

# Fatal angioedema induced by angiotensin conversion enzyme (ACE) inhibitors

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ACE inhibitors are often prescribed in the treatment of hypertension, heart failure and kidney disease. These drugs are on the Essential Drugs List, and are therefore used at primary to tertiary health care levels in South Africa. Angioedema is considered a rare, but potentially fatal side-effect of this agent, with a reported incidence of 0.1–0.2% worldwide.<sup>1</sup> Its incidence in the South African population is, however, unknown.

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## Case reports

We report on two cases that were recently referred for medico-legal autopsy at our mortuary, in which the cause of death was ascertained to be “asphyxia due to angioedema of the tongue and upper airway, due to ACE inhibitor therapy”.

The subjects were on treatment with the ACE inhibitors, enalapril and perindopril, for approximately 10 months and 4 years, respectively. No personal or family history of allergies or angioedema existed in either case. Swelling of the tongue and upper airways developed insidiously over a period of 8 hours in both cases. In one case the subject died en route to hospital, and in the other case the subject arrived at hospital but died after a failed endotracheal intubation and delay in placement of a tracheostomy. Other causes of angioedema were excluded in both cases by reviewing the past medical history, the presentation, and the macro- and microscopic autopsy findings, including total IgE and mast cell tryptase levels (these were within normal reference values).

The cause of death in both cases was classified as unnatural.

## Discussion

The use of ACE inhibitors is increasing and this could possibly lead to a concomitant increase in the incidence of ACE inhibitor-induced angioedema<sup>2</sup> and other related side effects. Although the mechanism for ACE inhibitor-induced angioedema is not yet fully understood, it is postulated to be related to bradykinin and substance P metabolism.<sup>1</sup> Angioedema usually occurs most commonly during the first week of therapy, but can occur after months and even years of treatment.<sup>3</sup> Studies have shown that the Black population may be at greater risk of angioedema, with an

odds ratio of 2.88 reported.<sup>4</sup> The hypothesis is that since urinary kallikrein levels are decreased in Black patients with hypertension, they may have lower endogenous bradykinin levels, which may render them more susceptible to ACE inhibitor-induced increases in bradykinin and thus to the induction of angioedema.<sup>1</sup>

Recently, Cupido and Rayner reported on 12 cases of life-threatening angioedema, with death resulting in four of these cases.<sup>4</sup> They stressed their concern for the South African situation, where Blacks are the majority population and hence many patients will be Black, and at high risk of developing angioedema.

We strongly suspect that angioedema-associated airway obstruction due to ACE inhibitor therapy is an underdiagnosed cause of death, for the following possible reasons:

- Angioedema of the airways is erroneously attributed to an anaphylactic or anaphylactoid reaction, and the association between the condition and ACE inhibitor treatment is not readily made.
- Co-pathology often exists in these patients (e.g. heart failure, diabetes mellitus, hypertension), and the cause of death may be attributed to the co-pathology, rather than a side-effect of medication.

Clinical presentation of laryngeal oedema in a patient on ACE inhibitor treatment is an ominous sign and immediate securing of the airway (endotracheal/emergency surgical airway/tracheostomy) is mandatory as there is no other effective emergency treatment presently available<sup>3</sup> Recommended long-term treatment includes drug withdrawal, and changing to a different class of medication.<sup>1,2,3</sup>

We contend that, in the light of a probable increase in cases of death due to ACE inhibitor-induced angioedema,<sup>3</sup> patients should be informed of the possible severity of this side-effect and advised to urgently seek medical attention when symptoms develop. The use of this medication is contra-indicated in patients with a previous personal or family history of angioedema.<sup>1,5</sup>

Health workers need to recognise the existence of this life-threatening complication and appreciate the importance of the referral of suspected cases to regional medico-legal laboratories for the performance of forensic autopsies, preferably by trained forensic pathologists, to confirm or exclude the diagnosis/cause of death. In cases where drug induced angioedema is confirmed as the mechanism of death, it should subsequently be reported to the Medicines Control Council of South Africa to ensure accurate recording of the number of cases. This will assist in ascertaining the incidence of this fatal complication in the South African population, and may facilitate further research and awareness in this field.

## References

1. Vleeming W, van Amsterdam JGC, Stricker BHC, de Wildt DJ. ACE inhibitor-induced angioedema: incidence, prevention and management. *Drug Safety* 1998 Mar;18(3):171-88.
2. Kyrnizakis DE, Papadakis CE, Fountoulakis EJ, Liolios AD, Skoulas JG. Tongue angioedema after long-term use of ACE inhibitors. *Am J Otolaryngol*.1998 Nov-Dec;19(6):394-6.
3. Sarkar P, Nicholson G, Hall G. Brief review: angiotensin converting enzyme inhibitors and angioedema: anesthetic implications. *Can J Anesth* 2006;53(10):994-1003.
4. Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. *S Afr Med J* 2007;97(4):244-5.
5. Dykewicz MS. Cough and angioedema from angiotensin-converting enzyme inhibitors: new insight into mechanisms and management. *Curr Opin Allergy Clin Immunol* 2004;4:267-70.



## 4<sup>TH</sup> ANNUAL PAIN SYMPOSIUM

Department of Family Medicine, University of Pretoria  
 Endorsed by Pain SA

Saturday, 18<sup>th</sup> September 2010  
 HW Snyman Clinical Building

7:30-8:00	Registration and Coffee.	
8:00-8:55	Introduction / overview Low back pain – current concepts	<i>Prof Helgard Meyer</i> <i>Dept of Family Medicine, University of Pretoria</i>
8:55-9:25	The role of non-steroidal anti-inflammatory drugs (NSAID's) in pain management	<i>Prof Lombie Odendaal</i> <i>Dept of Anaesthesiology, Univ Orange Free State</i>
9:25-9:55	Managing acute and procedural pain in the Emergency Unit:	<i>Dr N Rauf</i> <i>Dept of Family Medicine</i>
9:55-10:20	Diabetes and other common causes of neuropathic pain	<i>Dr Johan Smuts</i> <i>Neurologist, Wilgers Hosp</i>
10:20-10:30	Discussion	
10:30-11:00	TEA + BRUNCH	
11:05-11:35	Cancer pain – the critical issues	<i>Dr Sonia Hitchcock</i> <i>Dept of Family Medicine</i>
11:35-12:05	Combination analgesics – what is their role in pain management?	<i>Prof Lombie Odendaal</i>
12:05-12:35	Osteoarthritis – current concepts	<i>Dr Elsa van Duuren</i> <i>Rheumatologist</i>
12:35-13:00	Early diagnosis of rheumatoid arthritis – the 2010 guidelines	<i>Dr Christa Visser</i> <i>Rheumatologist</i>
13:00-13:45	Ethics: End-of-Life pain management	<i>Prof David Cameron</i> <i>Dept of Family Medicine</i>
13:45-14:00	Discussion and closure	

**Accredited for 5 + 2 Ethics CPD points**

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