CASE REPORT

Life-threatening ACE inhibitor-induced angio-oedema successfully treated with icatibant: a bradykinin receptor antagonist

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SUMMARY

We present a case of a 75-year-old woman treated with an ACE inhibitor, who presented with angio-oedema of the tongue and had difficulty speaking. No symptoms of anaphylaxis or urticaria were present. The patient was treated intravenously with antihistamine and glucocorticoid in combination with adrenaline inhalations. After 6 h in the hospital the swelling progressed, and the patient was admitted to the intensive care unit and treated with one injection of icatibant—a bradykinin receptor antagonist. The patient reported subjective relief after 20–30 min and the swelling resolved within 2 h. Although the angio-oedema was potentially life threatening, the patient avoided intubation and mechanical ventilation. ACE inhibitor-induced angio-oedema is most likely caused by an accumulation of bradykinin and substance P. Consequently, a bradykinin receptor antagonist is the rational treatment of choice instead of antiallergic medications, which have no proven efficacy in this condition.

BACKGROUND

Angio-oedema is a swelling of subdermis and/or submucosa with a predilection for the head and neck region including larynx. However, the extremities, abdomen and genitals can also be affected. Total obstruction of the airway, which causes asphyxia and a potential lethal outcome, has been described in patients suffering from the most severe types of angio-oedema. These comprise the genetic disease hereditary angio-oedema (HAE), acquired angio-oedema due to ACE inhibitors (ACEi) and angio-oedema due to anaphylaxis.¹ The risk of intubation or tracheostomy to maintain a safe airway in patients with angio-oedema is considerable and the aim of the initial pharmacological treatment is to avoid this scenario.² One-third of angio-oedema patients presenting to emergency departments have a drug history including ACEi and as many as one-third of them are admitted to an in-patient ward or intensive care unit (ICU).^{3–5} The incidence of patients in Denmark treated with ACEi has doubled within the past decade and was estimated to be 8.2% of the total population in 2009, with a relative risk of 7.7 for developing angio-oedema.^{4–5} As this condition is a non-histaminergic response (and thus not allergic/anaphylactic) mediated by accumulation of the potent vasodilators bradykinin and substance P, clinicians should be familiar with the benefit of using a

bradykinin B2 receptor antagonist to relieve ACEi-induced angio-oedema ([figure 1](#)). Patients who experience ACEi-induced angio-oedema should permanently avoid ACEi as a pharmaceutical group, and the contraindication must be noted in the medical record and the patient should be handed a written note. We present a case of potentially lethal ACEi-induced angio-oedema successfully treated with icatibant—a bradykinin receptor B2 antagonist.

CASE PRESENTATION

A 75-year-old Caucasian woman presented with swelling of the tongue and mouth. The patient had a history of hypertension and was treated with an ACEi (Lisinopril) during the past 3 years. She also had asthma, which was treated with standard asthma inhalers. No medical allergies were known.

The patient remembered two previous episodes of swelling of the tongue before the present angio-oedema episode. One was 8 months earlier with milder swelling of the tongue, where she experienced spontaneous recovery. The other episode was 6 months prior to this admission, where she received medical treatment for tongue swelling in the local emergency room (ER). The patient was treated with antihistamine and glucocorticoid with no further follow-up. Lisinopril was not stopped. The latest event is described in detail in this report ([figure 2](#)).

The symptoms started spontaneously in the morning with unilateral swelling of the tongue. The patient sought help at her general practitioner's office, where an ambulance was immediately called to admit the patient to the hospital. In the ER, treatment with intramuscular antihistamine and intravenous glucocorticoid together with adrenaline inhalations was initiated. The swelling did not respond to therapy 6 h after arrival, and numerous adrenaline inhalations and repeated corticosteroid infusions later, the swelling progressed and the patient experienced further difficulties in speaking and breathing. She was then transferred to the ICU for further observation and potential airway management. Vital values were stable and oxygenation was acceptable with a saturation of 97% with 2 L of oxygen supplement. The main aim of further treatment was to secure the airway patency and—if possible—avoid intubation and mechanical ventilation. Because the antiallergic treatment did not resolve the symptoms, the attending anaesthesiologist suspected a non-histaminergic

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Figure 1 The pathophysiology of bradykinin-mediated angio-oedema.

angio-oedema and administered the bradykinin receptor B2 antagonist, icatibant, 30 mg, subcutaneously. Within 20–30 min the patient reported subjective relief of the symptoms, and after 2 h the angio-oedema had subsided, and speech and breathing had normalised; she was discharged after only 5 h in the ICU. After 2 more days of observation in the medical ward and no recurrence of symptoms, the patient was finally discharged from the hospital. Lisinopril was discontinued and the patient was informed not to take an ACEi again.

INVESTIGATIONS

White cell counts were slightly elevated at 13.9 (reference interval 3.5 – 8.8) $\times 10^9/L$, most likely due to corticosteroid treatment, and C reactive protein was 28 (RI <10 mg/L). Urine test indicated an asymptomatic urinary tract infection and oral piv-mecillinam was initiated. No bradykinin-detecting blood analysis is currently available in Denmark (or the rest of Europe), but that would have been very relevant. A normal serum tryptase could have been used as a diagnostic clue (no mast cell activation), but the test was not performed.

DIFFERENTIAL DIAGNOSIS

- Hereditary angio-oedema (HAE): Hereditary genetic disorder with insufficient levels or function of complement C1 inhibitor. Most patients become symptomatic in childhood and experience recurrent angio-oedema episodes. Around 75% of patients have a family history of HAE.
- Acquired complement C1 inhibitor deficiency (AAE): Autoantibodies to or increased catabolism of complement C1 inhibitor cause acquired angio-oedema. The condition is most often seen with monoclonal B-cell disorders.

- Allergic/anaphylactic angio-oedema due to mast cell degranulation and histamine release. Often accompanied by urticaria, itching, hypotension, abdominal pain and bronchospasm. Antihistamine, glucocorticoid and adrenaline would relieve these symptoms because of the histaminergic origin of this condition. Serum tryptase will be elevated in this condition, but not in bradykinin-induced angio-oedema.

TREATMENT

The suspicion of ACEi-induced angio-oedema was strong due to the medical history and the fact that no known allergens were involved. No skin rash or itching presented, and the standard treatment with antihistamine and glucocorticoid was insufficient. This supported the suspicion of a non-histaminergic origin. The administration of icatibant 30 mg subcutaneously caused rapid remission of symptoms. No adverse reactions were observed apart from a localised tenderness at the injection site.

OUTCOME AND FOLLOW-UP

The patient experienced no return of angio-oedema. A contraindication against ACEi was noted in the chart.

DISCUSSION

ACEi-induced angio-oedema resembles HAE pathophysiologically, as ACEi-induced angio-oedema is mediated by accumulation of the vasoactive agent bradykinin originating from the contact activation system. Therefore, pharmacological agents used in the treatment of HAE have proved efficient in ACEi-induced angio-oedema.^{1 5–9}

An increasing number of patients receive ACEi today and up to 20% experience side effects, most often dry cough; but angio-oedema occurs in as many as 2.2%.^{10–13} Side effects can occur many years after initiation of ACEi, and this may mask the relationship between the drug intake and swelling episodes.¹⁴ The main aim of diagnosing and treating ACEi angio-oedema is to avoid airway obstruction and morbidity related to intubation or tracheostomy. Bas *et al* described eight cases of patients with ACEi-induced angio-oedema treated with icatibant compared with a historical cohort of 47 patients treated with standard therapy, of whom three received tracheostomy and two were intubated. Mean time to symptom relief in the icatibant arm was 50.6 min and complete relief, 4.4 h, which is similar to our case presentation.⁶ A later multicentre, double-blind, double-dummy, randomised phase 2 study showed the same efficacy in terms of complete relief within 8 h in the icatibant arm versus 27 h in the antihistamine and corticosteroid arm.¹⁵

Figure 2 Description of the symptoms and treatment of a patient with ACE inhibitor-induced angio-oedema (ER, emergency room; GP, general practitioner; ICU, intensive care unit; i.m., intramuscular; i.v., intravenous).

There is another perspective to the use of icatibant. The price of one dose is substantial and the cost–benefit ratio of avoiding treatment in the ICU with the morbidity related to intubation or tracheostomy is to be evaluated in each individual case. At the present time, the cost of icatibant 30 mg in Denmark equals the cost of half a day spent in the ICU (€1980). However, in terms of the patient's perspective, avoiding instrumentation of the airway is favourable.

Considering the price of icatibant, the alternative use of complement C1-esterase inhibitor concentrate is a possibility. A number of cases of ACEi-induced angio-oedema have been successfully treated with complement C1-esterase inhibitor concentrate, which in Denmark is approximately 25% cheaper per dose compared to icatibant (ie, Berinert 1000 U=€1400).^{8 9 16 17}

In conclusion, because of the increasing number of prescriptions of ACEi, clinicians should be aware of the non-histaminergic origin of the angio-oedema induced by this pharmaceutical, and consider the possibility of treating the condition with bradykinin receptor B2 inhibitor or complement C1-esterase inhibitor concentrate along with close clinical observation of the airway.

Learning points

- ▶ Angio-oedema is divided into histaminergic and non-histaminergic.
- ▶ Suspect ACE inhibitor (ACEi)-induced angio-oedema when the medical history involves an ACEi.
- ▶ Non-histaminergic angio-oedema is often bradykinin induced and should be treated with complement C1-esterase inhibitor concentrate or bradykinin receptor B2 antagonist icatibant (Firazyr).
- ▶ Remember to withdraw the ACEi, note the contraindication in the medical record and warn the patient against future use.

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