CASE REPORT

Using a bradykinin blocker in ACE inhibitor-associated angioedema in the emergency department

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SUMMARY

We report two cases of ACE inhibitor-associated angioedema and critical airway compromise, where the use of a selective bradykinin 2 receptor blocker resulted in rapid symptom resolution and prevented intubation to protect the airway.

BACKGROUND

Developments in the treatment of hereditary angioedema have resulted in the production of a selective bradykinin blocker that is marketed as an orphan drug for this condition. Recent publications suggest that ACE inhibitors can cause an elevation of bradykinin owing to its role in deactivation of bradykinin. A case series suggested that it might be effective in ACE inhibitor induced angioedema; however, an inconclusive case report, within *BMJ* case reports, called for further case reports.

The blocker was available within the department for logistical reasons and so was offered as a potential substitute to intubation in two cases.

As a result of our positive experience with this medication, we wish to submit these cases to inform debate.

CASE PRESENTATION**Case 1**

A man in his 70s presented to the emergency department (ED) having woken at 1:00 with a swollen tongue and neck, loss of speech and a feeling of imminent upper airway obstruction. This was the first episode of such a symptom.

With a history of angina, chronic obstructive pulmonary disease, hypertension and prostate cancer with recent hormone therapy, he had taken a first dose of ramipril the previous evening.

Assessment on presentation, at 05:00, revealed normal observations other than a mild tachycardia at 115.

Examination revealed swelling of the submental area, lower lip and tongue, resulting in tongue protrusion and drooling.

Case 2

An 86-year-old lady woke at 2:30 with swelling of her tongue. Her medications were unchanged and she had been on nicorandil for several years. She had suffered frequent minor lip and facial swellings over recent weeks, since an attack of discitis. She presented to the ED at 04:05.

She had a history of congestive cardiac failure, renal impairment, asthma, B12 deficiency and recent lumbar discitis.

Observations were normal, but examination revealed drooling, difficulty in speaking and marked submental and tongue swelling with protrusion.

INVESTIGATIONS

Routine blood tests in both cases were unremarkable.

In both cases, ear-nose-throat (ENT) assessment was sought and at 9 h after onset of symptoms, both underwent transnasal flexible laryngoscopy revealing severe supraglottic oedema and narrowing of the entrance to the larynx to such an extent that urgent intubation for airway protection was considered necessary with ENT support for a surgical airway if intubation failed.

DIFFERENTIAL DIAGNOSIS

The initial management of airway occlusion because of swelling is normally based on the belief that the condition is due to an allergic reaction triggered by an allergen via immunoglobulin-mediated mast cell release of histamine.

Allergy related swelling is associated with itching, superficial urticarial lesions, often a generalised rash, hypotension and wheeze. There is normally a rapid development of symptoms after an identifiable trigger. This pattern of response is normally responsive to antihistamines and epinephrine in the short term, and steroids over the longer term.

Angioedema presents with localised deep dermal or subcutaneous swellings, normally with a burning sensation or deep itch. The timescale is elongated, although there is typically a sudden acceleration phase described in cases of hereditary angioedema (HAE), lasting about 40 min, when airway occlusion can occur, and there is not normally an identifiable trigger, although the use of oestrogens, non-steroidal anti-inflammatory drugs (NSAIDs) and ACE inhibitors is seen commonly among HAE and non-HAE patients. Antihistamines and steroids do not have an effect and epinephrine is only mildly effective. Resolution usually takes over 24 h and can be up to 5 days.

TREATMENT**Case 1**

Intravenous chlorpheniramine and steroids were given shortly after arrival without apparent effect.

Case 2

Intravenous chlorpheniramine was given, followed by tranexamic acid and nebulised epinephrine. Following epinephrine, she suffered tachycardia

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and some mild chest pain which settled with oxygen and showed no ischaemic change on ECG.

Shortly after endoscopy, both patients were offered 'off licence' icatibant based on the belief that this was angioedema and that there was a logical reason to believe that the mediator was bradykinin.

Both patients accepted this treatment on that basis.

A 30 mg dose of icatibant from a preloaded syringe was injected subcutaneously into the abdominal wall at approximately 10 h after the onset of the attack.

30 min and case 2 patient's tongue had settled to only half the tongue being swollen.

By 4 h both were symptom-free, and able to converse and eat and drink normally.

During this period they were observed within the high-dependency unit. Both were discharged having had their ACE medication discontinued, and at the time of obtaining consent for this report, 1 month later, had suffered no further swelling events.

Neither patient has been investigated for C1 esterase levels given the late presentation and apparent link to ACEI.

OUTCOME AND FOLLOW-UP

At the time of injection, both patients felt that their symptoms were still getting worse.

At 20 min after injection, both were able to close their mouths and swallow saliva. Case 1 had a return of his voice at

DISCUSSION

The initial management of airway occlusion owing to swelling is routinely taught to include epinephrine, antihistamine and steroids; however, this will only work if the mediator is histamine.

Figure 1 Role of bradykinin pathway in angioedema.

Angioedema presents as attacks of intermittent, self-limiting, non-pruritic, subcutaneous or submucosal swelling, involving the skin, respiratory and gastrointestinal tracts, lasting between 1 and 5 days. The morbidity of an attack varies with the site, cutaneous attacks, often described as burning or a deep itch, causing facial disfigurement, or difficulty with driving or operating machinery when the hands are involved. Segmental gastrointestinal angioedema is very painful, is associated with vomiting and can lead to ascites and hypovolaemic shock and so can be mistaken for a surgical emergency.^{1–3}

Laryngeal attacks may be fatal, with the risk of sudden escalation to asphyxiation, and reported lifetime death rates between 10% and 30%, and with 25% of HAE families reporting a death caused by laryngeal oedema.³

Angioedema is differentiated from allergy (mediated by histamine) by its localised and often unilateral pattern at onset, depth of swelling and discomfort, rather than itch. It is also insensitive to antihistamine and steroids and only marginally sensitive to epinephrine.^{1 3 4}

The first biomarker linked to the condition was plasma C1 esterase inhibitor dysfunction which led to the definition of HAE (with an incidence of 1:50 000)⁵ that responds to inhibitor replacement.^{1 3 5}

There is a new hereditary group, currently being described, more common in, but not limited to, women, which seems to be oestrogen-driven, 20% of whom have been shown to have an abnormality of factor XII that results in increased sensitivity to contact autoactivation.⁵

The traditional management of HAE includes maintenance therapy to try and reduce attack frequency using tranexamic acid and androgenic steroids, both of which are only partially effective and in the case of steroids, cause significant side effects that reduce compliance. More recently, there has been an international consensus statement on the management of HAE advising the routine use of replacement C1 esterase and the use of a bradykinin blocker in an acute situation.

The syndrome is also seen to be triggered by drug sensitivities, particularly, ACE inhibitor⁶ where Angioedema is seen in about 1% of treated patients. Other triggers are thrombolytics, salicylates and NSAIDs and it is also seen in patients, associated with lymphoproliferative disorders.⁷

Recent work has shown that during all HAE types and ACE inhibitors-associated attacks, there is a sustained rise in the mediator bradykinin (figure 1).^{4 8}

In the traditional HAE group, the abnormal inhibitor allows uncontrolled, sustained rises in the mediator, accelerated by factor XII. In the newly described hereditary type, the factor XII seems more sensitive and more potent when the patient's contact system is stimulated.

Fundamentally, the syndrome appears to be an abnormality of the contact system of the complement cascade, that part triggered by viral and bacterial cell walls, and unfolded proteins such as Bence Jones and Amyloid in vivo and kaolin and other particles in laboratory studies.⁸

The enzyme ACE is known to be instrumental in the degradation of bradykinin at the B2 receptor on the cell membrane thereby terminating its action, hence the ACE Inhibitor extends the life of bradykinin in otherwise triggered patients.^{9 10}

This new evidence of bradykinin as the mediator of angioedema^{2 11} has led to the production of Icatibant, a B2-receptor blocker^{3 5 12} which has gained a licence for use in HAE types 1 and 2.¹³

This drug, till date, has had a low side-effect profile other than local erythema around the subcutaneous injection site causing some patients to complain of itch on injection. Neither of our patients complained of discomfort when asked.

Our case report increases the published experience of ACE inhibitors-associated angioedema adding to the previous cases reported in BMJ case reports including the one report where icatibant had only a marginal effect, although the details of timing of treatment are not clear, and a previous report of the successful use of fresh frozen plasma in cases.

Learning points

- ▶ ACE inhibitor angioedema can be severe enough to require intubation.
- ▶ Angioedema does not resolve with traditional treatments for allergy-associated airway compromise.
- ▶ Recent evidence suggests that the mediator for the syndrome in these cases is bradykinin, not histamine,
- ▶ Clinical history can be used to differentiate the two mediators.
- ▶ A selective bradykinin blocker currently licensed as an orphan drug for hereditary angioedema worked effectively to reverse severe airway compromise in two patients, thus preventing intubation and care on an intensive care unit.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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