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REVIEW ARTICLE

Angiotensin-converting Enzyme Inhibitor-induced Angioedema – A Dangerous New Epidemic

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Angioedema is a sudden localised and often asymmetric swelling of the skin or mucous membranes caused by transient increased endothelial permeability causing plasma extravasation. In the last decades the incidence of severe angioedema involving the upper airways and even fatal outcome due to asphyxia has increased. This is mainly due to pharmaceuticals such as angiotensin-converting enzyme inhibitors, which are extensively used worldwide. Some aspects of the pathophysiology have been elucidated and the vasoactive molecule bradykinin is shown to be one of the main causative agents. The diagnosis is often delayed and traditional treatment usually ineffective. Complement C1 inhibitor concentrate and bradykinin receptor antagonists, normally used to treat patients with hereditary angioedema, have shown good results when used in patients with bradykinin-mediated angioedema. This review discusses the disease, prognosis and treatment options. ***Key words: angioedema; angiotensin-converting enzyme inhibitors; hereditary angioedema; bradykinin; C1 inhibitor.***

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Angioedema is a non-pitting, non-itching rapid swelling of skin, mucosa and/or submucosa. The angioedema normally resolves without treatment within hours to a few days, but can in rare cases persist for up to one week. The first description of this symptom was published by Milton in 1872 and ever since the phenomenon has been extensively investigated identifying several causes for the symptom. There are numerous causes for angioedema such as allergic, drug-mediated, autoimmune or due to complement C1 inhibitor deficiency. However a large proportion of angioedema patients end up with no identifiable cause (idiopathic angioedema) (1). Most angioedema attacks are caused by mast cell activation and histamine release.

In the seventies angiotensin-converting enzyme inhibitor (ACEi) was marketed as an antihypertensive drug. Clinical trials showed good results and the treatment was implemented and was generally well tolerated. In 1977 and 1980 the first reports on ACEi as a cause of angioedema were published (2, 3). Since then ACEi has been widely approved for treatment of hypertension, congestive heart failure, diabetic nephropathy and coronary artery disease (4). Furthermore, ACEi is now also approved for use in children and young adults. The use of ACEi has thus increased significantly over recent years (5, 6) and more adverse reactions have been reported including severe angioedema of the upper airways and even death due to asphyxiation (7–10). This review will focus on epidemiology, clinical presentation, pathophysiology and discuss treatment of this condition.

EPIDEMIOLOGY AND RISK FACTORS

In recent years a significant increase in the use of ACEi has been observed and thus an increase in angioedema due to this class of drugs has been reported. Holm & Ovesen (5) found a 3-fold increase in the national use of ACEi from 2000–2009 and a 67% higher incidence of angioedema due to ACEi in 2005–2009 compared to 2000–2004 (5, 10). This is in concordance with other studies (11, 12). One of the most substantial studies on the incidence of angioedema caused by ACEi is a randomised, double-blind, controlled trial of 12,557 hypertensive patients treated with enalapril (13). In this study 0.68% of patients developed angioedema. Other well-designed studies showed an incidence of 0.2–2.5% (13–15). Among patients presenting to a hospital with acute angioedema, 39–46% were treated with ACEi (5, 16). In a specialised out-patient setting the incidence was found to be 11% (17). People of African origin have an up to 3 times higher risk of angioedema when treated with ACEi, which in some cases are caused by a genetic polymorphism (18, 19). Female gender, a history of smoking and age > 65 years also seem to be risk factors (13, 20). In patients suffering from other forms of angioedema (hereditary, acquired or idiopathic) ACEi seems to have a precipitating effect on the disease (21–23). Especially patients with hereditary angioedema (HAE) have a greatly increased risk of angioedema when treated with ACEi; this class of pharmaceuticals is thus contraindicated in these patients (24, 25). Further-

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more localised tissue trauma can precipitate angioedema in both HAE patients and patients treated with ACEi, suggesting a similar mechanism (26–28).

CLINICAL PRESENTATION

Angioedema due to ACEi is usually not accompanied by urticaria. The oedematous area is skin coloured or slightly red. In most cases the angioedema is located in the orofacial and/or perioral area and/or upper airways (Fig. 1) (17). A lump in the throat, drooling, stridor and a hoarse voice or aphonia are possible symptoms, when the airways are involved, signalling a severe situation with the need to act immediately and secure the airway (16, 22). Abdominal pain might be a rare and sometimes the only sign of ACEi-induced angioedema, since the swellings can be present solely in the abdominal organs, most often the intestines (29, 30).

PATOPHYSIOLOGY

Angioedema caused by ACEi treatment is a complex mechanism to assess and is not yet fully elucidated (Fig. 2). The function of Angiotensin Converting Enzyme (ACE: which also goes by the name of kininase II) is to convert angiotensin I to angiotensin II (22). The latter is a vasoconstrictor and is linked to an increased aldosterone secretion. Blocking ACE thus lowers the blood pressure by decreasing the actions of angiotensin II (31).

Bradykinin

ACE is also the main enzyme degrading the vasoactive molecule bradykinin, and the increased level hereof causes vasodilatation which contributes to the antihypertensive effect of ACEi (32). Localised accumulation of bradykinin is well known for its tendency to cause angioedema in patients suffering from HAE (24). It was early proposed that an increased level of this molecule was also causing angioedema and other cutaneous eruptions in hypertensive patients treated with ACEi (2). Anderson & deShazo (33) proved that ACEi combined with intradermal injection of bradykinin can cause vasodilation (flushing and increase in wheal size). They did also note a significant interpersonal difference in severity of symptoms, causing them to hypothesise upon that some people might be more predisposed to angioedema after ingestion of ACEi. This might be true, but has so far only been proven in black patients compared to Caucasians (18). Aminopeptidase P is the main enzyme responsible for degrading bradykinin when ACE is inhibited, and a decreased activity could theoretically signify an increased risk of angioedema due to bradykinin accumulation. Neutral endopeptidase, dipeptidylpeptidase IV and Carboxypeptidase N are other enzymes connected to bradykinin degradation. Another antihypertensive drug, omapatrilat, inhibits both ACE and neutral endopeptidase and the frequency of angioedema in the treated group was 0.7% which is higher than when only ACE is inhibited (34). Other studies also support the theory that bradykinin is the main causative agent in ACEi associated angioedema, however primarily by means of decreased inactivation and not by increased generation (22, 35).

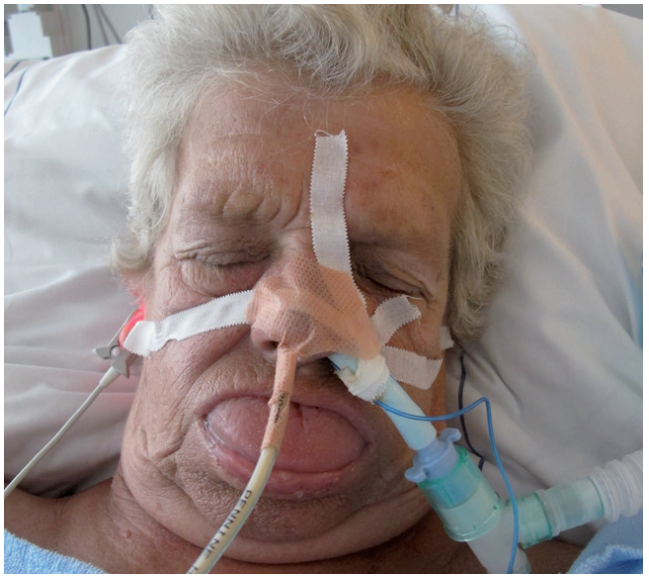

Fig. 1. Severe angioedema of tongue and orofacial area in a woman due to angiotensin-converting enzyme inhibitor treatment. Intubation and sedation was needed. Permission from the patient is given for publication of this figure.

Substance P

Accumulation of another vasoactive molecule, substance P, possibly adds to the risk of developing angioedema (36). ACEi is shown to decrease the degradation and hence cause accumulation of substance P in mice (37). Mainly aminopeptidase P and dipeptidyl peptidase IV degrade substance P during ACE inhibition. Adam et al. (38) has previously shown decreased aminopeptidase P activity in 39 patients with a history of angioedema caused by ACEi, and Byrd et al. (39) found decreased dipeptidyl peptidase IV activity in a similar group of patients. In diabetic hypertensive patients treated concomitantly with ACEi and dipeptidyl peptidase-IV inhibitors (a new class of antidiabetic agents) the incidence of angioedema is significantly increased (40). This strongly suggests an additive effect caused by accumulation of bradykinin and substance P due to decreased degradation rendering the patient more susceptible to angioedema formation.

Localised tissue trauma

Surgical procedures, injection of local anaesthesia and dental treatment might trigger angioedema in patients treated with ACEi (26, 28, 41). In HAE patients, trauma

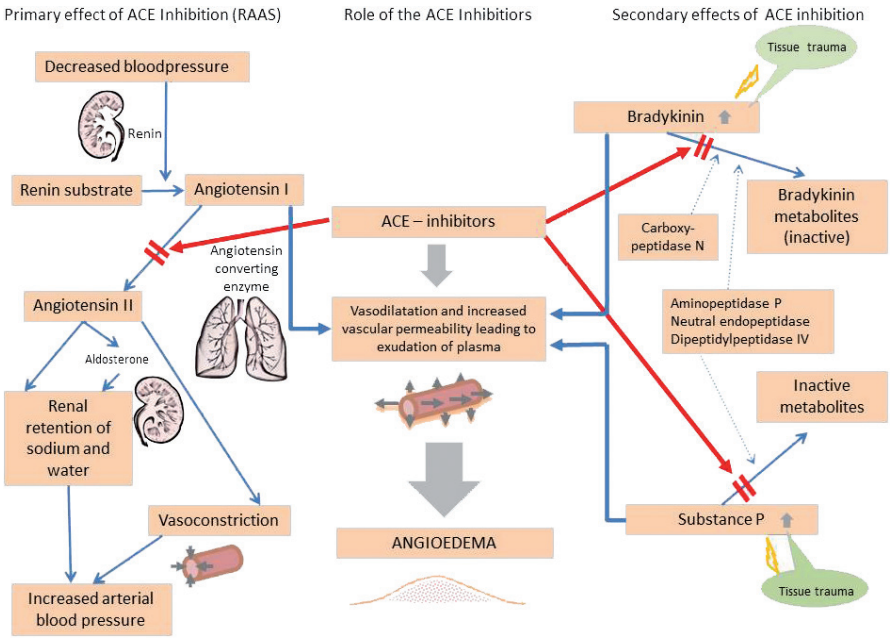

Fig. 2. Schematic presentation of the proposed mechanisms of angioedema formation due to pharmacological inhibition of Angiotensin Converting Enzyme (ACE). On the left hand side the Renin-Angiotensin-Aldosterone-System (RAAS) and the antihypertensive effect of ACE inhibition, is shown. ACE is the main enzyme degrading the vasoactive substances bradykinin and substance P. The right side of the figure illustrates how other enzymes (dotted lines) take over the process of degrading bradykinin and substance P during ACE inhibition. Inhibition or malfunction of any these enzymes will lead to localised accumulation of bradykinin and substance P, and hence increase capillary permeability and tendency to angioedema formation, as shown in the figure in the middle. Tissue trauma, on its own, can cause release of bradykinin and substance P, which in turn might increase the risk of angioedema.

is a well-known trigger factor precipitating swellings and probably this also holds true in angioedema caused by ACEi. Vibration of the soft palate and uvula due to snoring is known to potentially cause severe uvula oedema in HAE patients (42). The mechanism is not entirely clarified, but might be due to local release and pathological accumulation of vasoactive mediators due to inhibited degradation (bradykinin, substance P and others) in response to tissue trauma (28, 43, 44).

Histamine

The vasoactive molecule histamine might be involved in some aspects of the mechanism of ACEi induced angioedema (36), but since the classical treatment for allergic angioedema (adrenaline, antihistamine and corticosteroid) has no effect on the swellings, it seems unlikely that the contribution is significant (22, 43).

GENETIC ASPECTS

ACE polymorphisms do not seem to be associated with an increased risk of angioedema caused by ACEi or angiotensin II receptor blockers, but the C-2399A polymorphism of the *XPNPEP2* gene encoding the enzyme aminopeptidase P renders black men more susceptible to angioedema when treated with ACEi. White men also had a lower enzyme activity compared to women in general (black and white), but the polymorphism was not associated with increased risk of angioedema (19, 45). In rats, genetic dipeptidyl peptidase deficiency increases peritracheal angioedema due to ACEi treatment and it has been hypothesised that this might be of importance in humans too (46).

TREATMENT

The mainstay of treatment is to avoid further intake of the causative drug. The patient must refrain from using all types of ACEi (5, 6). Supportive measures including airway management, fluid replacement therapy and measurement of vital signs should be initiated promptly. The angioedema can progress rapidly, hence observation in a hospital setting for 12 to 24 h or until improvement is advised (47). Angioedema is self-limiting within hours to days, but in severe cases when the upper airways or gastrointestinal tract are involved, causing intense pain, the bradykinin receptor antagonist icatibant has been used as an effective treatment option (8, 48). Complement C1 inhibitor concentrate has recently been implemented in the French national guidelines for treatment of ACEi dependent angioedema, but data are still limited (49, 50). The proposed mode of action is a decreased production of bradykinin, which gives the remaining degrading enzymes a better chance to work. The fact that complement C1-inhibitor concentrate can be used as a treatment option, suggests that the accumulation of bradykinin, at least in part, is derived from the contact system (plasma kallikrein) as tissue kallikrein, the alternative source of bradykinin, is not inhibited by complement C1 inhibitor (49). Fresh frozen plasma does not yet have a well-documented role in the treatment of angioedema caused by ACEi, but could be tried in situations or countries with no other available therapeutic options (51). Theoretically ecallantide, a kallikrein inhibitor used in treatment of HAE, could be used in treatment of ACEi angioedema; however we have found no published studies on this subject yet. The treatment of the underlying condition i.e. hypertension should instantly be continued

with a drug of a different class. Haymore et al. (6) in their meta-analysis found a 9.4% risk of angioedema due to angiotensin II receptor blockers in patients who previously experienced angioedema due to ACEi treatment. A few cases of life-threatening laryngeal oedema have been reported after treatment with angiotensin II receptor blockers, and therefore health care providers should consider this risk when substituting with this class of drugs, although it is not strictly contraindicated (6, 52, 53). In fact, up to half of patients experiencing ACEi-induced angioedema continues to have intermittent swellings after discontinuation of the causative agent and this becomes a chronic disease in 0–16% (23, 54). These data suggest that the physician should discuss the benefits versus risks with the patient prior to drug substitution. Treatment of these patients is challenging, since angioedema episodes are unpredictable and might compromise the airway. In patients with conditions such as heart failure indicating an imperative need for ACEi, one could consider teaching well-informed patients to home treat with icatibant in case of relapsing angioedema, similar to HAE patients with the possibility of home therapy (55–57).

CONCLUSION

ACEi is an effective antihypertensive drug becoming a mainstay in antihypertensive therapy over the past decades and thus causing an increased total number of side effects. Angioedema is a potential adverse drug reaction, which can become lethal due to total airway obstruction. The mechanism still needs clarification but the vasoactive molecules bradykinin and possibly substance P are involved. Genetic polymorphisms of key pathway enzymes may be of importance when ACE is inhibited. Concomitant therapy with dipeptidyl peptidase inhibitors causes an increased risk of angioedema in patients treated with ACEi. It is mandatory to withdraw the causative drug, initiate appropriate observation and treatment instantly in order to avoid asphyxiation.

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