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

Fresh frozen plasma in the treatment of ACE inhibitor-induced angioedema

Michael Stewart, Ray McGlone

Emergency Department, Royal Lancaster Infirmary, Lancaster, UK

Correspondence to Dr Michael Stewart, michael@gradmedic.org

Summary

Angioedema secondary to the use of ACE-inhibitors is well recognised, with a high rate of airway intervention required. Several treatments have been described, but little evidence exists for any of them. We describe the successful use of fresh frozen plasma in two cases.

BACKGROUND

ACE inhibitors are commonly prescribed for primary and secondary prevention of cardiovascular disease. ACE inhibitor-induced angioedema is a rare complication, but can be life threatening.¹ At present, there are few case reports addressing the treatment of these patients, and no controlled trials. This small case series adds significantly to the published literature on treatment of these patients.

CASE PRESENTATION

Patient 1

A 52-year-old man presented at 14:21 with a history of facial swelling first noted on waking at 08:00. It had gradually been worsening since then. He had a complex medical history including hypertension, chronic kidney disease, asthma and previously coiled berry aneurysms. He was noted to be taking lisinopril and had been for several years, but had no known allergies. He described two previous episodes of tongue swelling that had settled spontaneously and had not been reported or investigated.

On examination he had marked swelling of the tongue, but was still able to speak and swallow normally.

Patient 2

A 79-year-old man presented at 19:05 with tongue swelling since 18:30. He had been taking ramipril for 8 months for control of essential hypertension. He was on no other regular medication, and was otherwise healthy. He described a similar episode of tongue swelling while in Spain 4 weeks earlier, which had been treated with steroids and antihistamines. This had resolved fully over the course of several hours. He had been well in the intervening time.

On examination he had significant swelling of the tongue, predominantly right sided. He was able to swallow saliva and had no speech changes. The swelling was noted to be progressively increasing in severity while in the department.

DIFFERENTIAL DIAGNOSIS

Angioedema:

- ▶ ACE inhibitor induced
- ▶ Allergic

- ▶ Pseudoallergic
- ▶ Hereditary.

TREATMENT

Patient 1

200 mg of intravenous hydrocortisone was given soon after arrival. Two units of fresh frozen plasma (FFP) were then administered, starting at 17:05. The infusion was complete by 19:30. He was admitted to the high dependency unit (HDU) for observation, but did not require intubation.

Patient 2

Two units of FFP were infused at 21:05 and 21:25, respectively, after the swelling continued to progress. He was also admitted to HDU, and again did not require intubation.

OUTCOME AND FOLLOW-UP

Patient 1

Facial swelling was noted to be resolving by the time the second unit of FFP was complete. The patient made a full recovery and was discharged home the following day. He has not had any further episodes of angioedema since stopping lisinopril.

Patient 2

His angioedema rapidly improved with infusion of FFP, and he elected to self-discharge from intensive care unit at 01:45 after full resolution of symptoms. He has also not had further episodes since stopping ramipril.

DISCUSSION

Unlike the histamine pathway involved in allergic angioedema, ACE-induced angioedema is mediated by bradykinin.² In addition to the widely recognised role in the renin-angiotensin-aldosterone system, ACE also degrades bradykinin into inactive peptides. ACE inhibitors can block this degradation pathway, leading to increased levels of bradykinin in the circulation. As bradykinin is a potent vasodilator and also increases vascular permeability, it is a recognised cause of angioedema.

The reaction is most common in the first week after starting an ACE inhibitor, but can occur at any later time,³ even after years of uneventful therapy, and without any identifiable trigger factor. The angioedema will frequently resolve spontaneously. These two observations suggest that another, currently unidentified, factor is involved in the development of angioedema in patients treated with ACE inhibitors. The potential for spontaneous regression also complicates observational studies of therapies, as many will recover despite, not because of, the treatment received.

This possibility also exists in the patients we describe. In addition, one received intravenous hydrocortisone in addition to FFP. Observing the time course of the condition, in both cases there was a gradual increase in severity until treatment with FFP was started, followed by relatively rapid improvement once they were receiving the infusion. While case reports cannot prove the causal link between the intervention and clinical improvement, we feel it is highly suggestive in these cases.

Previous studies have suggested airway intervention (intubation or tracheostomy) is required in 11% of patients with ACE-induced angioedema.⁴

As the histamine pathway is not involved, antihistamines are of limited benefit, and epinephrine and glucocorticoids have been found to have little effect.^{1–5} Three previously described therapies are C1 esterase inhibitor, bradykinin receptor antagonists (icatibant) and FFP.

C1 esterase inhibitor blocks the pathways from kininogen and plasma kallikrein to bradykinin to reduced bradykinin formation.⁶

Icatibant is a competitive antagonist at the B2 bradykinin receptor, acting to ameliorate the effects of bradykinin until it is metabolised.⁷

FFP contains C1 esterase inhibitor, but also kininase II which acts to break down bradykinin into non-functional peptides, and thus reduces formation and enhances metabolism of bradykinin.

The use of FFP has been described previously in single case reports, where angioedema has been documented to have resolved within hours of starting FFP infusion, in cases resistant to treatment with epinephrine, steroids and antihistamines.^{8–9} FFP has also been used to treat other (non-ACE induced) forms of bradykinin-mediated angioedema.^{10–11}

Compared to other blood products, FFP is associated with few adverse reactions (0.17 allergic-type reactions per 100 000 units given, no cases of haemolysis, infection or transfusion-related acute lung injury in 2010).¹²

Based on the proposed mechanism of ACE-induced angioedema, FFP should be effective in treating the condition. There are no trials of the therapy, and the limited number of previous case reports are reinforced by the two cases described here.

Learning points

- ▶ ACE inhibitor-induced angioedema carries a high risk of airway compromise and life-threatening illness.
- ▶ No treatment has been firmly established in a controlled trial.
- ▶ Fresh frozen plasma has been used previously to reverse the effects of ACE inhibitor-induced angioedema; the two cases described here add to the evidence that it can be an effective treatment.

Competing interests None.

Patient consent Obtained.

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