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Drug Allergy (L Mayorga, Section Editor)

Current Treatment of Angioedema Induced by ACE Inhibitors

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Abstract

Purpose of Review Angioedema is a well-known side effect of ACE inhibitors. Current knowledge shows that the underlying pathophysiological mechanism is an excess of bradykinin, most likely due to ineffective breakdown pathways. Since C1 inhibitor deficiency has the same pathophysiological background, it would be logical to assume that C1 inhibitor deficiency treatments could be of use in ACE inhibitor–induced angioedema. The objective of this review was to evaluate the evidence for treatment of ACE inhibitor–induced angioedema by means of drugs intervening in the bradykinin system.
Recent Findings We searched in the literature for double-blind placebo-controlled trials using either inhibitors of production of kallikrein, bradykinin receptor antagonists, C1 inhibitor concentrate, or fresh frozen plasma as treatment for ACE inhibitor–induced angioedema. The reference list of retrieved articles was checked for articles with the same subject (snowballing). The evidence for each treatment was evaluated by IT and DMC.
Summary Double-blind placebo-controlled trials were only found for ecallantide and icatibant. Both treatments did not show superiority over conventional treatment with histamine receptor antagonists and steroids. No double-blind placebo-controlled trials were found of fresh frozen plasma or C1 inhibitor concentrate. To date, there is insufficient evidence for the use of bradykinin receptor antagonists and kallikrein production inhibitors. Although case reports regarding the use of fresh frozen plasma and C1 inhibitor concentrate are positive, well-designed trials are lacking.

Introduction

Angioedema is a rare but potentially fatal side effect of angiotensin-converting enzyme inhibitor (ACEi) treatment. A recent systematic review by Aygoren-Pursun et al. found a prevalence between 0.12% and 0.3% [1]. In a recent retrospective cohort study by Do in heart failure patients starting ACEi, the incidence of angioedema was 3.27 per 1000 person years (PY) in the first year of treatment with a higher incidence in patients of African descendance (6.24 per 1000 PY) and women (5.16 per 1000 PY) [2]. The incidence was the highest in the first 30 days of treatment. These data confirm earlier findings of Reichman et al. [3]. The prevalence of mortality associated with drugs was 136 cases (8%) according to Kim et al. [4••]. Although this is a quite well-known side effect, diagnosis of angioedema caused by ACEi can take up to several years and is often mistaken for allergic symptoms despite the absence of urticaria or other symptoms of anaphylaxis. Consequently, treatment often consists of antihistamines and corticosteroids, which are considered to be not effective [5]. Since ACEi–induced angioedema can lead to life-threatening symptoms, more effective treatment is warranted. In this article, we will discuss clinical presentation, pathophysiology, and current developments in treatment.

Clinical Presentation

Usually, angiotensin-converting enzyme inhibitor–induced angioedema (ACEia) presents itself as swelling without urticaria, most prevalent in the face, lips, tongue, the floor of the mouth, and the upper airways, leading to hoarseness, inability to swallow, and difficulty of breathing. Other manifestations of angioedema, such as gastrointestinal or genital swellings, are rarely caused by ACE inhibitors [6]. The differential diagnosis of solitary angioedema includes hereditary or acquired C1 inhibitor deficiency, hereditary angioedema (HAE) with normal C1-inhibitor (former nomenclamenture HAE type III), angioedema caused by other drugs, and eosinophilic disorders such as Melkersson-Rosenthal's syndrome. When urticaria is present, an allergic cause is more likely [6].

The major risk of angioedema occurring in the head and neck region is a compromised airway. While swelling of the lips and/or mucosa in the oral cavity is usually harmless in this respect (given that the patient is able to breathe through the nose), edema of the pharynx and especially larynx is potentially life-threatening. Indeed, several authors have described asphyxiation as a result of angioedema, for example, in patients with HAE [7–9]. At the level of the vocal cords, the larynx represents the narrowest part of the upper airway. As such, a subtle mucosal swelling already gives rise to a significant reduction of the airway lumen. Therefore, the airway should always be evaluated by an ear-nose-throat (ENT) specialist in case of angioedema.

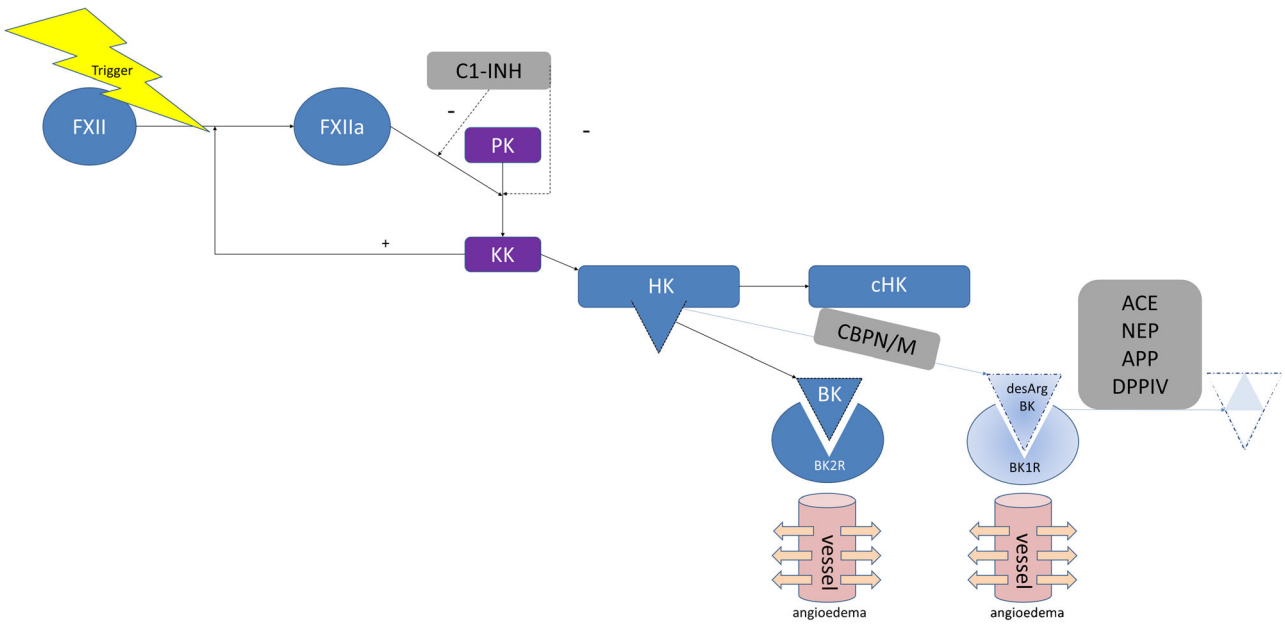
Several signs and symptoms indicate (relevant) edema in the upper airway, such as increased breathing frequency, use of accessory muscles of respiration, audible breathing, or even stridor. As the oxygen saturation will deteriorate only in the later stages of respiratory failure, it is dangerous to rely on a good saturation alone. In case a patient has signs of impaired breathing due to laryngeal edema (as confirmed with laryngoscopy), intubation might be necessary. In milder cases, admitting a patient for close observation and repeating the laryngoscopy after several hours can be sufficient.

Pathophysiology

Etiology of Angioedema

Angioedema can be driven by the contact activation route or by inappropriate release of histamine. The latter form, which is usually associated with urticaria and/or anaphylaxis, is primarily seen in allergic reactions and is beyond the scope of this review. The contact activation system consists of the zymogens factor XII, prekallikrein, high molecular weight kininogen, and factor XI. Factor XII is able to autoactivate through a conformational change following contact with negatively charged surfaces, e.g., glycosaminoglycans, mast cell heparin, inorganic polyphosphates, and misfolded proteins [10–14].

Activated factor XII is the initiator of the contact activation route, but it is also able to activate the intrinsic coagulation pathway, the fibrinolytic pathway, and the classical complement pathway. The contact-driven forms of angioedema occur as a result of either uncontrolled formation or inadequate degradation of the nonapeptide bradykinin (BK). BK is released after proteolytic cleavage from its precursor high molecular weight kininogen (HK) by kallikrein (KK) which in turn is cleaved from prekallikrein by factor XIIa (Fig. 1 see image) [15]. BK produces its effect through stimulation of the G-coupled receptors and the BK2-receptors (and subsequently, its proteolytically cleaved form *desargylated* BK through the BK1 receptor) [16]. Release of BK results ultimately in smooth muscle cell relaxation, vasodilation, and increased vascular permeability, most notably of the postcapillary venules [17••]. These processes are mediated by



FXIIa: activated factor VII; C1-INH: C1-inhibitor; PK: prekallikrein; KK: kallikrein; HK: high molecular weight kininogen; cHK cleaved high molecular weight kininogen; CBPN/M: carboxypeptidase N (kininase I) and carboxypeptidase M; BK: bradykinin; BK2R: bradykinin 2 receptor; desArg BK: desargylated bradykinin; BK1R: bradykinin 1 receptor; ACE: angiotensin converting enzyme; NEP: neutral endopeptidase; APP aminopeptidase P; DPPIV: dipeptidylpeptidase

Fig. 1. BK is released after proteolytic cleavage from its precursor high molecular weight kininogen (HK) by kallikrein (KK) which in turn is cleaved from prekallikrein by factor XIIa.

nitric oxide and prostaglandines. Uncontrolled formation of BK is typically seen in patients with C1 inhibitor deficiency (such as HAE), a condition that is characterized by impaired inhibition of both the classical complement pathway and the contact activation route (through impaired inhibition of factor XIIa and kallikrein [KK]). Angioedema can also occur due to inadequate degradation of BK, besides excessive formation. BK has a very short half-life of ± 17 s as it is rapidly metabolized by various metalloproteinases, such as ACE (also known as kininase II), carboxypeptidase N (kininase I), neutral endopeptidase (NEP), aminopeptidase P (APP), and—to a lesser extent—also dipeptidyl peptidase IV (DPPIV) [18].

Angiotensin-Converting Enzyme

Angiotensin-converting enzyme (ACE) is distributed throughout the vascular endothelium of the body, with the highest concentrations in the lungs [19]. Its main function is cleavage of a dipeptide from angiotensin I, thereby converting it to angiotensin II which is a potent vasoconstrictor when it binds to its receptors. Angiotensin II contributes to the renin-angiotensin-aldosterone axis, which affects the blood pressure through regulation of vascular tonus, sympathetic activity, vagal inhibition, antidiuretic hormone secretion, and tubular sodium secretion. Inhibition of this axis by ACEi has clearly been demonstrated to improve outcomes in congestive heart failure, diabetic nephropathy, hypertension, and coronary artery disease in large-scale trials [20–23]. The widespread use of ACEi can be explained by the high efficacy, combined with their overall good tolerability.

Risk Factors for Developing ACE-Induced Angioedema

Although any patient using ACEi is at risk for developing angioedema, some individuals may be at particular risk. According to a recent survey among 276,977 new ACEi users, risk factors for developing angioedema were age 65 years and higher, asthma and allergy, COPD, and rheumatoid arthritis, while diabetes seemed a protective factor. Furthermore, the use of calcium channel blockers and NSAID was associated with a higher risk [24]. A smaller study by Hallberg confirmed calcium blockers as a risk factor but also found a significant association with male sex and smoking [25] which is in contrast with the findings by Do et al., showing higher incidence in women and patients of African origin [2].

Treatment

In recent years, several new drugs have been developed for the treatment of HAE which have also been evaluated in patients with ACEia motivated by the assumed similar pathophysiological principle, being the excessive presence of BK. Theoretically, both inhibition of production (ecallantide) and prevention of the binding of BK to the receptor (icatibant) could be of use in ACEia. Likewise, treatment with C1 inhibitor by means of fresh frozen plasma or as C1 inhibitor concentrate could be advocated. We searched the literature for double-blind placebo-controlled trials regarding production inhibitors,

bradykinin receptor antagonists, C1 concentrate, and fresh frozen plasma.

Icatibant

Although the earliest reports of icatibant showed improvement of time to relief or resolution of ACEia when compared to an historical cohort or a group of patients that received standard therapy with antihistamines and corticosteroids, this observation could not be confirmed in larger randomized-controlled trials [26, 27, 28•, 29]. Sinert and colleagues randomized a total of 121 ACEia patients to either icatibant or placebo. The primary outcome, time to meeting the discharge criteria, was equal in both groups (median, 4 h) as was the secondary outcome, time to onset of symptom relief (2.0 h versus 1.6 h). A similar observation was reported from the trial performed by Straka et al., as a total of 13 ACEia patients that were randomly assigned to icatibant and 18 patients that received placebo had a similar time to relief of symptoms. Possible explanations for the lack of efficacy in the latter two trials might be the relatively long time between first symptoms and administration of icatibant (7.9 h and 10.3 h, respectively) compared to the first study by Bas, or icatibant's incapacity to block angioedema formation through activation of the BK1 receptor by desargylated BK.

Ecallantide

Ecallantide is a KK inhibitor with a proven efficacy in hereditary angioedema. [30, 31] It is of note that ecallantide is only licensed in the USA. To date, two randomized controlled trials evaluated the effect in ACEia. The first study, executed by Lewis et al., randomized a total of 79 patients to either placebo, 10, 30, or 60 mg of ecallantide, on top of regular therapy (H1 blockers, H2 blockers, corticosteroids, and/or adrenergic agonists), and not only scoring the Ishoo stage (location of edema) but severity as well [32•]. This study was terminated early since in all treatment arms, more patients than expected achieved the primary end point, which was eligibility for discharge. Ecallantide did not show superiority over placebo in the interim analysis. A subgroup analysis comparing Ishoo stages III and IV and moderate-to-severe symptoms to placebo showed a response rate of 83% while the placebo group reached 50%. Bernstein et al. performed a triple-blind, placebo-controlled study comparing conventional therapy (antihistamines and corticosteroids) plus ecallantide to conventional therapy plus placebo. In the ecallantide group, 31% met discharge criteria within 4 h compared to 21% of the placebo group [33]. In this study, as well as in the study by Lewis et al., the majority of patients had Ishoo class 1. Therefore, ecallantide has no clinically proven efficacy in ACEia in general, but its efficacy in the more severe attacks (Ishoo stages III and IV) remains a matter of debate. From a pathophysiological point of view, inhibition of KK is unlikely to counteract the decreased (desArg-)BK degradation.

C1 Inhibitor Concentrate

To date, no phase 3 clinical studies have been performed with C1 inhibitor concentrate in ACEia. However, several case reports and case series have reported successful outcomes with C1 inhibitor concentrate. The first case report using human C1 inhibitor concentrate (Berinert P) was published by Nielsen et al. in

2006 [34]. It described a 61-year-old female patient that despite treatment with corticosteroids and antihistamines showed progressive symptoms. After a gift of 1500 units of C1 inhibitor concentrate, improvement was seen within 20 min. Several other case reports confirmed successful treatment with C1 inhibitor concentrate [35–38]. Patients showed improvement on average 88 min and complete resolution in 10.1 h, without the need for other treatment such as intubation or corticosteroids or a second gift of C1 inhibitor concentrate.

Fresh Frozen Plasma

Fresh frozen plasma (FFP) has been used in patients with ACEia with mostly good results, e.g., resolution of complaints or cessation of progression. In 8 case reports and 1 case series, a total of 16 patients were treated with FFP after failure of antihistamines, steroids, and/or adrenaline/epinephrine. So far, no double-blind placebo-controlled trial to evaluate the value of FFP over placebo has been performed [38].

Secondary Prevention

The optimal intervention to prevent patients with ACEia from future attacks is to permanently stop the administration of ACEi. It is of note, however, that ACEia can also recur in the first months after discontinuation of this treatment. Angiotensin II receptor antagonists (ARBs) can be used as a safe alternative in the large majority of ACEia patients as cross reactivity is low and ARBs do not influence BK degradation.

Genetic Susceptibility

In the past years, several groups have tried to identify genetic susceptibility for developing ACEia which could potentially lead to preventive testing as has been proven very effective for example in treatment with Abacavir [39]. A meta-analysis by Mahmoudpour et al. showed that in three smaller studies, SNPs within the XPNPEP2 gene were associated with a lower aminopeptidase P activity and higher risk at angioedema [40]. A GWAS study by the same author showed 8 SNPs within 4 genes that reached the significance level (RBFOX3, GABRG2, SH2B1, and MBOAT1) but not for the XPNPEP2 gene. However, contrary to the first 3 studies, the population study of the GWAS did not contain confirmed angioedema cases but consisted of patients that switched from an ACE inhibitor to an angiotensin II receptor antagonist [41]. A study by Moholisa suggested lower ACE activity as well as B2 receptor polymorphism as a risk factor for developing ACEia. Again, these results need to be confirmed in larger studies [42].

Discussion

Since we have no possibilities to prevent or predict the development of ACEia, we are limited to pharmacological treatment in ACEia patients; as this review

shows, developments to date are disappointing. Both KK inhibitors and BK2 receptor antagonists showed no improvement over placebo or usual treatment despite several positive case reports. Two important factors to take into account is that ACE is only one of the many enzymes involved in the elimination of BK and that earlier reports have shown that patients with ACEia have lower activity of APP as well as DPP-IV [43]. Moreover, ACE not only breaks down BK but also substance P, which is also vasoactive. It could therefore well be that the effects of both KK inhibitors as well as BK2 receptor antagonists, which focus on the BK system alone, are too limited to exert clinical relevant effects, while FFP containing both ACE and C1 inhibitor could potentially improve the breakdown of both BK and substance P [44]. Since no randomized-controlled trials have been done with FFP, this point remains to be proven.

In conclusion, to date, convincing evidence warranting the use of KK inhibitors or BK2 receptor antagonists in ACE–induced angioedema is lacking. Fresh frozen plasma could be useful but has not been evaluated in randomized-controlled trials. Pharmacogenetics seems promising but also needs to be evaluated in larger trials.

Compliance with Ethical Standards

Conflict of Interest
I Terreehorst declares no conflict of interest.
S Reitsma declares no conflict of interest.
DM Cohn declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Aygoren-Pursun E, Magerl M, Maetzel A, Maurer M. Epidemiology of bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. Eur J Rare Dis. 2018;13(1):73.
2. Do TP, Seetasith A, Belleli R, Schlienger RG, Corda S, Burudpakdee C, et al. A database cohort study to assess the risk of angioedema among patients with heart failure initiating angiotensin-converting enzyme inhibitors in the USA. Am J Cardiovasc Drugs. 2018;18(3):205–11.
3. Reichman ME, Wernecke M, Graham DJ, Liao J, Yap J, Chillarige Y, et al. Antihypertensive drug associated angioedema: effect modification by race/ethnicity. Pharmacoepidemiol Drug Saf. 2017;26(10):1190–6.
4.•• Kim SJ, Brooks JC, Sheikh J, Kaplan MS, Goldberg BJ. Angioedema deaths in the United States, 1979-2010. Ann Allergy Asthma Immunol: official publication of the American College of Allergy, Asthma, & Immunology. 2014;113(6):630–4.

This study gives thorough insight in the causes of death due to angioedema.

5. Depetri F, Tedeschi A, Cugno M. Angioedema and emergency medicine: from pathophysiology to diagnosis and treatment. Eur J Intern Med. 2019;59:8–13.
6. Wadelius M, Marshall SE, Islander G, Nordang L, Karawajczyk M, Yue QY, et al. Phenotype standardization of angioedema in the head and neck region caused by agents acting on the angiotensin system. Clin Pharmacol Ther. 2014;96(4):477–81.
7. Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. J Am Dent Assoc. 2003;134(8):1088–94.
8. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012;130(3):692–7.
9. Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clin Proc. 2000;75(4):349–54.
10. Oschatz C, Maas C, Lecher B, Jansen T, Bjorkqvist J, Tradler T, et al. Mast cells increase vascular permeability by heparin-initiated bradykinin formation in vivo. Immunity. 2011;34(2):258–68.
11. Maas C, Govers-Riemslag JW, Bouma B, Schiks B, Hazenberg BP, Lokhorst HM, et al. Misfolded proteins activate factor XII in humans, leading to kallikrein formation without initiating coagulation. J Clin Invest. 2008;118(9):3208–18.
12. Kannemeier C, Shibamiya A, Nakazawa F, Trusheim H, Ruppert C, Markart P, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. Proc Natl Acad Sci U S A. 2007;104(15):6388–93.
13. Muller F, Mutch NJ, Schenk WA, Smith SA, Esterl L, Spronk HM, et al. Platelet polyphosphates are proinflammatory and procoagulant mediators in vivo. Cell. 2009;139(6):1143–56.
14. Morrison DC, Cochrane CG. Direct evidence for Hageman factor (factor XII) activation by bacterial lipopolysaccharides (endotoxins). J Exp Med. 1974;140(3):797–811.
15. Cohn DM, Zeerleder SS. Angioedeem: classificatie, diagnose en behandeling. Ned Tijdschr Hematol. 2017;14:282–7.
16. Marceau F, Hess JF, Bachvarov DR. The B1 receptors for kinins. Pharmacol Rev. 1998;50(3):357–86.
17.•• Cugno M, Nussberger J, Cicardi M, Agostoni A. Bradykinin and the pathophysiology of angioedema. Int Immunopharmacol. 2003;3(3):311–7.

This study gives a good overview of the pathophysiology of bradykinin and its relation with angioedema.

18. Shima C, Majima M, Katori M. A stable metabolite, Arg-Pro-Pro-Gly-Phe, of bradykinin in the degradation pathway in human plasma. Jpn J Pharmacol. 1992;60(2):111–9.
19. Yang HY, Erdos EG, Levin Y. A dipeptidyl carboxypeptidase that converts angiotensin I and inactivates bradykinin. Biochim Biophys Acta. 1970;214(2):374–6.
20. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429–35.
21. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The collaborative study group. N Engl J Med. 1993;329(20):1456–62.
22. van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J. 2012;33(16):2088–97.
23. Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2006;47(8):1576–83.
24. Mahmoudpour SH, Baranova EV, Souverein PC, Asselbergs FW, de Boer A, Maitland-van der Zee AH. Determinants of angiotensin-converting enzyme inhibitor (ACEI) intolerance and angioedema in the UK Clinical Practice Research Datalink. Br J Clin Pharmacol. 2016;82(6):1647–59.
25. Hallberg P, Nagy J, Karawajczyk M, Nordang L, Islander G, Norling P, et al. Comparison of clinical factors between patients with angiotensin-converting enzyme inhibitor-induced angioedema and cough. Ann Pharmacother. 2017;51(4):293–300.
26. Bas M, Greve J, Stelter K, Bier H, Stark T, Hoffmann TK, et al. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. Ann Emerg Med. 2010;56(3):278–82.

27. Bas M, Hoffmann TK, Kojda G. Icatibant in ACE-inhibitor-induced angioedema. N Engl J Med. 2015;372(19):1867–8.
28.• Sinert R, Levy P, Bernstein JA, Body R, Sivilotti MLA, Moellman J, et al. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema. J Allergy Clin Immunol Pract. 2017;5(5):1402–9.e3.
This study showes the lack of effect of icatibant on ACE induced angioedema.
29. Straka BT, Ramirez CE, Byrd JB, Stone E, Woodard-Grice A, Nian H, et al. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema. J Allergy Clin Immunol. 2017;140(1):242–8.e2.
30. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2017;72(2):300–13.
31. Katelaris CH. Acute management of hereditary angioedema attacks. Immunol Allergy Clin N Am. 2017;37(3):541–56.
32.• Lewis LM, Graffeo C, Crosley P, Klausner HA, Clark CL, Frank A, et al. Ecallantide for the acute treatment of angiotensin-converting enzyme inhibitor-induced angioedema: a multicenter, randomized, controlled trial. Ann Emerg Med. 2015;65(2):204–13.
This study like the Sinert study shows the lack of effect of HAE treatment in ACE induced angioedema.
33. Bernstein JA, Moellman JJ, Collins SP, Hart KW, Lindsell CJ. Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitor-induced angioedema in the emergency department. Ann Allergy Asthma Immunol. 2015;114(3):245–9.
34. Nielsen EW, Gramstad S. Angioedema from angiotensin-converting enzyme (ACE) inhibitor treated with complement 1 (C1) inhibitor concentrate. Acta Anaesthesiol Scand. 2006;50(1):120–2.
35. Greve J, Bas M, Hoffmann TK, Schuler PJ, Weller P, Kojda G, et al. Effect of C1-esterase-inhibitor in angiotensin-converting enzyme inhibitor-induced angioedema. Laryngoscope. 2015;125(6):E198–202.
36. Leibfried M, Kovary A. C1 esterase inhibitor (Berinert) for ACE inhibitor-induced angioedema: two case reports. J Pharm Pract. 2017;30(6):668–71.
37. Lipski SM, Casimir G, Vanlommel M, Jeanmaire M, Dolhen P. Angiotensin-converting enzyme inhibitors-induced angioedema treated by C1 esterase inhibitor concentrate (Berinert(R)): about one case and review of the therapeutic arsenal. Clinl Case Rep. 2015;3(2):126–30.
38. Riha HM, Summers BB, Rivera JV, Van Berkel MA. Novel therapies for angiotensin-converting enzyme inhibitor-induced angioedema: a systematic review of current evidence. J Emerg Med. 2017;53(5):662–79.
39. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet (London, England). 2002;359(9308):727–32.
40. Mahmoudpour SH, Leusink M, van der Putten L, Terreehorst I, Asselbergs FW, de Boer A, et al. Pharmacogenetics of ACE inhibitor-induced angioedema and cough: a systematic review and meta-analysis. Pharmacogenomics. 2013;14(3):249–60.
41. Mahmoudpour SH, Veluchamy A, Siddiqui MK, Asselbergs FW, Souverein PC, de Keyser CE, et al. Meta-analysis of genome-wide association studies on the intolerance of angiotensin-converting enzyme inhibitors. Pharmacogenet Genomics. 2017;27(3):112–9.
42. Moholisa RR, Rayner BR, Patricia Owen E, Schwager SL, Stark JS, Badri M, et al. Association of B2 receptor polymorphisms and ACE activity with ACE inhibitor-induced angioedema in black and mixed-race South Africans. J Clin Hypertens (Greenwich). 2013;15(6):413–9.
43. Kostis WJ, Shetty M, Chowdhury YS, Kostis JB. ACE inhibitor-induced angioedema: a review. Curr Hypertens Rep. 2018;20(7):55.
44. Lewis LM. Angioedema: etiology, pathophysiology, current and emerging therapies. J Emerg Med. 2013;45(5):789–96.