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Clinical Review

NOVEL THERAPIES FOR ANGIOTENSIN-CONVERTING ENZYME INHIBITOR–INDUCED ANGIOEDEMA: A SYSTEMATIC REVIEW OF CURRENT EVIDENCE

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☐ **Abstract—Background: Angiotensin-converting enzyme inhibitor (ACEI)–induced angioedema can occur at any point during therapy and, when severe, can require mechanical ventilation. Standard agents for anaphylactic reactions have limited efficacy for bradykinin-mediated angioedema and, therefore, agents approved for hereditary angioedema are increasingly prescribed for these patients. Objective of the Review: This systematic review critically evaluates evidence describing the off-label use of fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), complement 1 esterase inhibitor (C1-INH), icatibant, and ecallantide for treatment of ACEI-induced angioedema. Discussion: A PubMed search was conducted and articles were cross-referenced for additional citations. All full-text clinical trials, case series, and case reports published in the English language describing pharmacologic treatment of ACEI-induced angioedema were included. Thirty-seven publications detailing FFP, PCC, and regimens approved for hereditary angioedema, including icatibant, ecallantide, and C1-INH, are reviewed extensively. Conclusions: While findings of decreased time to symptom resolution or a cessation in symptom progression have been reported with each of these therapies, additional data showing clinically relevant implications, such as reduced intensive care unit length of stay or avoidance of mechanical ventilation, are warranted, especially when taking cost into consideration. FFP has limited evidence demonstrating a benefit for treatment of ACEI-induced angioedema without consistent dosing strategies. However, given its wide availability and low potential for adverse reactions, FFP therapy may be reasonable. Of the novel agents traditionally used for hereditary angioedema, icatibant has the highest level of evidence and has been reported to be successful in limiting the progression of angioedema.**

☐ **Keywords—angiotensin converting enzyme inhibitor; angioedema; C1-esterase inhibitor; ecallantide; emergency medicine; icatibant; intubation**

INTRODUCTION

Angioedema is characterized by sudden, self-limited swelling of the dermis, subcutaneous, and submucosal tissues (1,2). Approximately 15–25% of the general population will experience angioedema, with women affected more frequently (2,3). While different forms of angioedema exist, all exhibit nonpitting edema as a result of increased permeability of post-capillary venules (3). Most commonly, swelling is noted in the periorbital area, lips, tongue, larynx, and pharynx (1,2). However, other areas of involvement may include the extremities, gastrointestinal tract, and genitalia (1). Although rare, of most concern is airway swelling and compromise,

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which can lead to complications such as intubation, tracheostomy, and mortality (4).

Angioedema can be broken down further into two main categories: histamine-mediated and bradykinin-mediated, the latter including hereditary angioedema (HAE), acquired angioedema, and angiotensin-converting enzyme inhibitor (ACEI)–induced angioedema. Differentiation based on symptoms alone may be difficult. A thorough medical history including familial history or previous episodes of similar symptoms, current medications, exposure to any known allergens, and timing of the episode plus a physical examination can often assist in distinguishing between forms (3).

Bradykinin-mediated angioedema occurs as a result of a proteolytic cascade of events more complex than allergic or immunoglubulin E–mediated angioedema. Kinins are pharmacologically active peptides released after enzymatic activity of kallikreins on kininogens (2). The kallikrein–kinin cascade begins with activation of factor XII through binding to damaged tissue. Factor XIIa converts prekallikrein to plasma kallikrein, and through a positive-feedback loop, the proteins continue to autoactivate each other (2). The final step involves the cleavage of bradykinin from high-molecular-weight kininogen (HMWK) by plasma kallikrein. Bradykinin is then available to bind to receptors (bradykinin $\beta 2$) to cause vasodilation with subsequent vascular permeability leading to angioedema.

Hereditary Angioedema

HAE is a rare condition affecting approximately 1 in 50–100,000 individuals (5,6). The autosomal-dominant disorder results from C1 esterase inhibitor (C1-INH) deficiency. C1-INH regulates several inflammatory pathways and physiologic reactions (5,6). In healthy individuals, these include inhibition of factor XII and prekallikrein activation, plasmin breakdown of fibrin, and conversion of HMWK to bradykinin (6). Because C1-INH plays a key role in the inhibition of three enzymes within the kallikrein–kinin cascade (factor XIIa, factor XIIf, plasma kallikrein), any deficiency or dysfunction will result in uncontrolled activation and subsequent bradykinin accumulation. Edema seen with HAE commonly affects the gastrointestinal tract, and gastrointestinal symptoms are apparent in up to 93% of cases (6). Airway edema occurs in 50–60% of patients with hereditary angioedema. Symptoms generally worsen over a period of up to 36 h with resolution occurring over 48–72 h (6).

Acquired Angioedema

Acquired angioedema is more uncommon than HAE, with prevalence believed to be 1 in 100–500,000 cases (2). This disorder, primarily affecting older adults, is associated with lymphoproliferative diseases (2,3). It also results from C1-INH deficiency, however, is not related to a genetic mutation.

Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema

ACEI-induced angioedema is the focus of the remainder of this review. While occurring in only 0.3–0.68% of patients on ACEI therapy, widespread use of ACEIs allows this otherwise small percentage to become significant (7). Angioedema, like cough, is a class effect, and possible with any single agent. Therefore, if ACE-I angioedema occurs, the offending drug should be discontinued and it should be considered a contraindication to substitute with a different agent in the same pharmaceutical class.

While the incidence is highest within the first month of therapy, angioedema can occur at any point throughout therapy; cases occurring after several years of therapy are well documented (3,8). ACEI-induced angioedema rarely manifests with urticaria and most commonly involves swelling of the lips and tongue (2). African Americans are four to five times more likely than Caucasians to experience angioedema, largely due to a genetic polymorphism in a critical enzyme necessary for ACEI metabolism (2). Other risk factors identified for ACEI-induced angioedema include age >65 years, chronic heart failure or coronary artery disease, female sex, tobacco use, or history of any drug rash (9).

In addition to the inhibition of the conversion of angiotensin I to angiotensin II, ACE (kininase II) is the enzyme responsible for bradykinin degradation. Thus, through ACE inhibition, the half-life of bradykinin is prolonged and can result in accumulation and increase in activity over time (7). Although the exact mechanism of ACEI-associated angioedema is yet to be fully elucidated, this physiologic relationship is clearly implicated.

DISCUSSION

Due to the potential for ACEI-induced angioedema to cause life-threatening airway edema and its strong similarity in symptoms of histamine-mediated angioedema, standard initial management strategies typically include airway stabilization, antihistamine therapy, glucocorticoids, and epinephrine rescue. A retrospective analysis of 228 patients characterizing ACEI-induced angioedema found that of 12 patients who required intubation and had available chart records, those given histamine-1 (H1) receptor antagonists (n = 7) were extubated sooner than patients without this therapy (mean 34 h vs. 62 h, respectively; $p = 0.05$) (10). It must be noted that the baseline characteristics of this small sample size were not