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Treatment of Life-Threatening ACE-Inhibitor–Induced Angioedema

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ABSTRACT
Incidence of angioedema associated with angiotensin-converting enzyme inhibitors (ACE-I) has been estimated at 0.1%–2.2% of patients receiving treatment. Despite the potential severity of this disease state, standardized treatment is lacking. Traditional pharmacotherapy options include medications that target inflammatory mediators and the angiotensin pathway. However, because ACE-I-induced angioedema is caused by accumulation of bradykinin, these medications fail to target the underlying pathophysiology. Recently, novel therapies that target the kallikrein–bradykinin pathway have been studied. These include icatibant, ecallantide, C1 esterase inhibitors, and fresh-frozen plasma. Recent randomized controlled trials exhibit contradictory results with the use of icatibant. This is a focused review on traditional and novel treatment strategies for ACE-I-induced angioedema.
Key words: ACE inhibitors, adverse drug reactions, emergency medicine, hypersensitivity

THE PATHOPHYSIOLOGY of angiotensin-converting enzyme inhibitors–induced angioedema (ACE-I AE) is complex and multifactorial. Cases of angioedema (AE) can vary greatly in presentation and severity. A study of 91 patients with ACE-I AE reported a mortality rate of 1.4%, an admission rate of 66%, and an intubation rate of 6.5% (Roberts, Lee, & Marthers, 2012). Up to 10% of ACE-I AE cases progress to sudden airway obstruction and death (Bas et al., 2015). Given the severity of this condition and recent therapeutic advancements, the purpose of this review is to describe the incidence and pathophysiology of ACE-I AE as well as current and emerging management strategies for its treatment.

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PATHOPHYSIOLOGY

ACE-Inhibitor–Induced AE

As a class, ACE-Is act on the renin–angiotensin–aldosterone system (RAAS),

which is typically initiated by the release of renin (see Figure 1; Atlas, 2007). Renin is secreted from the juxtaglomerular cells of the kidneys in response to decreased renal perfusion pressure, sodium, β-1 sympathetic stimulation, or due to negative feedback (Atlas, 2007; Hoover, Lippmann, Grouzmann, Marceau, & Herscu, 2010; Lewis, 2013). Renin causes cleavage of angiotensinogen to angiotensin I, which is further broken down to angiotensin II via ACE (Atlas, 2007). Angiotensin-converting enzyme is found on a variety of cells including the lungs, endothelial cells, and renal epithelial cells (Gradman, 2009; Hoover et al., 2010). Angiotensin II works on both angiotensin receptors 1 and 2 (AT1 and AT2), which when activated cause a variety of cellular effects that ultimately result in endothelial dysfunction, proliferation of smooth muscle, atherosclerosis, and vascular hypertrophy (Chrysant, 2007; McConnaughey, McConnaughey, & Ingenito, 1999).

Bradykinin, a potent vasodilator, is quickly metabolized in the presence of ACE (see Figure 1). ACE-Is block the breakdown of bradykinin; subsequent vasodilation may contribute to the efficacy of ACE-Is but also to increased vascular permeability. The accumulation of bradykinin may lead to AE, primarily due to vasodilation from nitric oxide and prostaglandin I2 formation (Campo,

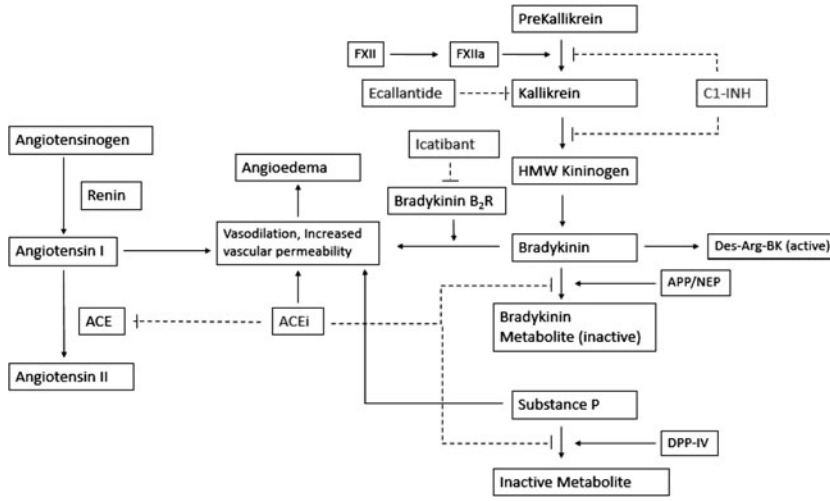

Figure 1. Pathophysiology of ACE-I AE. The diagram shows the effect of an ACE-I on the renin angiotensin system, bradykinin, and substance P. The ACE-Is inhibit ACE from converting angiotensin I to angiotensin II. The ACE-Is also inhibit the breakdown of two substances: bradykinin and substance P. Pre-Kallikrein is converted to kallikrein by FXIIa, which is then converted to HMW kininogen and eventually bradykinin. Bradykinin is usually metabolized by APP/NEP to an inactive metabolite or converted to Des-Arg-BK, which is an active metabolite. The ACE-Is inhibit the APP/NEP pathway and prevent the breakdown of bradykinin. Excess bradykinin binds to B2 receptors and leads to vasodilation and increased vascular permeability, increasing the risk of angioedema. Similarly, it inhibits the breakdown of substance P to an inactive metabolite by DPP-IV, leading to vasodilation and increased vascular permeability. Some ACE-I AE treatment drugs act on this pathway: C1-INH and ecallantide inhibit conversion of bradykinin and icatibant is a selective antagonist of the bradykinin receptor. ACE = angiotensin-converting enzyme; ACE-I = ACE-inhibitor; APP = aminopeptidase P, B_2R: B_2 receptor; C1-INH = C1 esterase inhibitors; DPP-IV = dipeptidyl peptidase IV; FXII = factor XII; FXIIa = factor XIIa; HMW = high molecular weight; NEP = neutral endopeptidase. From "The Renin-Angiotensin Aldosterone System: Pathophysiological Role and Pharmacologic Inhibition," by S. A. Atlas, 2007, *Journal of Managed Care Pharmacy, 13*(8 Suppl. B), pp. 9–20.

Fernandez, Canto, & Mayorga, 2013; Hoover et al., 2010; Lewis, 2013). Degradation of bradykinin can occur via two salvage pathways in the presence of ACE-I: aminopeptidase P (APP) and neutral endopeptidase (NEP). In addition, dipeptidyl peptidase IV (DPP-IV) and kininase I play a role (Kitamura, Carbini, Simmons, & Scicli, 1999).

In addition to degrading bradykinin, ACE, NEP, and DPP-IV (though not APP) break down substance P. Accumulation of substance P results in increased vascular permeability, thus further contributing to the development of ACE-I AE. All of these factors can additively contribute to the pathogenesis of AE (Hoover et al., 2010).

Hereditary Angioedema

Hereditary angioedema (HAE) is a rare autosomal-dominant disorder resulting in AE that differs from ACE-I AE as it results from increased production of bradykinin, rather than inhibition of its degradation (see Figure 1). There are three types of HAE, of which Types I and II result from a deficiency of C1 esterase inhibitors (C1-INH; Zuraw et al., 2013). A detailed discussion on the pathophysiology of HAE is outside of the scope of this review and may be found elsewhere (Zuraw & Christiansen, 2016).

PRESENTATION

Angioedema is localized, nonpruritic, nonpitting edema of the dermis and subcutaneous tissue. It is typically localized to the face, lips, tongue, oropharynx, upper respiratory tract, and intestinal lining (Hoover et al., 2010). As of 2010, at least 21 cases of abdominal AE were documented, though the incidence of abdominal ACE-I AE remains unknown and is likely underreported, given it is a diagnosis of exclusion (Campbell, Peckler, Hackstadt, & Payor, 2010). Although symptoms of hereditary and drug-induced AE often overlap, ACE-I AE primarily affects the face and upper airways. Cases of HAE can present with more extremity and abdominal involvement (Banerji et al., 2008; Bluestein et al., 2009; Javaud et al., 2015; Nzeako, 2010).

Allergic reactions, including anaphylaxis, may also result in similar facial swelling. However, unlike ACE-I AE or HAE, these reactions are IgE-mediated, precipitating acute onset and inducing mast cells, inflammatory cytokines, and histamine release based on prior exposure to an allergen (Fonacier, Dreskin, & Leung, 2010). This results in cutaneous symptoms that include pruritus, hives, and systemic involvement (i.e., respiratory distress, hypotension; Sampson et al., 2006). Although ACE-I AE and anaphylaxis have some overlapping characteristics, a detailed history and physical should differentiate these conditions. Angioedema accompanied with urticaria and systemic signs is often due to an allergic reaction, whereas ACE-I AE is more likely to occur with the main problem of AE. However, because every case does not present the same and there is overlap, it is important to assess the patient and protect the airway, while getting an accurate history such as medications, allergies, and so forth when the situation is nonemergent or stabilized (Kaplan, 2008).

INCIDENCE AND RISK FACTORS

Medication-induced AE is most commonly due to ACE-Is. Angioedema has been estimated to occur in 0.1%–2.2% of patients receiving an ACE-I (Grant, Deeb, & Chia, 2007; Nzeako, 2010). World usage of ACE-Is is estimated in up to 40 million patients, leading to an annual incidence of 40,000–880,000 cases of ACE-I AE (Illing, Kelly, Hobson, & Charters, 2012). This wide range in incidence is due to inconsistencies in diagnosis and coding. Because of variability of prescribing practices and formularies, it is unknown whether some ACE-Is lead to AE more than others. Approximately one-fourth of patients experience onset within the first month; however, many cases occur years later, with up to 27% of ACE-I AE events occurring greater than 6 months after initiation (Knecht, Dunn, & Macaulay, 2014; Nzeako, 2010).

Outside of ACE-Is, little is known about which medications precipitate AE. A retrospective study conducted over a 5-year period showed that ACE-Is are implicated in more than half of medication-induced AE cases (Grant et al., 2007). Other culprits included angiotensin receptor blocking agents, aliskiren (a renin inhibitor for the treatment of hypertension), nonsteroidal anti-inflammatory drugs, and antimicrobials (White et al., 2010). Angioedema may also occur after tissue plasminogen activator therapy due to activation of plasma prekallikrein (Fernandez-Gotico, Lightfoot, & Meighan, 2017; Simao, Ustunkaya, Clermont, & Feener, 2017). This is extremely rare, with only one case occurring in a retrospective cohort of 498 subjects (Fernandez-Gotico et al., 2017).

Although no precipitating factors have been identified, risk factors include African American ethnicity, C1-INH deficiency, smoking, increased age, female sex, heart failure, trauma, history of allergies or drug rash, and previous adverse drug reactions (Hoover et al., 2010). African Americans have a substantially increased risk of ACE-I AE compared with Caucasians with an adjusted relative risk of 4.5 (95% confidence interval [CI]: 2.9–6.8). This finding was consistent despite adjustment for dose, specific type of ACE-I, and concurrent medications (Brown, Ray, Snowden, & Griffin, 1996).

The DPP-IV inhibitors are used for the treatment of diabetes (e.g., sitagliptin). Because DPP-IV is a salvage mechanism for bradykinin metabolism, inhibition can also increase the risk of ACE-I AE. The ACE-Is are recommended for many patients with diabetes (Zuraw et al., 2013). In addition, one case control study indicated that patients with a solid organ transplant might be at higher risk, with an occurrence of 4.3% in kidney transplant recipients and 2.8% in heart transplant recipients. A proposed mechanism is a decrease in the activity of free DPP-IV caused by immunosuppressant medications (Byrd et al., 2010). Angioedema occurred more often in those taking ACE-Is concomitantly with sirolimus than with calcineurin inhibitors in a dose-dependent fashion.

Finally, genetic variation of bradykinin and the kallikrein system have been implicated as risk factors for the development of both ACE-I AE and HAE. Mutations in genes encoding in ACE and APP, as well as bradykinin receptors 1 and 2 have been implicated (deBlois & Horlick, 2001; Gainer, Stein, Neal, Vaughan, & Brown, 2001; Lung, Chan, & Zuraw, 1997).

MANAGEMENT

Traditional Management

Individuals on an ACE-I should discontinue therapy with anticipated symptom resolution within 24–72 hr (Chiu et al., 2001). If a patient presents with minimal swelling, supportive care and airway monitoring are recommended. However, if a case includes respiratory distress, stridor, drooling, or edema of the tongue or floor of the mouth, intubation and mechanical ventilation may be required for airway protection (Winters, Rosenbaum, Vilke, & Almazroua, 2013). A study reviewing the disposition of patients presenting with ACE-I AE noted that 11% of the patients were admitted to the intensive care unit (ICU) for invasive airway management (Banerji et al., 2008).

Traditional pharmacologic treatment options for AE target the inflammatory response and bronchoconstriction but do not interfere with the bradykinin pathway. These agents include epinephrine, antihistamines, and corticosteroids (Lieberman et al., 2010; Wilkerson, 2012; see Table 1). Epinephrine acts on α and β receptors leading to smooth muscle vasoconstriction and airway muscle relaxation, thus decreasing swelling and enabling the patient to breathe more easily. Intramuscular epinephrine is preferred for AE caused by anaphylaxis due to predictable absorption and fast onset (Wilkerson, 2012). There are no prospective studies assessing its efficacy in ACE-I AE; however, a case report on a 71-year-old man on enalapril showed no improvement in symptoms after the

Table 1. Management of ACE-I AE[a]

Drug class/drug	Dose	Suggested place in therapy
H1RA (Lieberman et al., 2010)	Diphenhydramine 25–50 mg IVP ×2 in 15 min (up to 25 mg/min)	Low evidence
H2RA (Lieberman et al., 2010)	Ranitidine 50 mg IV over 5 min Cimetidine 4 mg/kg IV (maximum: 300 mg)	Low evidence, preferred as adjunct with H1 antihistamine
Epinephrine (Wilkerson, 2012)	0.2–0.5 mg IM ×2 in 15 min 0.1 mg IV 1-4 mcg/min IV infusion	Low evidence, IM preferred
Corticosteroids (Bartal et al., 2015; Tang, 2003)	Hydrocortisone 5 mg/kg (250 mg maximum) IV over 30 s Prednisone 20–50 mg po. Methylprednisolone 125-mg IVP over 3–15 min	Low evidence
Fresh-frozen plasma (Hassen et al., 2013)	2 units IV	Low evidence
Ecallantide (Wilkerson, 2012; Zuraw et al., 2013)	30 mg SC (three 10-mg/1-ml injections) Can repeat with additional 30 mg within 24 hr Separate injection sites by 2 in.	Not recommended
C1-INH concentrate (Wilkerson, 2012; Zuraw et al., 2013)	20 Units/kg IV (infuse 4 ml/min)	Not recommended
C1-INH concentrate (Wilkerson, 2012; Zuraw et al., 2013)	1,000 units IV every 3 or 4 days (infuse 1 ml/min)	Not recommended
Icatibant (Bas et al., 2015)	30 mg SC, repeat q6h if inadequate response or symptom recurrence (maximum 90 mg) Inject into the abdomen over 30 s or more	Consider in severe or life-threatening cases

Note. C1-INH = C1 esterase inhibitors; H1RA = H1 receptor antagonist; H2RA = H2 receptor antagonist; IM = intramuscular; IV = intravascular; IVP = intravascular push; Low evidence = limited data and/or limited efficacy in ACE-I AE; po = orally; p.r.n. = pro re nata (as needed); q6h = every 6 hr; SC = subcutaneous.

[a]From Bartal et al. (2015); Bas et al. (2015); Hassen et al. (2013); Lexi-Comp Online. (n.d.); Lieberman et al. (2010); Wilkerson (2012); and Zuraw and Christiansen (2016).

administration of an unknown dose of epinephrine. Therefore, monotherapy with epinephrine is not recommended (Bramante & Rand, 2011).

Histamine-1 receptor antagonists (H1RAs), such as intravenous (IV) diphenhydramine, reduce skin swelling resulting from nonpruritic urticaria that can be present in ACE-I AE (Yadav & Bajaj, 2009). Histamine-2 receptor antagonists (H2RAs) may be used in combination with diphenhydramine, as 15% of cutaneous histamine receptors are H2. Corticosteroids act by inhibiting T helper cells and the production of inflammatory mediators. Therefore, the delayed effects of corticosteroids are thought to be beneficial in preventing symptom recurrence (Wilkerson, 2012). Because of the lack of efficacy, consensus guidelines

recommend against routine use of steroids and histamine receptor antagonists, unless the cause of AE is unclear (Zuraw et al., 2013).

Fresh-frozen plasma (FFP) anecdotally targets the bradykinin pathway. Fresh-frozen plasma contains kininase II, which is similar in activity to ACE, leading to the degradation of bradykinin and subsequent resolution of AE. Although no randomized controlled trials exist to support this intervention, a case series of seven patients illustrated symptom improvement of AE within 2–4 hr after the administration of one to three units of FFP (Hassen et al., 2013). Contrary to this finding, a case report followed a patient with ACE-I AE who received intravenous steroids and antihistamines (medication and dose not stated), followed by two units of FFP, who then had worsened swelling 2 hr later leading to emergent intubation (Adebayo & Wilkerson, 2017). In addition to very limited data, FFP requires time to thaw and is associated with transfusion-associated adverse outcomes, including acute lung injury, circulatory overload, immunomodulation, and allergic reactions (Gorlinger & Saner, 2015). Use of FFP in the treatment of ACE-I AE is unadvisable until more robust data become available.

Bradykinin-Mediating Therapies

Treatment modalities that directly target the bradykinin pathway include C1-INH, ecallantide, and icatibant. C1-INH and ecallantide are primarily used to treat HAE as they inhibit conversion of precursors to bradykinin. C1-INH is an endogenous inhibitor of plasma kallikrein, which converts kininogen to bradykinin (see Figure 1). As there is a lack of kininogen regulation and excess bradykinin, supplementing exogenous C1-INH is warranted to inhibit plasma kallikrein and decrease conversion to bradykinin. In a recent case report, a patient with ACE-I AE received 2,000 units (18 units per kg) of C1-INH concentrate intravenously for more than 10 min. He was reassessed via fiber-optic bronchoscope at 5 hr and was found to have significant improvement, as well as complete resolution within 24 hr (Hermanrud, Duus, Bygum, & Rasmussen, 2016). It is unclear how much of this resolution can be attributed to C1-INH. Another report found subjective improvement, though occasionally with recurrent symptoms (Leibfried & Kovary, 2017). With all treatment options, hypersensitivity is a concern, but with C1-INH concentrates patients should also be monitored for thromboembolic events (Zuraw et al., 2013).

Ecallantide is a recombinant protein that inhibits the conversion of kininogen to bradykinin, thereby reducing the plasma concentration of bradykinin (Zuraw et al., 2013). A Phase 2, multicenter, randomized controlled trial compared subcutaneous ecallantide with placebo in 79 patients experiencing ACE-I AE within 12 hr of presentation. Inclusion criteria dictated that patients received a dose of ACE-I within 36 hr of presentation and could also receive any physician-directed corticosteroids, antihistamines, or epinephrine. There was no difference in the primary end point of eligibility for discharge within 6 hr of treatment (72% vs. 88%, 95% CI: 11–41), and the study was terminated early because of futility (Lewis et al., 2015). Given that ACE-I AE is due to a lack of bradykinin metabolism rather than overproduction, it is not surprising that the study failed to find benefit. Data supporting these interventions in ACE-I AE are limited, and given the cost of these interventions, they should not be used unless HAE is suspected.

Icatibant's current Food and Drug Administration approval is for the treatment of acute HAE events. It competitively antagonizes the bradykinin B2 receptor; therefore, it is a treatment for both HAE and ACE-I AE, though the latter is an off-label indication (Zuraw et al., 2013). Case reports and a recent randomized trial have addressed the use of icatibant in patients with ACE-I AE. Icatibant is available as a 30-mg subcutaneous injection. If symptoms persist or recur, two additional doses may be administered within 24 hr, with each dose separated by at least 6 hr. Icatibant is well-tolerated, with injection-site reactions (97%),

pyrexia (4%), and elevated transaminase levels (4%) occurring most frequently (Cole & Lundquist, 2013).

Thirteen case reports or series totaling 44 patients have administered icatibant for the treatment of ACE-I AE (see Supplementary Digital Content Table 2 available at: http://links.lww.com/AENJ/A37; Bartal, Zeldetz, Stavi, & Barski, 2015; Bas et al., 2010; Bova et al., 2015; Charmillon, Deibener, Kaminsky, & Louis, 2014; Crooks, Patel, Diwakar, & Smith, 2014; Fok, Katelaris, Brown, & Smith, 2015; Gallitelli & Alzetta, 2012; Illing et al., 2012; Kaeslin & Huber, 2012; Manders, van Deuren, Hoedemaekers, & Simon, 2012; Pucar, O'Sullivan, Goudie, Marr, & Brusch, 2015; Schmidt, Hirschl, & Trautinger, 2010; Volans & Ferguson, 2013). All but one patient exhibited a positive outcome; one patient displayed no immediate benefit after one dose of icatibant and slowly recovered over 48 hr (Illing et al., 2012). This lack of improvement may be due to suboptimal dosing as no subsequent doses were administered. Although symptom improvement and resolution of AE definitions varied between cases, relief occurred as early as within 10 min to 90 min, with complete resolution ranging up to 10 hr (Bartal et al., 2015; Bas et al., 2010; Bova et al., 2015; Charmillon et al., 2014; Crooks et al., 2014; Fok et al., 2015; Gallitelli & Alzetta, 2012; Illing et al., 2012; Kaeslin & Huber, 2012; Manders et al., 2012; Pucar et al., 2015; Schmidt et al., 2010; Volans & Ferguson, 2013). A randomized trial of 27 subjects with ACE-I AE was conducted in which patients received icatibant ($n = 13$) or standard therapy ($n = 14$; prednisolone 500 mg IV and clemastine 2 mg). The primary end point was time to complete resolution of edema evaluated on the basis of investigator and self-assessment of six symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and pressure), as well as an AE score. The primary end point of median time to complete resolution was 8 hr with icatibant versus 27.1 hr with standard therapy ($p = 0.002$). The median time to symptom relief was also significantly faster in the icatibant group (2.0 hr vs. 11.7 hr, $p = 0.03$). Three patients in the standard therapy group required rescue therapy (icatibant 30 mg subcutaneous and prednisolone 500 mg IV) compared with none in the icatibant group (Bas et al., 2015).

Although this first randomized controlled trial offered promising results, it should be interpreted with caution. The standard therapy group used a steroid dose, which far exceeded that of standard practice, and clemastine is not widely available in the United States. In addition, all study patients had low baseline severity of AE and only one patient required an advanced airway (in the placebo group; Atlas, 2007). A second randomized placebo-controlled trial including 30 patients ($n = 12$ in icatibant group) did not confer the same benefit. Patients received intervention within 6 hr of hospital presentation and all patients received two doses. There was no difference in time to the resolution of symptoms (times not provided, $p = 0.192$). A majority of patients received H1RAs, H2RAs, and corticosteroids, and only three study patients required intubation. There was no baseline assessment of AE severity (Cicardi et al., 2017). These studies demonstrate that pervasive use of icatibant for ACE-I AE is not advisable and future studies should focus on end points such as prevention of mechanical ventilation, duration of mechanical ventilation, and ICU admission.

Recently, a multicenter, Phase III, randomized study evaluated the use of icatibant in patients with at least moderately severe AE. Patients in either group (icatibant and placebo) could receive "conventional medications," which included antihistamines, corticosteroids, and epinephrine. This study failed to illustrate a difference in the primary outcome of time to discharge criteria. There was also a lack of improvement in time to symptom relief, admission, or intubation. One patient in the icatibant group was intubated (1.5 hr after receiving icatibant; Sinert et al., 2016).

The severity of the patients within this randomized controlled trial, given their time to discharge (median of 4 hr in both groups)

and intubation rate provides an opening for criticism (Sinert et al., 2016). Also, the results of the study by Sinert et al. (2016) vastly contradict the results by Bas et al (2015). Important things to consider are the use of other medications in these trials differs, as does severity, and the allowance of subsequent doses of icatibant (Bas et al., 2015; Sinert et al., 2016). Icatibant is a costly intervention, so institutional restriction to life-threatening AE is warranted. A case series utilized icatibant in 13 patients refractory to epinephrine and/or steroids, of which intubation was avoided in eight patients who received the dose early in the treatment course. Three intubations occurred before receiving icatibant and two patients received icatibant concomitantly with advanced airway placement, with an unclear sequence and timing of events (Fok et al., 2015). Although the retrospective nature of this case series makes timing difficult to interpret, it implies that early icatibant therapy prior to intubation provides increased benefit. Overall, 2.3% of patients given icatibant in these studies were intubated, with prior retrospective studies reporting intubation rates of 6.5% in patients with ACE-I AE (Roberts et al., 2012). Further research is warranted to determine whether icatibant prevents emergent intubation and decreases admissions or hospital length of stay. Given the high cost of this intervention, icatibant should be reserved for life-threatening ACE-I AE.

RESUMING RAAS-MEDIATED THERAPIES

ACE-Is should be immediately discontinued upon presentation with ACE-I AE. This class possesses the potential to decrease morbidity and mortality in multiple disease states such as hypertension, myocardial infarction, heart failure, and chronic kidney disease, and alternative RAAS-altering agents may be considered (Hunt et al., 2005). After resolution of symptoms, an angiotensin receptor blocker or aliskiren can serve as an alternative treatment; however, as AE has been reported with these agents, close monitoring, patient education, and an assessment of the risk versus benefit should be evaluated on a case-by-case basis (Hunt et al., 2005; Zuraw et al., 2013).

CONCLUSION

Patients who present with severe or life-threatening ACE-I AE may require intubation and ICU admission. Traditional management targets the inflammatory process but does not decrease the production of bradykinin. The use of epinephrine, antihistamine, and corticosteroid is not supported by literature. Ecallantide's randomized trial showed no difference, so there is currently no support. Although the use of FFP and C1-INH has mixed reviews and has been shown to be successful, more data are needed. Icatibant has shown promise in several case reports and a randomized controlled trial. However, a more recent trial contradicts the prior. Further studies focusing on repeat doses and higher severity are warranted. Literature on ICU admission and advanced airway management is needed to weigh the cost considerations of icatibant administration, and controlled trials in severe cases are lacking.

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