Successful treatment of ACE inhibitor-induced angioedema with icatibant, a bradykinin B2 receptor antagonist

ACE inhibi tors are commonly used in the management of hypertension, and of cardiac and renal disease. Angioedema occurs in 0.1%–0.68% of patients, more commonly within 90 days of the introduction of ACE inhibitors, although it can occur later.

After cessation of medication, patients can develop recurrent angioedema, typically within the first month but sometimes several months later. ACE inhibitors account for 30% of ED presentations with angioedema, and although most are discharged directly from ED, 11% require ICU management for an average of 2.9 days at considerable cost.

ACE inhibitor-induced angioedema is mediated by bradykinin, and empiric therapy with adrenaline, steroids and antihistamines targeted at histaminergic responses is largely ineffective. Bradykinins bind B2Rs and induce potent vasodilation. ACE (also known as kininase II) promotes bradykinin degradation, so ACE inhibition prolongs the half-life of bradykinin.

Dipeptidyl peptidase-4 (DPP-IV) is a secondary enzyme in bradykinin breakdown. Concomitant use of ACE inhibitors and DPP-IV inhibitors such as vildagliptin, used to treat type 2 diabetes, or DPP-IV modulation in the context of immunosuppression after transplant, puts patients at increased risk of angioedema. The use of other medications that can cause urticaria and angioedema, such as aspirin or non-steroidal anti-inflammatory drugs, is associated with increased risk of angioedema among patients taking ACE inhibitors.

Various epidemiological factors are associated with increased incidence of angioedema with ACE inhibitor use. Patients of African descent have a threefold higher risk compared with those of European descent, while women have a 50% higher risk than men. Patients aged over 65 years, smokers and those subject to trauma, particularly involving the airway, are also at increased risk. ACE inhibitor use in heart failure is associated with higher risk compared with its use in hypertension and coronary artery disease, probably due to higher baseline levels of bradykinin. Our patient, apart from being a female smoker, did not have any additional risk factors. Factors predisposing to ACE inhibitor-induced angioedema are summarised in the Box.

Icatibant, a synthetic decapeptide competitive inhibitor of B2R, is a treatment for hereditary angioedema listed on the Pharmaceutical Benefits Scheme. It is administered as a single 30 mg subcutaneous injection at a cost of about $2500 per dose.

Given the bradykinin-driven mechanism of ACE inhibitor-induced angioedema, icatibant offers an appealing therapeutic option. There are no randomised controlled trials examining the use of icatibant in ACE-inhibitor induced angioedema. However, a small case series compared eight patients...
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with ACE inhibitor-induced upper-airway angioedema treated with icatibant with 47 historical controls treated with steroids and antihistamines.\(^7\) Patients receiving icatibant avoided intubation and improved in a mean of 51 minutes, with complete relief at 4.4 hours, compared with 33 hours in the historical controls.\(^7\)

To our knowledge, our case is the first documenting a positive response to icatibant in a patient with an immi-

iently threatened airway. Icatibant is expensive, but the incidence of ACE inhibitor-induced angioedema requir-
ing intubation is fortunately low. Review of local data from Fremantle Hospital, a 450-bed tertiary acute care hospital with 58 000 ED presentations annually, identified

120 presentations with angioedema from 2011 to 2013. Of these presentations, seven had severe airway-threatening ACE inhibitor-induced angioedema requiring critical care admission for 1–3 days at an estimated cost of $5000 per day. Two patients were intubated at considerable cost in terms of theatre time, equipment and involve-
mant of multiple teams (Dr Yusuf Nagree, Emergency Physician and Academic, Fremantle Hospital, personal communication). Our patient was admitted to the ICU for only 2 hours for observation after receiving icatibant, and avoided intubation.

We propose that icatibant may be an effective treatment for severe airway-threatening ACE inhibitor-induced angioedema, a condition that can be associated with significant morbidity and is typically refractory to other therapies. However, further randomised controlled trial data are needed to confirm efficacy, and evaluation of cost-effectiveness is required before consideration of its use in routine clinical practice.

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References are available online at www.mja.com.au.