CLINICAL PRACTICE

Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril

Clint Cupido, Brian Rayner

Angiotensin-converting enzyme (ACE) inhibitors are widely used and effective drugs in the treatment of a broad range of cardiovascular and renal disorders. The recent death of a patient as a result of angio-oedema related to enalapril use prompted us to review all admission records of the intensive care units (ICUs) of Victoria, G F Jooste, New Somerset and Groote Schuur hospitals.

The index patient was a 54-year-old married man with 2 children. There was an unconfirmed report of drug allergy in his history. He had longstanding hypertension, and had received enalapril and atenolol until 2002, when he stopped medication of his own accord. In 2004 he visited his general practitioner and his blood pressure was found to be elevated at 170/100 mmHg. He was commenced on a low-dose thiazide diuretic, but after failing to respond he was referred to the local clinic in 2005. He was commenced on atenolol and enalapril, and at 05h00 the next morning after his first dose of enalapril he developed swollen lips and tongue. He was rushed to the local emergency unit and was assessed as being in anaphylactic shock. He was given intramuscular adrenaline, hydrocortisone and promethazine. After 2 hours the patient developed stridor and the doctor was unable to intubate him. He had 2 cardiopulmonary arrests, and with assistance from a senior colleague, an emergency cricothyroidotomy was performed. The patient was transferred to Victoria Hospital, and a diagnosis of angio-oedema associated with enalapril was made. The patient showed signs of severe anoxic brain injury and his Glasgow coma scale was 4T. A tracheostomy was performed, but there was no neurological recovery and the patient died 2 weeks later.

After reviewing the records of all admission to the ICUs in our academic region we found a further 9 cases of angio-oedema requiring intubation related to enalapril. Two of these patients died of anoxic brain damage, and the remainder made uneventful recoveries. A further case of angio-oedema requiring intubation was seen by one of the authors (BR) at Conradie Hospital. The patient recovered without sequelae.

Clint Cupido is currently a medical registrar in the Department of Medicine and Brian Rayner Head of the Division of Hypertension, Groote Schuur Hospital and University of Cape Town.

Corresponding author: *B Rayner (brian.rayner@uct.ac.za)*

One death was reported from the emergency unit of Groote Schuur Hospital, viz. a patient who died after failed intubation and delayed cricothyroidotomy (Craig Arendse – personal communication). All patients were either black or coloured, and all patients were receiving enalapril 5 mg or 10 mg twice daily. Anecdotally non-life-threatening angio-oedema is frequently seen in the hypertension and nephrology clinics at Groote Schuur Hospital.

Although angio-oedema is a well-recognised complication of ACE inhibitor use, only isolated reports of death have appeared in the literature.[1,2] However in a study from Columbus, Ohio,[3] 7 deaths, all of African Americans, were reported in an autopsy series from 1998 to 2000. The OCTAVE study[4] was a large prospective study examining the prevalence of angio-oedema related to the ACE inhibitor enalapril. It involved 12 557 patients, including 1 200 blacks, with an overall prevalence rate of 0.68%. None of the cases was severe enough to require intubation and no deaths were reported. Increased risk for angio-oedema was found in blacks (odds ratio (OR) 2.88), in patients with a history of drug rash (OR 3.78) or seasonal allergy (OR 1.70), and in patients over the age of 65 years (OR 1.65). Most cases occurred during the first months of therapy, but it is well recognised that angio-oedema can occur more than 10 years after initiation of treatment.

Our reports of death and life-threatening angio-oedema out of keeping with trends in other parts of the world are of major concern to us. ACE inhibitors are essential and widely used drugs for the treatment of hypertension, cardiac disease and kidney disease. Several issues need to be addressed. The OCTAVE study showed that although not uncommon, angio-oedema was seldom severe. This probably does not represent the real world situation. In that study, because of health professional and patient education and awareness, angio-oedema was probably recognised early and therapy was terminated immediately. However, in clinical practice angio-oedema is frequently missed, misdiagnosed or attributed to other causes, and with continuation of treatment attacks become worse and even life threatening.[5,6] Furthermore, in a country where the majority of patients are black the nearly 3-fold increased prevalence in this population is of significant concern. It is also recognised that this complication is related to genetic polymorphism (C-2399A variant in XPNPEP2), the frequency of which is unknown in the South African population.[7]

We are also concerned that the angio-oedema we have reported is related to enalapril, but this is only anecdotal evidence of association. Reports in the literature[8] suggest that angio-oedema may occur with one ACE inhibitor and not another. In our experience angio-oedema was uncommon in our clinics when perindopril or ramipril was the ACE inhibitor coded for the Western Cape. A prospective study is needed to determine the exact prevalence in South Africa, particularly among blacks, but it is important that health professionals report severe cases to the Medicines Control Council.

In the interim there is a need for doctors, nurses and pharmacists to inform patients of this complication, and to report any suspicious symptoms and signs to their doctor immediately. We believe that a 'black box warning' should appear on all ACE inhibitor medication. ACE inhibitors are contraindicated in patients with C1-esterase deficiency and a history of angio-oedema. Health professionals should provide extra counselling to black patients, elderly persons, and patients with a history of drug or seasonal allergy before prescribing an ACE inhibitor. It is unfortunate that angio-oedema is not listed as a compelling contraindication to ACE inhibitors in the latest South African Hypertension Guideline.[9] Emergency units need to be equipped and have personnel trained to perform cricothyroidotomy. Steroids and antihistamines are ineffective as the mechanism of the reaction is not allergic but related to bradykinin.[6] Adrenaline may be helpful but if there is suspicion of airway compromise endotracheal intubation should be performed immediately and if unsuccessful an emergency cricothyroidotomy or tracheostomy should be performed.

Lastly, the Health Department of the Western Cape needs to give consideration to coding an alternative ACE inhibitor.

This report has also been sent to the Medicines Control Council of South Africa.

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