Current Hypertension Reports (2018) 20: 55
https://doi.org/10.1007/s11906-018-0859-x

GUIDELINES/CLINICAL TRIALS/META-ANALYSIS (JB KOSTIS, SECTION EDITOR)

ACE Inhibitor-Induced Angioedema: a Review

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Published online: 8 June 2018

Abstract

Purpose of Review This study aims to examine current knowledge on the occurrence, pathophysiology, and treatment of angioedema among patients who receive angiotensin-converting enzyme inhibitors.

Recent Findings Angiotensin-converting enzyme inhibitors (ACE-I), a medication class used by an estimated 40 million people worldwide, are associated with angioedema that occurs with incidence ranging from 0.1 to 0.7%. The widespread use of ACE-I resulted in one third of all emergency department visits for angioedema. Angioedema occurs more frequently in African Americans, smokers, women, older individuals, and those with a history of drug rash, seasonal allergies, and use of immunosuppressive therapy. The pathophysiology of ACE-I-induced angioedema involves inhibition of bradykinin and substance P degradation by ACE (kininase II) leading to vasodilator and plasma extravasation. Treatment modalities include antihistamines, steroids, and epinephrine, as well as endotracheal intubation in cases of airway compromise. Patients with a history of ACE-I-induced angioedema should not be re-challenged with this class of agents, as there is a relatively high risk of recurrence.

Conclusion ACE-I are frequently used therapeutic agents that are associated with angioedema. Their use should be avoided in high-risk individuals and early diagnosis, tracheal intubation in cases of airway compromise, and absolute avoidance of re-challenge are important.

Keywords Angiotensin II · Angioedema · Angiotensin-converting enzyme inhibitors · Hypertension · Bradykinin

Introduction

> "In one instance, possibly in two, death resulted from a sudden oedema glottides [1]."
> - William Osler

Angioedema is a well-documented and occasionally lethal side effect of angiotensin-converting enzyme inhibitors (ACE-I). Angioedema is a pale, non-pruritic, well-demarcated, non-pitting edema involving the skin and subcutaneous tissue or submucosa. When involving the airway, the feeling of impending asphyxia may be terrifying for the sufferer [2, 3]. A retrospective analysis identified angioedema as the most common non-asthmatic acute allergic reaction leading to hospitalizations in New York State from 1990 to 2003 [4]. In the four decades since the development of captopril in 1975 (FDA approval 1981), ACE-I have become the some of the most prescribed medications in the USA, with lisinopril being the second most prescribed agent in 2016 [5]. Concurrent with the growing use of ACE-I, the rate of hospitalization for angioedema in the USA has increased from 3.3 to 4.0 per 100,000 within 15 years [6].

The History of Angiotensin-Converting Enzyme Inhibitors

Workers in Brazil who were bitten by the Brazilian pit viper *Bothrops jararaca* die within minutes from severe hypotension. Mauricio Rocha e Silva and his student, Sergio Ferreira, at the University of São Paulo, studied the effects of the snake venom and identified peptides thought to potentiate the action of bradykinin [7]. Ferreira brought the bradykinin potentiating

This article is part of the Topical Collection on *Guidelines/Clinical Trials/Meta-Analysis*

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factor (BPF) to the research group of Sir John Vane at the Royal College of Surgeons in London, who were working on the development of antihypertensive compounds, and who determined that BPF also inhibited the action of ACE in converting angiotensin I to angiotensin II [8]. Vane collaborated with the Squibb Institute for Medical Research in New Brunswick, NJ, where Miguel Ondetti, Bernard Rubin, and David Cushman succeeded in developing captopril, the first oral ACE inhibitor in 1975 [9, 10].

Pathophysiology

Angiotensin-Converting Enzyme

Angiotensin-converting enzyme, a peptidyldipeptide carboxyhydrolase, also known as kininase II, is distributed throughout the vascular endothelium of the body with highest concentrations in the lungs [11]. ACE cleaves a dipeptide from angiotensin I, converting it to angiotensin II, a potent vasoconstrictor and an active component in the renin-angiotensin-aldosterone (RAA) cascade. Angiotensin II binds to angiotensin receptors, the site of action of angiotensin II receptor blockers (ARBs), and exerts a variety of physiologic effects (Table 1). In addition, ACE also degrades the vasodilator bradykinin and substance P (Fig. 1) [12, 13•]. The RAA cascade is more complex than displayed in Fig. 1, which does not include AT-(1-7), AT-3, AT-4, etc., however this is beyond the scope of this review.

Angiotensin-Converting Enzyme Inhibitors

As the name suggests, the class of ACE-I class of drugs competitively inhibit ACE, thereby reducing its activity [14]. By blocking the synthesis of angiotensin II, ACE-I mediate arterial and venous vasodilatation, inducing a hypotensive effect through a reduction in both preload and afterload. These effects contribute to improved outcomes in patients with hypertension and in patients with heart failure with reduced ejection fraction. Unlike beta blockers, where their actions on multiple subtypes of adrenergic beta receptors influence clinical effects, there are no clinically significant differences among ACE-I with respect to tissue-specific effects, the type of zinc ligand, the need for bioactivation after ingestion (of ACE-I that are prodrugs), pharmacokinetics, potency, or onset of action [15].

Table 1 Actions of angiotensin II

Vasoconstriction	40 times stronger than norepinephrine Arteriolar > venous Skin, kidney > muscle, brain
Aldosterone secretion	
Sympathetic activation	Central enhancement Peripheral facilitation Ganglionic stimulation
Vagal inhibition	
Cardiac stimulation	Ca++ channel
ADH secretion	
ACTH secretion	
Dipsogenic effect	
Renal effects	Renin release (negative feedback) Vasoconstriction (efferent>afferent) Increased tubular sodium secretion Glomerular mesangial constriction

Mechanism and Genetics of Angioedema

The development of angioedema induced by ACE-I is initiated by kallikrein, which cleaves the active nonapeptide bradykinin from the macromolecule kininogen. Bradykinin causes vasodilatation and increased vascular permeability, most notably in the postcapillary venules via generation of nitric oxide and prostaglandins [16]. Bradykinin is primarily degraded by ACE, neutral endopeptidase (NEP), and aminopeptidase P (APP), as well as dipeptidyl peptidase IV (DPP-IV) and kininase I [13•, 17]. Inhibition of bradykinin degradation by ACE-I results in plasma extravasation into the submucosal tissue leading to angioedema. In addition, kininase I breaks down bradykinin to a secondary active metabolite, des-Arg^9-bradykinin, which has similar properties [13•]. Individuals with an intrinsic defect in the degradation of bradykinin, des-Arg^9-BK, and substance P have a propensity to develop angioedema with ACE-I [13•, 18]. Substance P is another vasodilator peptide that is degraded by ACE. While bradykinin exerts its effects by binding to bradykinin type 2 (B2) receptors, substance P exerts its effects through the neurokinin 1 (NK1) receptor. Both substances participate in the development of angioedema in humans. In a case-control study of patients with history of ACE-I-induced angioedema, the degradation half-life of substance P was decreased in sera from ACE-I patients with history of angioedema as compared to ACE-I patients without angioedema history [13•, 19, 20]. Patients with ACE-I-induced angioedema also have a lower plasma activity of APP, an enzyme that degrades both bradykinin and substance P.

Decreased DPP-IV and APP activity has been observed in patients with a history of ACE-I-induced angioedema as compared to patients exposed to ACE-I who did not develop angioedema [13•, 20]. Individuals with the ACE gene D/D polymorphism have higher incidence of hypertension but do not appear to have increased susceptibility to angioedema secondary to ACE-I [21–23]. On the other hand, the C-2399A polymorphism of aminopeptidase P (encoded by the XPNPEP2 gene) increases the incidence of ACE-I-induced angioedema [24•]. Genetic dipeptidyl dipeptidase deficiency has been

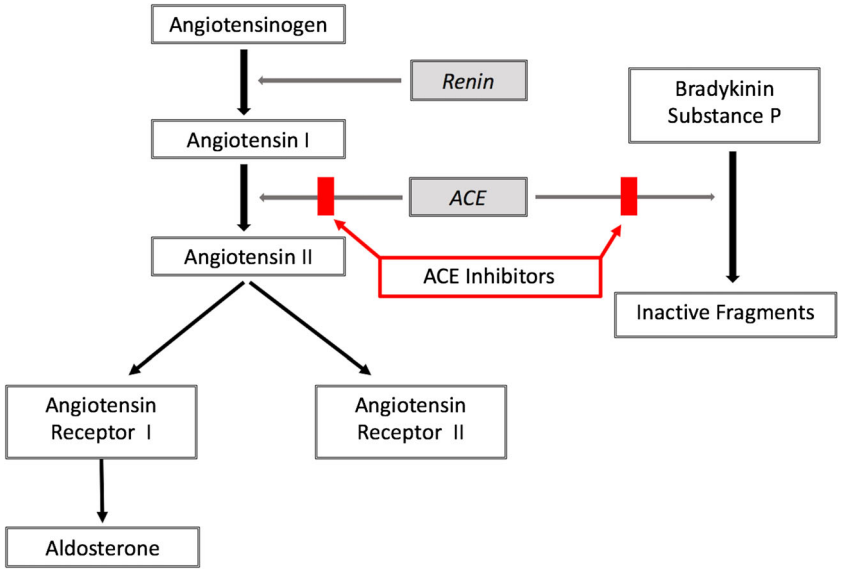

Fig. 1 Simplified diagram of the renin-angiotensin system

associated with an increased incidence of angioedema after ACE-I ingestion [19, 25•].

Incidence of Angioedema in ACE-I Users

The occurrence, time course, and outcomes of ACE-I-induced angioedema was studied in the OCTAVE trial, which was a multicenter, randomized, double-blind, active-controlled trial conducted across 12 countries that studied 25,302 patients with uncontrolled or untreated hypertension that compared the safety and efficacy of omapatrilat to enalapril. Omapatrilat, a molecule with dual active sites, inhibits neutral endopeptidase (neprilysin) as well as ACE. Neprilysin and ACE are responsible for the degradation of substance P, which like bradykinin, can cause plasma extravasation via NK1 receptors and contribute to angioedema [26]. In Phase III clinical trials, omapatrilat exhibited superior antihypertensive efficacy compared to lisinopril. In the OCTAVE trial, with blind expert adjudication for angioedema, there was a markedly higher rate of angioedema with omapatrilat (2.2%) as compared to enalapril (0.7%) [27]. Omapatrilat was ultimately not approved by the FDA due to this concern. Among the 12,557 OCTAVE patients who were randomized to enalapril (the control group), the highest incidence of angioedema occurred during the first month after initiation of therapy (3.6 events per 1000 patients) and declined thereafter [28•]. There was a sharp decline in incidence until weeks 9–12, as shown in Fig. 2. After week 12, there was a low but constant incidence rate (0.3 to 0.6 events per 1000 patients) that may represent the ambient risk due to other causes, including drug interactions and the nocebo effect [28•]. In another large dataset, Slater et al. reported that the rate of enalapril-related angioedema peaked in the first week of use and declined steeply thereafter [29]. The reported overall incidence of angioedema in patients taking ACE-I varies from 1 to 7 events per 1000 patients [28•, 29, 30, 31]. In the largest meta-analysis conducted on the subject, Makani et al. included 26 trials and a total of 74,857 patients in the ACE-I arm. They reported a weighted incidence of angioedema of 3 events per 1000 patients in this group [32]. Despite this low incidence rate, ACE-I account for one third of all emergency department visits for angioedema because of their widespread use [33, 34•].

Groups at Higher Risk of Developing Angioedema

Analysis of the enalapril group of OCTAVE identified four types of patients who had statistically significant higher incidence of angioedema: those older than 65 years, African Americans, and patients with a history of drug rash or seasonal

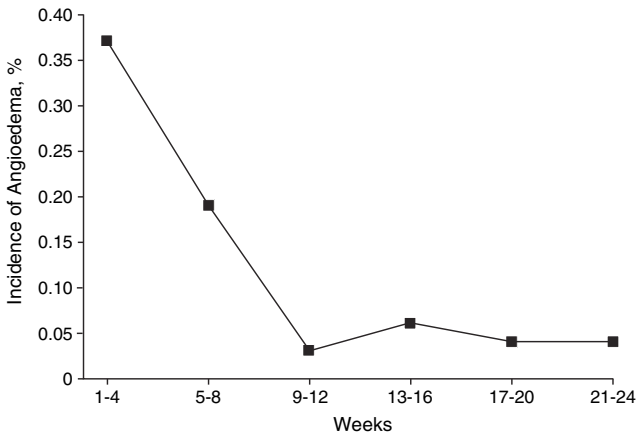

Fig. 2 The incidence of angioedema in the weeks after randomization in the enalapril randomized group of OCTAVE. Reproduced with permission from Kostis et al. [28•]

allergies [27, 28•]. The observation of increased incidence of angioedema after 65 years of age in the OCTAVE trial is in agreement with the findings of decreased levels of dipeptidyl peptidase IV (DPP-IV), an enzyme involved in degradation of bradykinin [35]. Automated sequential recursive partitioning from the enalapril data in the OCTAVE study indicate that non-White patients of age over 40 and with a history of seasonal allergies had a relatively high (2.5% or 25 events per 1000 patients) rate of developing angioedema following enalapril administration [36]. These patients should be prescribed medications of alternate classes. Patients without these characteristics are likely to be at very low risk of angioedema due to ACE-I. Numerous studies have verified the higher incidence of angioedema among African Americans. Though the exact cause is still uncertain, Brown et al. proposed that this could be because they are more sensitive to bradykinin, both ACE-I induced and exogenous, than the general population [37–39]. An autopsy series from a county coroner's office in Ohio reported seven deaths from asphyxia due to angioedema of the tongue. All seven cases were of African American descent [40].

Women, smokers, and patients with prior history of angioedema are also at higher risk of developing angioedema. Estrogen induces the expression of prekallikrein or the bradykinin type 2 (B2) receptor and suppresses expression of the ACE gene. This may explain the minor differences in incidence of angioedema between men and women [41, 42]. Smokers have significantly lower serum DPP-IV activity and are at a higher risk of angioedema [13•]. Concomitant use of aspirin, statins, DPP-IV inhibitors, and mTOR inhibitors (e.g., sirolimus) is also associated with an increased incidence of angioedema. Patients on immunosuppressive therapy with mammalian target of rapamycin (mTOR) inhibitors after organ transplantation who were on ACE-I had higher incidence of angioedema. These agents deplete lymphocytic DPP-IV [43•] and alternative antihypertensive drugs should be considered in these patients. Patients with diabetes were also found to have a lower incidence of angioedema than the general population and DPP-IV activity has been found to be increased in sera of these patients [13•]. A retrospective cohort study identified a 10-fold increase in risk of angioedema recurrence in patients who were continued on ACE-I despite occurrence of angioedema [44]. Patients who develop angioedema on one ACE-I are very likely to develop a recurrence when another ACE-I administered and such re-challenge should be avoided.

Expected Rise in Incidence of Angioedema

There is now growing interest in the use of a "polypill" that includes low doses of pharmacologic agents of different classes [45]. For example, a single pill administered once a day (a Polycap containing hydrochlorothiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg, simvastatin 20 mg, and aspirin 100 mg) has been successfully used for primary prevention in individuals without cardiovascular disease, aged 45–80 years, and with one risk factor [46]. Such strategies have the potential to expose millions of people to ACE-I and result in a large number of patients who develop angioedema.

Approach to ACE-I-Induced Angioedema

The clinical manifestations and pathophysiology of ACE-I-induced angioedema are different from those of hereditary angioedema. While ACE-I-induced angioedema usually affects the face and upper airway, hereditary angioedema has a proclivity for the abdomen [47]. Unlike hereditary angioedema, in which assessment of C1 esterase inhibitor, C4, and C2 levels aids in diagnosis, there are no routine laboratory tests to help diagnose ACE-I-induced angioedema. The first and most obvious step in the management of angioedema is immediate discontinuation of the ACE-I. There is no consensus on the best pharmacologic treatment. Antihistamines, steroids, and epinephrine are used. If the patient's condition deteriorates despite these interventions, tracheal intubation may be required. A multicenter, randomized, double-blind, double-dummy Phase II study conducted with icatibant (a competitive antagonist of the bradykinin B2 receptor) in 27 patients with ACE-I-induced angioedema reported more rapid symptom resolution when compared with standard therapy (500 mg IV prednisolone + 2 mg clemastine) [48•]. However, a follow-up Phase III, 2-armed, randomized double-blind clinical trial showed no appreciable benefit of icatibant in ACE-I-induced angioedema of the airway [49]. Icatibant is currently approved by the FDA only for use in hereditary angioedema. Ecallantide, a recombinant protein inhibitor of kallikrein, was shown to be no more effective than placebo in ACE-I-induced angioedema [50]. Moreover, a high rate of hypersensitivity/anaphylaxis (3%) limits its use to supervised settings [51, 52•]. Given the success of C1-inhibitor concentrate in acute hereditary angioedema management, it has been used in several cases of ACE-I-induced angioedema, but its role in this setting remains unproven [51].

Fresh frozen plasma (FFP) has intrinsic ACE and C1-esterase inhibitor activity, which can catabolize accumulated bradykinin [53]. Though cheap, easily available, and frequently used, recipients should be closely monitored for initial worsening of angioedema as FFP also contains kininogen and high molecular weight kallikrein, precursors of bradykinin [54•]. Volume overload, allergic reactions, and the risk of transfusion related infections should also be taken into account [47, 55].

Table 2 Functions of angiotensin II mediated via its two main receptors—AT1 and AT2

Angiotensin II receptor type 1 (AT1)	Angiotensin II receptor type 1 (AT2)
More common in adults	Less common in adults—present in the fetus and expressed in adults in times of stress and injury
Mediates vasoconstriction	Mediated vasodilatation
Aldosterone release	Apoptosis
Oxidative Stress	Anti-inflammation
Cellular hypertrophy	Oxygen release
Increases thirst—ADH release	Bradykinin production
Increased renal tubular sodium reabsorption	Anti-proliferative
LDL-C increase	Nitrous oxide release
Increase in proteinuria—due to increased intraglomerular pressures secondary to efferent arteriolar constriction	
Decreases endothelium function	
Promotes connective tissue deposition	
Promotes platelet aggregation and adhesion	

Alternatives to ACE-I in Patient Subsets at Increased Risk of Angioedema

Angiotensin II Receptor Blockers

Angioedema is rarely encountered with other RAA pathway inhibitors. Angiotensin II exerts its physiologic effects primarily via two types of receptors, AT1 and AT2 (Table 2). ARBs work by blocking AT1 receptors but, unlike ACE-I, play no known role in the degradation of bradykinin, which may partly explain the lower incidence of angioedema with their use. A retrospective study that compared the incidence of angioedema in both drug classes found the cumulative incidence per 1000 persons was 1.79 for ACE-I and 0.62 for ARBs [56•].

Aliskiren

Aliskiren, a direct renin inhibitor, was found to have a slightly lower cumulative incidence of angioedema as compared to ACE-I [56•]. That said, the ALTITUDE study, designed to assess the safety of dual RAA blockade (aliskiren in combination with an ACE-I or ARB), was terminated prematurely due to concern for safety and lack of efficacy [57].

Neprilysin Inhibitors

Omapatrilat, which inhibits both neprilysin and ACE, failed to obtain FDA approval due to the high incidence of angioedema, despite its superior antihypertensive effect as compared to enalapril. The increased incidence of angioedema was thought to be due to the combination of neprilysin and ACE inhibition. It was hypothesized that the combination of a neprilysin inhibitor and an angiotensin II receptor blocker, rather than an ACE-I, would confer superior antihypertensive effect without a similarly high risk of angioedema. The combination of sacubitril (a neprilysin inhibitor) and valsartan (Entresto) was recently approved for the treatment of heart failure with reduced ejection fraction. PARADIGM-HF compared the efficacy of Entresto to enalapril [58•]. The incidence of angioedema was 0.5% with Entresto as compared to 0.2% with enalapril. However, 6532 of the 8442 patients enrolled in the trial had previous exposure to ACE-I, and all had received enalapril during the single-blind run-in period. Thus, there may have been selection bias with under-representation of angioedema in the trial since > 50% of ACE-I-induced angioedema occurs within the first week of exposure and these patients may have been excluded prior to randomization. In addition, only 5% of the enrolled population in PARADIGM-HF was African American, a group at higher risk for angioedema [59]. The rate of angioedema may be higher in ACE-I-naïve patients started on Entresto.

Conclusion

ACE-I are an effective class of medications used by an estimated 40 million people worldwide. These numbers will likely grow, especially if polypill strategies are widely adopted. Their use has been associated with angioedema, an adverse reaction that on rare occasions may be fatal. The incidence of ACE-I-induced angioedema is estimated to be 0.1 to 0.7%. It occurs more frequently in African Americans, those with a history of drug rash, seasonal allergies, age > 40, smokers, women, and those on immunosuppressive therapy. In such patients, medications other than ACE-I should be used. In patient subsets at high risk, for angioedema with ACE-I treatment, early diagnosis, tracheal intubation in cases with airway compromise, and absolute avoidance of re-challenging patients with ACE-I are important.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent No human or animal data were collected in writing this review.

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