CASE REPORT

ACE-inhibitor induced angio-oedema treated with complement C1-inhibitor concentrate

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SUMMARY

ACE-inhibitor is an antihypertensive drug which is increasingly used to treat a wide range of medical conditions. A known adverse reaction is angio-oedema of the head and neck, which can become fatal when the upper airway is involved, causing asphyxia. We present a Caucasian man, who developed severe angio-oedema of the tongue and floor of the mouth. He was successfully treated with complement C1-concentrate causing the swelling to regress within 20 min. This treatment option can be an effective alternative to bradykinin antagonists, which might not be available in the emergency room, or more invasive measures like intubation or emergency airway puncture.

BACKGROUND

Angio-oedema due to ACE-inhibitor (ACEi) is a condition with increasing incidence over the past decade caused by a rapid growth of its use,[1 2] partly related to a broadening of the indications making this class of drug first choice in a wide range of medical conditions.[3] ACEi-related angio-oedema has a predilection for the head and neck area and can be fatal due to obstruction of the airway causing asphyxiation.[4] The pathophysiology is not fully understood, but a local accumulation of the vasoactive molecules bradykinin and substance P has been shown to be the main cause.[5–7] In this case we present a patient with severe angio-oedema of the tongue, soft palate, uvula and floor of the mouth who was successfully treated with complement C1-inhibitor concentrate, a drug licensed for treatment of hereditary angio-oedema.[8 9] We want to raise the awareness to this possible alternative to intubation or cricothyrotomy and monitoring in an intensive care unit.

CASE PRESENTATION

A 63-year-old Caucasian man was acutely transported from the emergency room of a local hospital to our department of otorhinolaryngology, because of severe angio-oedema of the tongue and soft palate. The patient awoke in the morning with a swollen tongue and the symptoms worsened over the next couple of hours, which caused him to contact his local emergency room. He was treated with drugs for anaphylaxis (epinephrine, antihistamine and corticosteroid), but the angio-oedema progressed and also began to involve the soft palate and uvula. Before the ambulance left the local hospital a telephone consult was made between the anaesthesiologist and the on-call otolaryngologist, and it was unravelled that the patient was taking an ACEi, which raised a suspicion of ACEi-related angio-oedema.[8 10] Based on this suspicion the otolaryngologist considered acute treatment with complement C1-inhibitor concentrate or icatibant. In the ambulance the patient was escorted by an anaesthesiologist and a nurse trained in airway management, since his airway was deemed compromised. When the patient arrived 20 min later 1000 units (11 units/kg) of Berinert (complement C1-inhibitor concentrate) had already been administered intravenously over 10 min and the angio-oedema had regressed significantly. Vital signs were normal aside from slightly elevated blood pressure and a pulse of 95, both ascribed to anxiety. Glasgow Coma Scale score was 15. The objective otorhinolaryngological assessment showed moderate angio-oedema of the right side of the tongue and the floor of the mouth. Speech was impaired by the swelling of the tongue, but respiration was uninhibited and fibreoptic assessment of the hypopharynx and larynx showed no pathology. The patient had no other symptoms besides angio-oedema (ie, urticaria, hypotension, bronchospasm and vomiting) and anaphylaxis was excluded. The patient was known to have hypertension and hypercholesterolaemia and suffered in the past from depression. At the time of admission he received an ACEi, a statin, acetylsalicylic acid and a serotonine norepinephrine reuptake inhibitor. He had been taking the ACEi for 6–7 years and had no history of angio-oedema. Two hours after arrival and treatment with C1-inhibitor concentrate, the angio-oedema had resolved. The patient was observed in the inpatient department for 24 h and was thoroughly instructed never to take ACEi again since the adverse reaction is class-specific.

INVESTIGATIONS

No other investigations than objective assessment was deemed relevant for this patient.

DIFFERENTIAL DIAGNOSIS

- *Hereditary angio-oedema*: Usually there would be a history of previous episodes of angio-oedema in these patients. A diagnosis of hereditary angio-oedema is made on the basis of complement C1-inhibitor level and activity and complement C4 and complement C1q.[11]
- *Acquired angio-oedema*: This entity can have a similar clinical picture and usually presents itself in people after their fourth decade. The angio-oedema arises due to a decreased level of complement C1-inhibitor due to increased catabolism most often related to malignant disease.[12]

- *Allergic angio-oedema*: Usually other symptoms would be present, that is, urticaria, hypotension, bronchospasm and vomiting. The patient would swiftly respond to epinephrine, antihistamine and corticosteroids.[13]

TREATMENT

We treated this patient with complement C1-inhibitor (Berinert) due to other reports on the successful outcome for patients with angio-oedema due to ACEi.[14] Complement C1-inhibitor is indicated in patients suffering from hereditary angio-oedema to treat acute episodes, but can be used 'off-label' in patients with angio-oedema due to ACEi.[15]

The effect ensued within 20 min from injection and after 2 hours the swelling had resolved. Intubation and admission to the intensive care unit, which is usually instituted in patients with severe angio-oedema involving the airways, was thus avoided.

The probable mechanism of complement C1-inhibitor concentrate is an inhibition of the production of bradykinin, which gives other enzymes a better chance to degrade the excess bradykinin. The fact that complement C1-inhibitor concentrate is working on angio-oedema due to ACEi suggests that the accumulation of bradykinin, at least in part, is derived from the contact system as tissue kallikrein, the alternative source of bradykinin, is not inhibited by complement C1-inhibitor.

OUTCOME AND FOLLOW-UP

The patient has had no further episodes of angio-oedema, and had no side-effects from the complement C1-inhibitor concentrate.

DISCUSSION

Very few cases have been reported of ACEi-induced angio-oedema treated with C1-inhibitor concentrate.[14 16] Usually angio-oedema due to ACEi causes the patient to be admitted either to the inpatient department (airway not compromised) or the intensive care unit with or without intubation or cricothyrotomy (compromised airway).[17 18] Other reports describe successful outcome when treating ACEi-induced angio-oedema with fresh frozen plasma or the bradykinin receptor antagonist icatibant.[19–21] Fresh frozen plasma should only be used when other options are unavailable due to the risk of transmission of infectious diseases and a theoretical risk of exacerbating the angio-oedema in a manner similar to that of hereditary angio-oedema.[22]

Learning points

- Angio-oedema due to ACE-inhibitor is a potential life-threatening condition with increased incidence.
- Symptoms are believed to be mediated by local accumulation of bradykinin and substance P.
- The condition is treatable using complement C1-inhibitor concentrate or the bradykinin receptor antagonist icatibant.
- Hereditary and acquired angio-oedema has a similar clinical picture and these diagnoses should be considered.
- The adverse drug reaction is class-specific.

Contributors ERR was responsible for the idea, treatment of patient, writing the manuscript, finding the references and approval of final manuscript. AB was responsible for the idea, critical revision, finding references, approval of final manuscript.

Competing interests ERR has performed one lecture sponsored by MSD Norway regarding angio-oedema. AB has been involved in scientific and educational work sponsored by CSL Behring, Jerini/Shire, Swedish Orphan Biovitrum and Viropharma.

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