced angioedema. The incidence is 0.1% to 0.7% among subjects who take these medications, with up to a 5 times greater risk in Americans of African heritage.[8-10] Also, ACEi are contraindicated in subjects with a history of any form of angioedema. Two thirds of ACEi-induced angioedema occurs within the first 3 months of starting these medications, but reactions may occur after many years of use.[8] If such a reaction is not properly identified and the medication is not discontinued, the angioedema may resolve, but can once again return and become a severe or life-threatening problem.[11,12] The proposed mechanisms or pathways involved in RAAS blocker-induced angioedema are discussed below.

Angiotensin-converting enzyme inhibitors. The classic example of drug-induced angioedema occurs with ACEi. The mechanism involves the inhibition of bradykinin degradation, leading to activation of vascular B2 receptors. Excessive amounts of bradykinin cause overactivation of B2.[13] When ACE is inhibited, as in the use of ACEi, the other degrading enzymes play a larger role in the breakdown of bradykinin. Therefore, individuals who have decreased activity in one or more of these enzymes (ie, APP, dipeptidyl peptidase IV) have a higher risk for ACEi-induced angioedema.[14] Genetic polymorphisms in these degradation enzymes may explain why Americans of African heritage are at increased risk for angioedema.[15]

Angiotensin II receptor blockers. A complete understanding of how ARBs cause angioedema is still uncertain. Research in human subjects suggests that ARBs increase bradykinin levels via indirect mechanisms. ARBs prevent angiotensin II from binding the angiotensin type 1 receptor, resulting in elevated angiotensin II levels. Elevated angiotensin II may stimulate angiotensin type II (AT2) receptors, which normally reduce ACE activity. Stimulation of AT2 receptors therefore may reduce ACE activity and result in increased bradykinin levels.[16] ARBs are thought to cause considerably less angioedema than ACEi perhaps because they increase only bradykinin levels, whereas ACEi increase both bradykinin and kallidin levels.[16] Bradykinin and kallidin are very similar molecules both derived from kininogens. Plasma kallikrein forms bradykinin from kininogens, whereas tissue kallikrein forms kallidin from kininogens. Improved endothelial function in coronary artery disease is attributed to increased levels of bradykinin and nitric oxide.[16,17] The TRANSCEND trial ("Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease") was designed to evaluate the effectiveness of