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Fresh-frozen plasma as a treatment for life-threatening ACE-inhibitor angioedema

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To the editor:

Angiotensin-converting enzyme inhibitors (ACE-I) are widely prescribed drugs that are effective in many conditions, including hypertension and cardiac failure.

ACE-I related angioedema is a well-recognized side effect; in rare instances, it can be life-threatening. The estimated incidence of angioedema during ACE-I treatment is 0.1% to 0.2%. Typically it occurs early, 60% of cases commencing during the first week of treatment.¹ The angioedema most frequently affects the head and neck, but visceral edema also occurs. Agostoni et al² noted ACE-I-related angioedema in 39 (17%) of 231 patients with angioedema without urticaria attending an outpatient clinic.

A 75-year-old Afro-Caribbean man presented with marked tongue swelling developing over several hours. The patient's history included ischemic heart disease and hypertension, for which he was taking lisinopril. There was no history or family history of angioedema. On examination, we found no facial or lip swelling, and normal vocal cords were visualized at nasoendoscopy.

Treatment consisted of intravenous chlorpheniramine and hydrocortisone and intramuscular epinephrine. Despite these measures, the patient's tongue swelling continued to progress, necessitating intubation and ventilation. Further epinephrine and corticosteroid had no effect, and he continued to require respiratory support. Given his lack of response to therapy over a period of 24 hours, he then received a trial of fresh-frozen plasma (FFP). Within 2 hours of the beginning of an intravenous infusion of 4 units FFP, there was a dramatic improvement in his tongue swelling. After further improvement, he was extubated and began to breathe spontaneously.

Investigations revealed a normal C1 esterase inhibitor level and a normal total IgE. Since that time, he has discontinued his ACE-I and there have been no further episodes of angioedema.

ACE-I are effective in a wide variety of serious medical conditions, and the recognition and management of ACE-I angioedema is thus important to consider. ACE-I can cause localized angioedema—in our case, the tongue alone was affected. Kyrmizakis et al³ reported isolated tongue angioedema in 2 patients receiving ACE-I, though both patients improved with epinephrine and corticosteroids. Racial origin might also be relevant. Our patient was of Afro-Caribbean extraction, and the incidence of ACE-I angioedema is higher in black patients.¹ It has been postulated that the increased incidence in African Americans might relate to their lower endogenous bradykinin levels and hence to a higher sensitivity to increases in bradykinin caused by ACE-I therapy.⁴

The standard approach to management consists of discontinuation of the ACE-I in all patients who develop ACE-I angioedema. Treatment of the underlying condition should be continued with an appropriate drug of a different class. Most cases are at the mild end of the spectrum, causing minor head and/or neck angioedema. Treatment of mild episodes involves short-term use of antihistamines and/or corticosteroids, though there are no controlled studies confirming their efficacy.^{1,5} More severe forms, causing upper respiratory obstruction, are less common. In such life-threatening episodes, epinephrine and maintenance of airway patency—eg, by early intubation or cricothyroidotomy—might be necessary.¹ Our experience suggests that FFP might also be of benefit in unresponsive cases of severe ACE-I angioedema. We noted a dramatic improvement in our patient, whose condition had been resistant to antihistamines, corticosteroids, and epinephrine. Administration of FFP is associated with risks, including allergic reactions, circulatory overload, and potential viral transmission, but these must be balanced against the danger to the patient from life-threatening angioedema.⁶ Hauser et al⁷ reported a patient with acquired C1 esterase inhibitor deficiency and paraproteinemia who developed pulmonary edema after receiving FFP.

Bradykinin is thought to be the major mediator of ACE-I angioedema as well as of hereditary angioedema. The main inactivator of bradykinin is kininase II, which is identical with

angiotensin-converting enzyme. High levels of bradykinin have been reported during attacks of ACE-I angioedema⁸. Blais et al⁹ reported that 50% of their patients with ACE-I angioedema had an enzyme defect in the metabolism of des-Arg9-bradykinin, resulting in its accumulation.

FFP has been shown to be of benefit in hereditary angioedema, in which its main action is to replace the deficient C1 esterase inhibitor. In the treatment of ACE-I angioedema, FFP might provide further kininase II, which breaks down accumulated bradykinin, and might also provide functional enzyme in those patients with enzyme defects in bradykinin metabolism.**1/8/121313**

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