Novel treatment (new drug/intervention; established drug/procedure in new situation)

Icatibant and ACE inhibitor angioedema

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Summary

Icatibant is a selective bradykinin 2 receptor antagonist, currently licensed for use in hereditary angioedema. Its benefit in ACE inhibitor angioedema is yet to be fully established. A handful of preliminary case reports suggest that it may be of benefit in reducing both symptom severity and possible hospital or intensive care admission. To date, there are no case reports of the usage of Icatibant in the emergency department in the UK. Here we report our experience of Icatibant in a 62-year-old gentleman presenting with severe oral, pharyngeal and laryngeal oedema while on an ACE inhibitor.

BACKGROUND

Worldwide, up to 40 million people are currently on an ACE inhibitor. With the most common side effects being; persistent dry cough, symptomatic hypotension, angioedema and renal dysfunction.¹

ACE inhibitor angioedema accounts for up to 30% of all accident and emergency admissions with angioedema, or 0.7 per 10 000 A+E visit;² a significant work load of potentially very unwell patients, needing urgent medical attention for the emergency department.

Randomised, double-blind trials have been conducted showing 30 mg of subcutaneous Icatibant to be effective in reducing both the length and severity of symptoms of patients with hereditary angioedema. Minimal side effects have been reported.³

Angioedema due to ACE inhibitors commonly occurs within the first few weeks of treatment but has been reported up to 7 years after the start of this medication. In 1999, Gibbs *et al*⁴ described 70% of angioedema cases occurring within 4 weeks of starting ACE inhibitor treatment, as well as found three cases where angioedema occurred greater than 24 months after the start of an ACE inhibitor. Wemze described angioedema following ACE inhibitor prescription up to 7 years later. It was also noted that late-onset (>6 months following ACE induction) angioedema appears to be on the increase.⁵

To date, no other case reports on the use of Icatibant in a UK hospital can be found.

CASE PRESENTATION

In March 2012, a 62-year-old gentleman was admitted to the accident and emergency department with sudden onset airway compromise, drooling and obvious tongue swelling. Treatment with hydrocortisone and chlorphenamine while en route in the ambulance made no clinical improvement.

His medical history included hypertension, previous cerebrovascular accident (CVA) and back pain. He was on a number of long-term medications including ramipril, which was started 5 years previously in 2007 following his CVA. He had no previous history of allergy, asthma,

hayfever, eczema or drug reactions. There was no family history suggestive of hereditary angioedema.

INVESTIGATIONS

On admission to the resuscitation room, flexible laryngoscopy was performed and showed an oedematous tongue base and epiglottis but clearly visible vocal cords.

Owing to the severity of his symptoms and impending airway obstruction, minimal further investigations were carried out.

Routine bloods at the time of cannulation showed no evidence of any infective process, nor was he pyrexial. There were no symptoms of signs suggestive of anaphylaxis, for example, wheeze, abdominal pain, vomiting or rash. C1 esterase levels were requested, these were within normal limits.

DIFFERENTIAL DIAGNOSIS

Acute onset upper airway compromise can be caused by a number of different pathologies including allergy and infection.

There was no evidence of an infective process occurring in the history or on routine blood tests (full blood count and C reactive protein). He was afebrile at admission. No exudate was visualised on flexible nasendoscopy.

Anaphylaxis is an increasingly common medical phenomenon. This gentleman gave no history of asthma, eczema or previous allergic reaction. Symptoms of anaphylaxis vary considerably; however, there was no evidence of rash, vomiting, abdominal pain or wheeze.

Oral allergy syndrome or pollen food allergy is a well-documented condition presenting with oral or upper airway swelling but no systemic symptoms. Typically, it occurs in hayfever sufferers soon after the ingestion of raw fruit and vegetables, due to cross reactivity between the remnants of tree or weed pollen found in certain fruit and vegetables. Our patient gave no history of hayfever or the ingestion of raw fruit and vegetables prior to the onset of his symptoms.

Foreign body inhalation may present as acute upper airway obstruction, more commonly seen in children. A clear history normally leads to a prompt diagnosis.

Malignancy of the upper aerodigestive tract can first present as upper airway obstruction. Thankfully, this is rare and thorough history taking commonly reveals other symptoms, for example, throat and ear pain, progressive swallowing problems, weight loss and palpable lymphadenopathy.

ACE inhibitor-induced angioedema is a phenomenon of acute onset, often occurring months to years after the medication has been started. The mechanism is bradykinin-mediated activation of the vascular B2 receptors, causing vascular permeability, as in hereditary angioedema, but, unlike anaphylaxis which is mast cell mediated.

TREATMENT

Owing to the severity of our gentleman's airway oedema and no improvement with steroids, epinephrine nebulisers and antihistamines, he was given a single dose of Icatibant 30 mg subcutaneously. No intramuscular epinephrine was given, as it was felt, on balance, he was more likely to have ACE inhibitor-induced angioedema rather than anaphylaxis.

Despite a good view of the vocal cords when nasendoscopy was initially performed, the patient's symptoms deteriorated despite maximal medical therapy, with progressive upper airway oedema, drooling and an inability to speak.

It was felt appropriate to intubate the patient as complete airway obstruction was a significant and imminent possibility.

Intubation using an awake fiberoptic technique with a remifentanyl infusion was performed by a senior consultant anaesthetist. At this time, the vocal cords were not clearly visualised and progressive oedema was seen.

He was transferred to the intensive care unit where he remained intubated and ventilated for 48 h.

OUTCOME AND FOLLOW-UP

Following admission to the intensive care unit, the gentleman remained intubated for 48 h before he was successfully extubated.

No immediate benefit was seen with 30 mg of subcutaneous Icatibant. Owing to the minimal benefits seen, a decision was made not to give him a further dose.

Intravenous steroids we continued, along with intravenous fluids. Slow resolution of the angioedema was seen over 48 h and he was successfully extubated.

Following this he was discharged to the ward where he made a full recovery and was discharged home a few days later, with no oedema, hoarseness of voice or problems eating and drinking.

Advice was given to the patient, his general practitioner and documented in his medical records on the need for lifelong avoidance of ACE inhibitors.

DISCUSSION

To date, a randomised, double-blind trial has been conducted showing 30 mg of subcutaneous Icatibant to be effective in reducing the length and severity of symptoms in patients with hereditary angioedema.³ Hereditary angioedema is thought to occur through the same pathways as ACE inhibitor angioedema; a bradykinin-mediated activation of B2 vascular receptors. This is a different

pathway to anaphylaxis which is mast cell mediated and treated with subcutaneous epinephrine.

Further case reports have shown Icatibant to be beneficial in the management of other symptoms of hereditary and acquired angioedema, for example, the resolution of oedema in cutaneous and abdominal sites;⁶⁻⁹ however, extra-oral sites are not commonly involved in ACE inhibitor-induced angioedema.

No randomised trials have been carried out on the benefit of Icatibant in the management of ACE inhibitor-induced angioedema, but as it occurs following the same pathway as hereditary angioedema, Icatibant has been used as a treatment in this condition, with only one case series being available.

The case series showed a mean improvement in symptoms within 50.6 min and a complete resolution of symptoms within 4.4 h. No patient receiving Icatibant required intubation or tracheostomy and the only side effect was a self-limiting reaction around the injection site, which has previously been well documented.¹⁰

Despite no patient in the above case series requiring intubation or tracheostomy, asphyxia secondary to ACE inhibitors has been well documented in the literature,¹¹ as has intensive care admissions and emergency tracheostomies.¹² The clinical condition of the patient should always dictate the level of medical treatment received. Although, Icatibant shows promising results in the above small case series, clinicians should always be alert to the need for timely treatment escalation.

In our gentleman, with ACE inhibitor-induced angioedema, there was no obvious rapid resolution of symptoms. This highlights the important point that, although Icatibant is clearly a very useful medication and an advance in the management of angioedema, it does not always provide a rapid and complete resolution of symptoms caused by angioedema.

This is of high importance; as such patients will need continuous monitoring and timely conventional management with alternative treatments, for example, steroids, intramuscular epinephrine and securing of the airway.

The gentleman's slow but continual improvement in intensive care is most likely due to the supportive care, intravenous steroids, discontinuation of ramipril and the natural course of angioedema.

Chi *et al* discussed the management of ACE inhibitor-induced angioedema prior to the introduction of Icatibant. They found that within 48 h, the majority of patients with ACE inhibitor induced angioedema had resolution of their symptoms when treated with oxygen, intravenous steroids and antihistamines and discontinuation of the ACE inhibitors.¹³ This is in keeping with our patient presentation and progression.

The one available case series, described above found complete resolution of symptoms within 4.4 h when patients were treated with Icatibant. There was no such significant improvement in our patient's angioedema within 4-5 h, suggesting any benefit of Icatibant was limited.

Further case reports of Icatibant and its use within the emergency department setting are necessary in order to evaluate its benefit. To date, no other case reports are available from a UK accident and emergency department.

Learning points

- ▶ ACE inhibitor angioedema can occur months to years after the medication has been started.
- ▶ Consider Icatibant in such patients as it may reduce symptoms and preventing hospital or intensive care admission.
- ▶ Only minor side effects (dizziness, headache, rash, erythema and injection site reaction) are documented following Icatibant.
- ▶ Further case reports and series are needed in order to fully establish its role in the treatment of ACE inhibitor-induced angioedema.

Competing interests None.

Patient consent Obtained.

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