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Angioedema: a rare and sometimes delayed side effect of angiotensin-converting enzyme inhibitors

Laurent Davin^{a,b}, Patrick Marechal^a, Patrizio Lancellotti^{a,b}, Christophe Martinez^a, Luc Pierard^{a,b} and Regis Radermecker^c

^aUniversity of Liege Hospital; CHU Sart Tilman Liege Belgium; Department of Cardiology; ^bGIGA Cardiovascular Sciences University Hospital of Liege; ^cDiabetes, Nutrition and Metabolic disorders Unit CHU Liege; Clinical Pharmacology, Liege University, Belgium

ABSTRACT

The effects of angiotensin converting enzyme (ACE) inhibitors result from the inhibition of the ACE (kininase II) to ultimately influence both the renin–angiotensin system and the degradation of the bradykinin (BK) metabolism. ACE inhibitors block the degradation of BK and substance P by ACE. In addition, an active metabolite of BK (Des-Arg9-BK) is catalysed by kininase I and its degradation is controlled in part by the conversion enzyme. These molecules have been associated with increased plasma extravasation associated with ACE inhibitors. ACE inhibitors are the leading cause of drug-induced Angioedema (AE). Symptoms of AE mainly occur after the first month of treatment by ACE. However, very late onset cases, sometimes after several years of stable therapy, are also described in the literature. It has been observed that patients previously stable under ACE inhibitor will most likely develop AE soon after the addition of another medication, including the combination of aspirin or non-steroid anti-inflammatory drugs with ACE inhibitor which has proved to be the most common cause, accounting for close to 50% of all AE cases related to ACE inhibitors. This side effect of ACE inhibitors, sometimes very late and rare, deserves to be recalled

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Acting mechanism of ACE inhibitors

The renin–angiotensin–aldosterone (RAA) pathway is used by the body to regulate systemic blood pressure and renal blood flow. When renal perfusion pressures decrease the juxtaglomerular nephron cells produce renin. The angiotensinogen precursor produced in the liver is converted by renin to produce angiotensin I, which has vasoconstrictive properties. Angiotensin I is then metabolised in the lungs by the angiotensin-converting enzyme (ACE) (kininase II) to produce angiotensin II, a vasoconstrictor-effect molecule that acts on the vascular endothelium through angiotensin I and II receptors (Figure 1).

The physiological response of the organism subjected to angiotensin II comprises: increased norepinephrine release and decreased nitric oxide (NO) activity of the endothelium, leading to an increase in peripheral and renal vasoconstriction. As a result, there is an increase in cardiac preload and afterload. Angiotensin II has additional effects by promoting the release of aldosterone from the adrenal cortex, which activates the sodium–potassium ATPase pump in

nephrons resulting in sodium retention, potassium depletion and volume expansion. In addition, angiotensin II has effects on inflammation resulting in three specific reactions: (1) local release of inflammatory signals with activation of macrophages and monocytes, (2) alteration of the tissue plasminogen activator/plasminogen inhibitor type I ratio leading to increased thrombotic activity and (3) stimulation of smooth muscle cells leading to hypertrophy and cardiac remodelling.

The effects of ACE inhibitors result from the inhibition of the ACE (kininase II) to ultimately influence both the renin–angiotensin system and the degradation of the bradykinin (BK) metabolism. The initial effects of ACE inhibitors lead to an almost complete blockage of angiotensin II production from angiotensin I and in turn vasodilation. However, this inhibition is of short duration and the level of angiotensin II returns to its initial level due to alternative pathways [1].

ACE is also the first peptidase incriminated in the degradation of BK (Figure 2) The kininogen precursor is cleaved by kallikrein to produce the active forms of

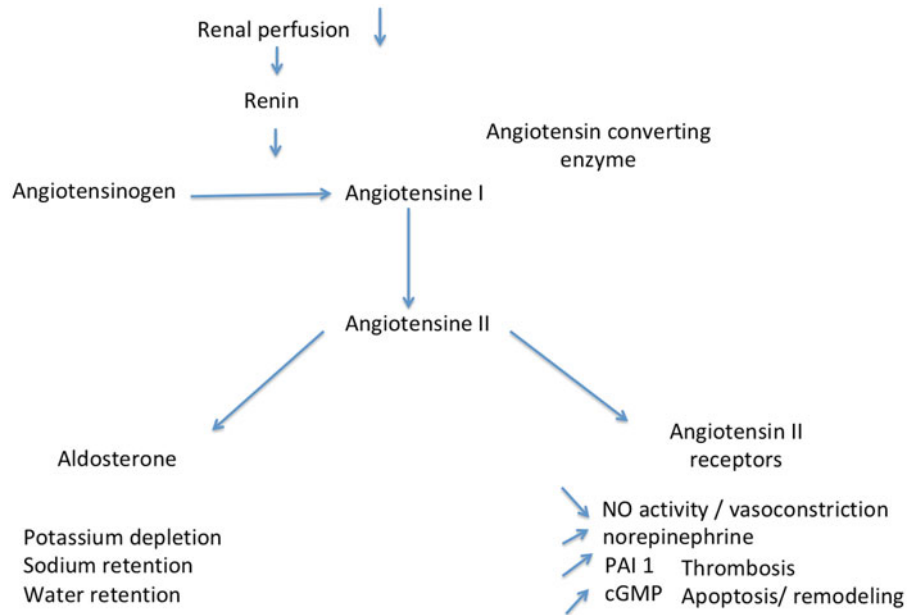


Figure 1. The renin-angiotensin-aldosterone (RAA) pathway.

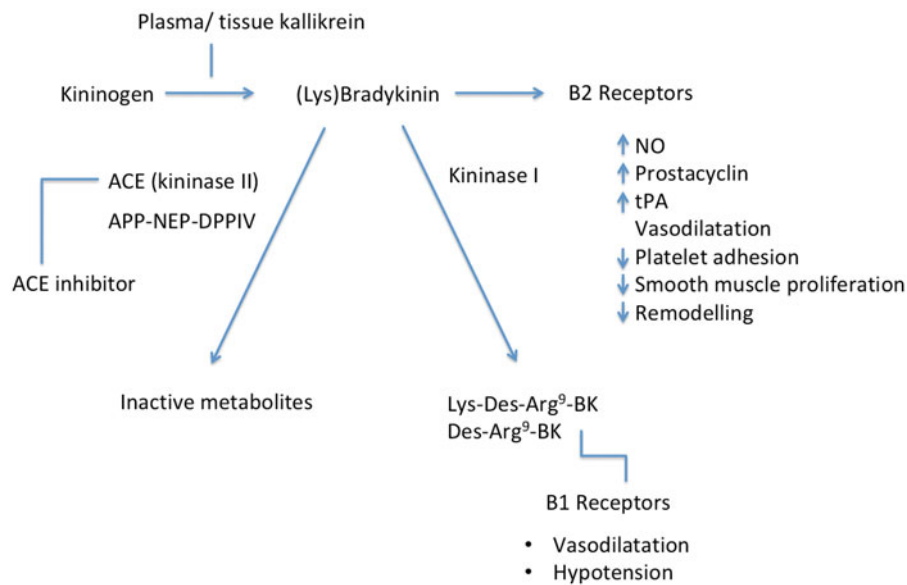


Figure 2. ACE is the first peptidase incriminated in the degradation of BK.

BK that have very short half-lives as a result of their degradation by the ACE, neutral endopeptidase (NEP), aminopeptidase P (APP) and by dipeptidyl peptidase IV (DPPIV) [2]. ACE inhibitor prolongs the half-life of BK, which produces its effects through the stimulation of G-protein receptors, BK2 receptors and results in NO-related vasodilatation and hypotension which is also due to the prostaglandin formation linked to the release of prostacyclin [3]. The effects of ACE inhibitor on cardiac remodelling are related to decreased collagen accumulation and smooth muscle

cell proliferation secondary to stimulation of BK2 receptors [4].

Angioedema and ACE: physio-patho-metabolic mechanism

Angioedema (AE) was first described by Quincke in 1882. AE induced by ACE inhibitors is very rare but represents the leading cause of drug-induced AE. Its incidence ranges between 0.1% and 0.7%. The incidence rate seems to be constant over the subsequent

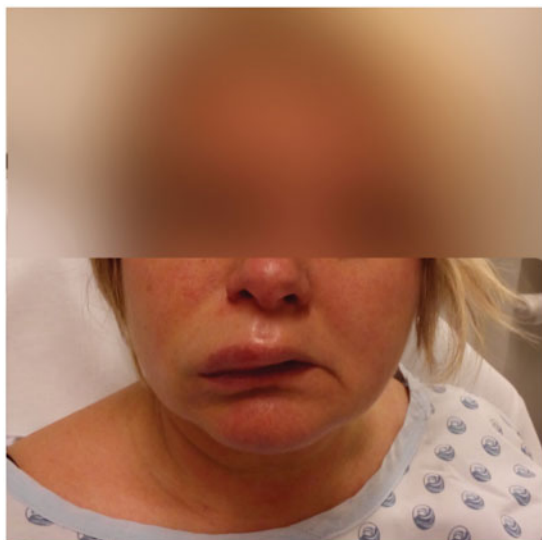


Figure 3. Facial angioedema.

5 years [5]. Most AEs are described as mild and resolve within 48–72 hours after discontinuation of therapy. It is characterised by localised oedema of the dermis and subcutaneous tissues, non-pruritic, linked to rapid plasma extravasation from post-capillary venules [6]. Others reactions under ACE are described in the retrospective study of Banerji et al., cough is the most commonly reported (5.3%), followed by AE (0.7%), hyperkalaemia (0.4%) and bronchospasm/wheezing (0.3%). These symptoms are mainly described after the first month of treatment by ACE but should be considered even after years of uneventful ACE inhibitor therapy. Inherited AE (autosomal dominant disease) is very rare and most often secondary to a C1 esterase inhibitor (C1 INH) deficiency. Acquired AE (AAE) refers to all AEs that occur unrelated to any family history, including AE induced by several drugs or environmental agents (food or inhaled allergens, tobacco, trauma, etc...), idiopathic forms and deficiencies acquired in C1 INH (of paraneoplastic or autoimmune origin). Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, radiological contrast agents, oestrogens, DPPIV inhibitors and some psychotropic drugs have been associated with AE. However, ACE inhibitors appear to be the most frequent cause, accounting for 30–60% of AE cases [7–9]. Alternative use of angiotensin II antagonists should also be avoided due to the risk of AE with this type of ACE-related treatment. While the exact mechanism of AEs related to ACE inhibitors is not completely understood, it appears that ACE inhibitors block the degradation of bradykinin (BK) and substance P by kininase II (ACE). In addition, an active metabolite of bradykinin (Des-Arg9-BK) is catalysed by kininase I and its degradation

is controlled in part by the conversion enzyme. These molecules have been associated with increased plasma extravasation associated with ACE inhibitors [10–12]. BK is a local intermediary of vasodilatation and vascular permeability, mainly of the post-capillary venules. The substance P increases vascular permeability through its action on NK1 receptors [13]. An impairment of cytokine degradation with an increase in the level of C-reactive protein (CRP) has also been implicated as being the primary mechanism of AE under the use of ACE inhibitor drugs. Patients with ACE-related AE have a significant increase in CRP compared with patients with AE from other causes, and the CRP level normalises within 3–6 months after the EA episode and the withdrawal of ACE inhibitor [14]. CRP can increase the formation of kinin through its stimulation of interleukin-6 [15]. Given the multiple pathways described in the development of AE under ACE inhibitor, many genes, sometimes with minor effects, are probably incriminated. The main more specific genes are those that encode the peptidases involved in BK degradation, substance P, Des-Arg9-BK and the receptors of these peptides.

AE-related epidemiological factors under ACE inhibitor

Ethnic differences in the kallikrein–kinin system and increased sensitivity to bradykinin may also explain an increased risk of AE. Black or Hispanic patients appear to be more at risk [16, 17]. A meta-analysis revealed a risk nearly three times higher in these patients [18]. The female sex and age above 65 years were also observed as risk factors [19, 20]. For environmental factors, drugs, tobacco and certain foods or other allergic triggers are reported as promoting factors [21]. In addition, some traumatic situations (facial impairment, anaesthesia, intubation, transplantation, cardiac catheterization) have been incriminated in the occurrence of these AEs. Tissue aggression would increase the activity of certain receptors and the level of des-Arg9-BK [22, 23].

It has been observed that patients previously stable under ACE inhibitor can most likely develop AE soon after the addition of another medication, including the combination of aspirin or NSAIDs with ACE inhibitor which has proved to be the most common cause, accounting for close to 50% of all AE cases related to ACE inhibitors [5, 24]. A typical event was observed in a 46-year-old female who presented to the emergency department of the University Hospital Centre of Liège with sudden onset facial oedema and respiratory difficulties that had been rapidly progressing for one hour. The

Risk factors for AE under ACE inhibitors

Genetic	Environmental	Genetic/environmental
<ul style="list-style-type: none"> • Black race • C1INH deficiency • Female gender 	<ul style="list-style-type: none"> • Trauma • Smoking • Aspirin • NSAIDS • Immunosuppressive agents • Lidocaine • DPPIV inhibitors 	<ul style="list-style-type: none"> • Age >65 • History of cough under ACE inhibitor • History of drug rash • Seasonal allergies • Food/contact allergies

Figure 4. Risk factors for AE under ACE inhibitors.

patient had been successfully treated for 3 years with indapamide (2.5 mg daily) and perindopril (5 mg daily) for systemic hypertension. The diagnosis of a symptom corresponding to an AE and related to a side effect of the ACE inhibitor drug was rapidly posed. The outcome was favourable after discontinuation of the ACE inhibitor drug and intravenous administration of corticosteroids (methylprednisolone 125 mg) (Figure 3).

However, the mechanisms for such a case remain unclear. NSAIDs can cause AE by either immunological (IgE-mediated) or nonimmunological reactions, where the latter are due to increased leukotriene production from inhibition of cyclooxygenase [6]. In the case of the patient, the consumption of acetyl salicylic acid to treat a headache the day before the episode was certainly the trigger of AE. Other medications (immunosuppressive drugs, lidocaine) have also been described as potential triggers. The increase in DPPIV activity associated with hyperglycaemia would explain the lower incidence of AE in diabetic patients [25]. However, another study found an increased severity of AE events in case of diabetes and obesity [26] (Figure 4).

Clinical presentation and discussion

The areas most commonly affected by oedema are: tongue, lips, pharynx and nasal mucosa with associated respiratory or digestive symptoms (<5%) [27]. AE is not painful and there is usually no pruritus. The occurrence of this side effect of ACE inhibitor usage occurs most frequently within hours of taking the drug and sometimes after a few days of administration. A large retrospective study found that two-thirds of episodes occur within the first 3 months of therapy [28]. Prior reports described symptoms of AE occurring within the first weeks of treatment [29]. However, very late onset cases, sometimes after several years of stable therapy, have also been described [30, 31]. One patient out of two will have another episode of AE during the following five years if the ACE inhibitor is not withdrawn [32, 33].

Some patients can sometimes present an AE in spite of stopping the ACE inhibitor, most often secondary to another factor favouring the side effect [34, 35].

The use of antihistamines, corticosteroids and epinephrine is sometimes necessary and facilitates the resolution of more severe episodes. In cases of HAE, more specific treatments (inhibitor of C1 esterase) can be administered.

Conclusion

Recurring AE events remain frequent prior to proper diagnosis with a study showing that 50% of cases had multiple episodes before the ACE inhibitor is incriminated and withdrawn. Identification of this side effect and its relationship to ACE inhibitor treatment are both related to the timeframe between the onset of medication and the occurrence of AE but also to the lack of knowledge about this nosological entity due to the rarity of this reaction [36, 37]. This side effect of ACE inhibitors, sometimes very late and rare, deserves to be reiterated. Paramedics should especially be made aware of these side effects from ACE inhibitors in order to help in the rapid and adequate management of these patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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