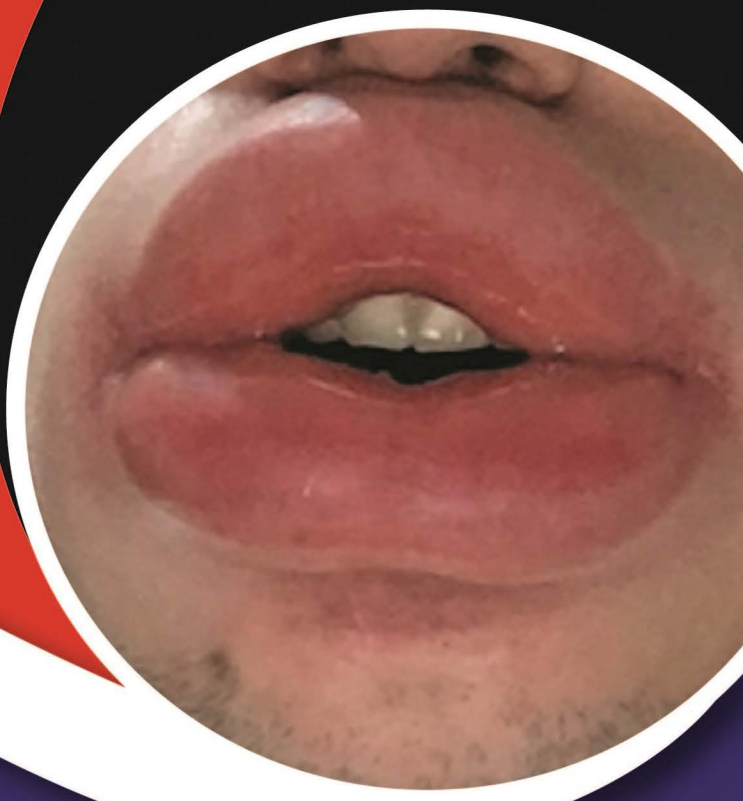

Handbook of Angioedema

An initiative of the Global Allergy and Asthma European Network (GA²LEN) Angioedema Centers of Reference and Excellence (ACARE)

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CHAPTER

Drug-induced Angioedema

Maia Gotua, Jonathan Peter

INTRODUCTION

Drug-induced angioedema (DI-AE) is the most common cause of isolated angioedema (AE) (without urticaria) presenting to emergency departments globally, with the most common offending agents being angiotensin-converting enzyme inhibitors (ACEIs), nonsteroidal anti-inflammatory drugs (NSAIDs), and antibiotics.[1-4]

The challenge with drug-induced forms of AE is that the mechanisms, and consequently required treatments, differ. Drugs can lead to AE through three major mechanisms including—(1) degranulation of mast cell mediators, (2) imbalances in vasoactive leukotrienes and prostaglandins, and (3) increased production or decreased metabolism of bradykinin (BK) and/or related vasoactive peptides, for example, substance P **(Fig. 1)**.

The largest group of DI-AE is BK-mediated. These reactions are documented for several medications used in cardiometabolic diseases, mostly aimed at modifying the renin–angiotensin–aldosterone system (RAAS), including ACEIs, angiotensin receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNIs). In addition, dipeptidyl peptidase 4 (DPP-4) inhibitors are a class of oral diabetic agents that affect BK and substance P degradation and, therefore, can lead to AE. In this chapter, we outline the epidemiology, pathogenesis, risk factors, and management of DI-AE, with a focus on common drug classes and nonhistaminergic mechanisms.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR-INDUCED ANGIOEDEMA

Epidemiology

Hypertension is a global epidemic, and growing rapidly, especially in the low- and middle-income countries (LMIC) populace, including

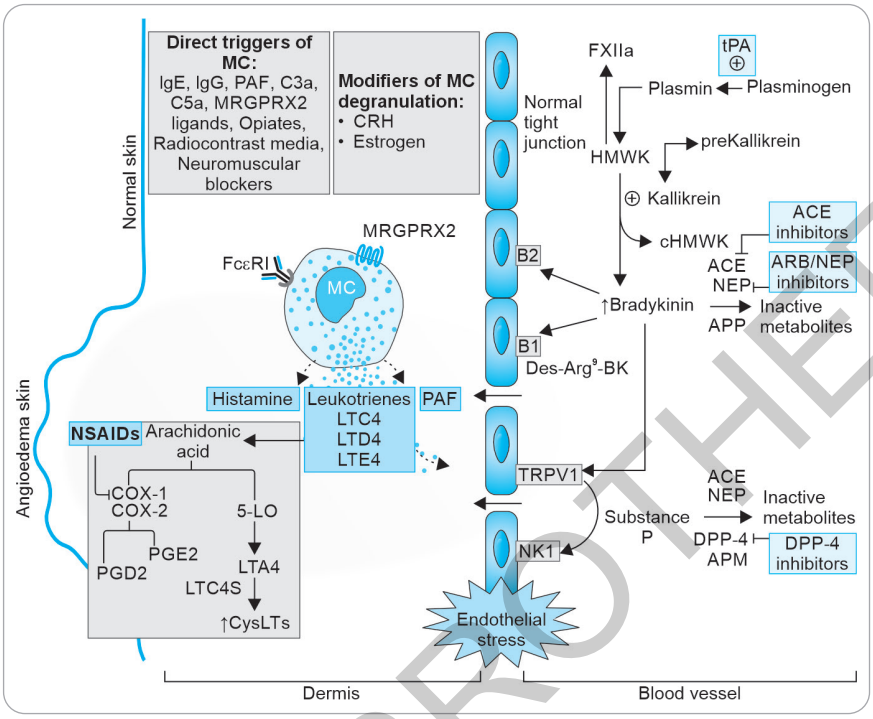

FIG. 1: Mechanisms of drug-induced angioedema.

(5-LO: 5 lipoxygenase; ACE: angiotensin-converting enzyme; APM: angiotensinase-peptidase M; APP: aminopeptidase P; ARB: angiotensin receptor blocker; B2: BK type 2 receptor; BK: bradykinin; C3a and C5a: complement components C3a and C5a; COX: cyclooxygenase; CRH: corticotropin-releasing hormone; CysLTs: cysteinyl leukotriens; Des-Arg9-BK: carboxypeptidase metabolite of BK acting as an agonist for the type 1 (B1) BK receptor; DPP-4: dipeptidyl peptidase 4; FcεRI: high-affinity IgE receptor; FXIIa: active enzyme of FXII; HMWK: high-molecular-weight kininogen; IgE: immunoglobulin E; IgG: immunoglobulin G; LTA, LTC, LTD, LTE: leukotrienes A,C,D,E; MC: mast cell; MRGPRX2: mas-related G-protein coupled receptor member X2; NEP: neprilysin; NK1: neurokinin-1; NSAIDs: nonsteroidal anti-inflammatory drugs; PAF: platelet-activating factor; PGD: prostaglandin D; PGE: prostaglandin E; tPA: tissue plasminogen activator; TRPV1: transient receptor potential vanilloid 1)

Asia, Africa, and South America.[5] ACEIs are used worldwide as pharmacologic inhibitors of RAAS to treat millions of people with hypertension, myocardial infarction, heart failure, left ventricular dysfunction, diabetes including nephropathy, or stroke, providing organ protection and reducing morbidity and mortality. The most frequent adverse events for ACEI are cough (88.2%), symptomatic hypotension (4.1%), AE (1.3%), or renal dysfunction (1%).[3]

Angiotensin-converting enzyme inhibitors are the most common cause of AE seen in the emergency department[2,6] and a very frequent cause seen in inpatient allergy consult service.[7] The overall incidence of AE in patients receiving ACEIs ranges between 0.1 and 0.7%,[3] and even as high as 6% in some clinical trials, accounting for up to 40% of emergency visits for AE.[2,6] The incidence of angiotensin-converting enzyme inhibitor-induced

angioedema (AE-ACEI) is up to five times greater in people of African descent and uncommon in Asian populations.[1,3]

It is associated with high morbidity and healthcare expenditure due to hospitalizations, including intensive care unit admissions for intubation. Unfortunately, fatal reactions have also been reported.[1-4]

Clinical Presentation, Diagnosis, and Risk Factors

Angiotensin-converting enzyme inhibitor-induced angioedema most commonly occurs in the first month following initiation of therapy. One study found a 0.07 and 0.23% incidence of AE-ACEI within 1 month and 1 year following prescription, respectively, with a 0.1–12% constant annual incidence in the subsequent 4 years. Cases have also been reported several years after initiation.[3,8]

Clinically, AE-ACEI typically affects the lips, tongue, and face, although visceral AE with acute abdominal pain is described. Urticaria and itching are absent. Life-threatening AE relates to laryngeal involvement, with an estimated 16% of cases that present to the emergency room (ER) requiring intubation.[4]

Early signs of laryngeal AE may include hoarseness of the throat and inspiratory stridor, which may progress to airway obstruction in up to 10% of cases. Rarely, fatalities due to massive tongue swelling and asphyxiation are reported.[9]

Angiotensin-converting enzyme inhibitor-induced angioedema occurs episodically, and each episode follows a relatively predictable time course of 2–5 days. Edema usually develops over minutes to hours, peaks, and then resolves over 24–72 hours, although complete resolution may take days in some cases. Risk factors known to increase the likelihood of AE-ACEI include older age, atopy, smoking, immunosuppressant use, rheumatoid arthritis, and organ transplant.[3,7,8]

The diagnosis of AE-ACEI is made clinically, as there are no definitive laboratory tests or biomarkers that are routinely available to diagnose it. In unusual cases, such as abdominal visceral AE-ACEI, imaging may be required with computed tomography (CT) or magnetic resonance imaging (MRI); typical findings include dilated bowel loops, a "doughnut" or "stacked coin" appearance, thickened mucosal folds, mesenteric edema, perihepatic fluid, and/or ascites. MRI and invasive endoscopy should be reserved for cases where ultrasound and CT are nondiagnostic, and there is still a high clinical suspicion.[2,6,7]

Resolution following discontinuation of ACEIs confirms the diagnosis. However, the impact of discontinuation may only be clear after several months, as some patients will have a small number of recurrent episodes, particularly in the first few months after the ACEI was discontinued. Such patients should remain off ACEI. Referral to an allergy expert should be considered for patients who continue to have episodes of AE after 6 months.[7]

Angiotensin-converting enzyme inhibitors can "unmask" an underlying genetic BK-mediated AE, and therefore screening with C4 measurement is recommended. This happens particularly if there is a family history of AE, it is a recurrent or lymphoproliferative disorder (such as monoclonal gammopathy of uncertain significance or lymphoma), or other malignancy is present. If the C4 is low, further testing is required, including C1 inhibitor (C1-INH) function and protein levels and C1q levels.[1,10]

Pathophysiology and Genetics

Angiotensin-converting enzyme inhibitor is thought to predominately relate to decreased degradation of the vasoactive peptide BK, leading to extravasation of fluid into the interstitium. ACE is part of a system of enzymes, including neutral endopeptidase [neprilysin (NEP)], carboxypeptidase N, DPP-4, and aminopeptidase P (APP), that are involved in the rapid degradation of BK and other vasoactive peptides, such as substance P **(Fig. 1)**. It is likely that individuals developing AE-ACEI may have less overlapping redundancy in these enzyme systems under the "stress" of ACE inhibition. Furthermore, several environmental or inflammatory factors may decrease the activity of these non-ACE pathways, thereby serving as the inciting trigger for AE, perhaps even after years of treatment.[11]

Several investigators have looked for genetic risk factors for AE-ACEI.[12] One study of AE-ACEI in black and mixed-race South Africans found an association with a 9-base-pair deletion in the BK B2 receptor (B2R) that increased sensitivity to BK,[12] but no studies have found other associated variants in either ACE or the B2R. In other genetic studies, including two genome-wide association studies (GWAS), several other genes have been implicated, including polymorphism in two non-ACE genes—*NEP*[13] and APP (*XPNPEP2* gene),[14,15] two genes involved in immune regulation—protein kinase C (*PRKCQ*) and ETS variant gene 6 (*ETV6*), and one in blood coagulation—factor V.[16]

Management

The primary acute treatment of AE-ACEI is important until the AE resolves. Careful attention to the airway is critical, especially if tongue or laryngeal AE is present because airway obstruction occurs in up to 10% of cases. It is essential for patients who present with severe and worsening AE, potentially compromising the airway, in whom symptoms began approximately 6 hours earlier. In these patients, BK-targeting therapies may be beneficial. Sometimes, intubation and mechanical ventilation may be required. Therapies for hereditary AE (HAE), such as B2R antagonists, may be beneficial in AE-ACEI, but studies are conflicting. Currently, no therapy is yet registered for use, and early administration appears to be critical.[7]

Special Recommendations and Patient Education

Patients with a history of AE-ACEI should be informed that AE can recur in the first few months after stopping an ACEI and given advice about how to proceed if symptoms develop again.

Earlier systematic reviews described a 1.5–10% of recurrent AE in patients with a history of AE-ACEI who were switched to ARBs. Subsequent studies have not found ARBs to be associated with higher rates of AE than other antihypertensives (e.g., beta-blockers) and indicated association was explained by delayed action of the discontinued ACEI. However, special caution should be given to patients as some cases of ARBs-induced AE have already been demonstrated.[17]

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR-INDUCED ANGIOEDEMA

Angioedema has been reported with ARNIs at rates comparable with those with ACEI [0.5% vs. 0.2% with enalapril in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial].[18] Sacubitril, an ARNI, in combination with valsartan, is used for the treatment of heart failure. It can lead to DI-AE, especially when used in combination with ACEI. The incidence of AE in black patients was significantly higher—2.4% with sacubitril–valsartan and 0.5% with enalapril.[18] Therefore, the risk of AE should always be considered, especially in ambulatory patients who may not have rapid access to intensive care.[17]

DIPEPTIDYL PEPTIDASE 4 INHIBITORS-INDUCED ANGIOEDEMA

Dipeptidyl peptidase 4 inhibitors (e.g., sitagliptin, linagliptin, vildagliptin) are a class of oral diabetic agents that affect BK and substance P degradation and can lead to AE. DPP-4 primarily degrades substance P at its amino terminus when ACE is inhibited and facilitates the development of AE by the activation of neurokinin receptor 1. The majority of AE induced by DPP-4 inhibitors occurs during concomitant treatment with ACEI and is likely mediated by the overactivation of BK type 2 receptors (B2).[17,18]

TISSUE PLASMINOGEN ACTIVATOR-INDUCED ANGIOEDEMA

Tissue plasminogen activator (tPA) is a protein involved in the breakdown of blood clots. AE induced by tPA occurs in approximately 1–5% of patients receiving thrombolysis for ischemic stroke and can be life-threatening.[19]

The currently recommended fibrinolytic is recombinant tPA (rtPA), an enzyme that catalyzes the conversion of plasminogen to plasmin, resulting in fibrinolysis. Patients with concomitant ACEI treatment are at an increased risk of AE following rtPA, especially in patients with ischemic strokes of the middle cerebral artery and in the presence of C1-INH deficiency. Awareness of the possibility of AE development following rtPA administration among physicians using this drug is very important.[19] Although most cases require only supportive care, there are some cases in the scientific literature about rapidly progressive AE requiring emergent intubation.[20]

HORMONE (ESTROGEN) TRIGGERED ANGIOEDEMA

Exogenous estrogens are the most frequently reported medication to worsen symptoms of HAE in women. Estrogens increase the reactivity of BK B2R, and ACEIs, which diminish the metabolism of BK, may provoke the onset of HAE attacks in a previously healthy patient or exacerbate previously diagnosed HAE. Many female patients have an exacerbation of the disease when pregnant or taking estrogen hormone replacement therapy, while others are not influenced by these factors. In some patients, withdrawal of estrogens is sufficient to prevent most attacks, and no other prophylactic therapy is needed. Hormonal contraception with progesterone-only pills may be beneficial for many women with HAE-1/2.[21]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS-INDUCED ANGIOEDEMA

Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase and consequently prostaglandin synthesis, switching arachidonic acid metabolism to the lipoxygenase pathway, and the generation of leukotrienes resulting in AE.

Nonsteroidal anti-inflammatory drugs-induced angioedema was detected in 20% of patients with AE.[10] Facial AE (periorbital and lips) is the most common form of clinical presentation.[10,22,23]

There are two cutaneous phenotypes of NSAID hypersensitivity reactions: NSAID-exacerbated cutaneous disease (NECD) and NSAID-induced urticaria/AE (NIUA). In NECD, patients have a history of chronic urticaria/AE, which can be exacerbated by aspirin/NSAID exposure. Patients with NIUA develop urticaria, AE, and/or anaphylaxis only after exposure to at least two NSAIDs with distinct chemical structures. Single NIUA and/or anaphylaxis (SNIUAA) is caused by the production of immunoglobulin E (IgE) antibodies to a single NSAID or NSAIDs with similar chemical structures.[22]

Aspirin was reported to be the most common culprit of NSAID-induced chronic urticaria/AE in Western countries (27–35%),[23] whereas ibuprofen (57%) was the most common NSAID that caused AE in Asia (Thailand).[10]

The diagnostic algorithm should include a precise clinical history, physical examination, and specific provocation tests. Currently, there are no fully validated in vitro testing.[22]

To prevent exacerbations, patients should be educated on how to avoid culprit NSAID/cyclooxygenase (COX)-1 inhibitors and use selective COX-2 inhibitors; if necessary, the possibility of aspirin/NSAID desensitization should be discussed. Newly developed COX-2 selective inhibitors, very rarely (0.008%), may also induce hypersensitivity reactions. In subjects with hypersensitivity to NSAIDs and intolerance to paracetamol, selective COX-2 inhibitors should be administered as a controlled, incremental dose provocation test to assess tolerance.[24]

CONCLUSION

Identification of the causative drug and underlying mechanism of DI-AE is essential to provide adequate treatment in time. Mast cell mediated angioedema (AE-MC) responds to classical treatment with antihistamines, corticosteroids, and epinephrine, whereas AE-BK will not be resolved with these drugs. Therefore, AE attacks should be treated with an antagonist of the human B2R, C1-INH concentrate, kallikrein inhibitor, or fresh frozen plasma. Theoretically, these therapies should also be helpful in DI-AE-BK, but available studies are conflicting, and further research is needed. Immediately upon DI-AE diagnosis, the culprit drug should be stopped. General care of HAE patients includes education and avoidance of possible trigger drugs such as ACEIs, estrogens, and DPP-4. Special caution is needed with ARNIs, ARBs, and fibrinolytics. The combination of ACEIs with indicated drugs inducing BK-mediated reactions increases the risk of AE-BK.

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Handbook of Angioedema

Salient Features

- *Handbook of Angioedema* is an initiative of the Global Allergy and Asthma European Network (GA²LEN) Angioedema Centers of Reference and Excellence (ACARE)
- This book covers different chapters related to angioedema including clinical presentation and management
- The chapters are written by world renowned authors from Angioedema Centers of Reference and Excellence (ACARE)
- Clinical images, tables, and figures added in the chapters (as appropriate) make this book clinically oriented and reader friendly
- The book is useful for consultant physicians, intensivists, dermatologists, and postgraduate students in dermatology who are involved in management of patients with angioedema.

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