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Angioedema secondary to angiotensin-converting enzyme inhibitors

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Abstract
Angioedema secondary to angiotensin-converting enzyme (ACE) inhibitors is rare, but it is a side effect which is likely to be seen more frequently because of the increased use of these drugs to treat cardiac failure and hypertension. Presentation is variable and the diagnosis may go unrecognized for many months or years. The cases reported illustrate problems both in the diagnosis and management of this life-threatening condition.

Key words: Angioneurotic oedema; Kininase II; Airway obstruction; Tracheostomy

Introduction

Angioedema is a condition characterized by well-demarcated non-pitting oedema. Quinke (1882) is usually credited with the earliest account of the condition: however a series of cases was reported six years earlier (Milton, 1876). Any area of the body may be involved, but most commonly it affects the face, oral cavity, larynx and genitalia. Its importance to the otolaryngologist was highlighted in a recent review of 143 patients (Haddad *et al.*, 1985). In this series 94 per cent had head and neck symptoms and in 24 per cent this was the only region affected.

During the 1980s ACE inhibitors became available for the treatment of hypertension and congestive cardiac failure. They have rapidly developed a reputation for being effective and well tolerated, with a relatively low incidence of side effects. Angioedema, although rare, is a recognized side effect and maybe life threatening. These cases illustrate many of the difficulties associated with the diagnosis and management of angioedema secondary to ACE inhibitors.

Case reports

Case 1

A 31-year-old hypertensive black woman presented to the Accident and Emergency Department, feeling unwell with discomfort in her throat. A diagnosis of an upper respiratory tract infection was made and she was discharged with antibiotics. She returned two hours later with increasing difficulty in breathing, pain on swallowing and a muffled voice. On examination she was noted to be obese (136 kg), afebrile and stridulous. It was also noted that she had a tracheostomy scar. Blood gases indicated that she was hypercarbic (PaO_2 10.79 KPa; $PaCO_2$ 6.54 KPa; pH 7.4 on air). Her chest X-ray and full blood count were normal.

Her stridor progressed despite 400 mg of hydrocortisone i.v. and 1 mg of 1 in 1000 adrenaline i.m. She was transferred to the operating theatre where ventilation with a face mask was initially successful but endotracheal intubation failed due to gross oedema of the larynx and hypopharynx. A tracheostomy was performed through the previous incision (Figure 1). This was a technically difficult procedure because of marked venous congestion resulting in a rapid blood loss of approximately 2 l. Temporary Venturi ventilation was initiated via a 14 Fg i.v. cannula inserted into the tracheal lumen. Once haemostasis had been secured the tracheostomy was completed. On the basis of the laryngoscopic findings a diagnosis of angioedema was made. She was transferred to the intensive care unit where she made a rapid recovery and was discharged on the eighth post-operative day.

She had been admitted two months previously with a similar episode which had been diagnosed as epiglottis and treated by tracheostomy. She had made a swift and uneventful recovery and been discharged after five days. A close review of her history revealed that she had had five episodes of upper or lower lip swelling in the preceding six months. On each of these occasions the swelling had lasted for less than 12 hours, there was no associated stridor and the symptoms had always resolved spontaneously. There was no specific relation to diet, although some of the episodes followed the eating of fish or shellfish. She had a past history of childhood asthma, eczema and seasonal allergic rhinitis, and in addition she remarked that she reacted markedly to insect bites. She had been diagnosed hypertensive four years previously and was well controlled on lisinopril and hydrochlorothiazide (Carace Plus) which she had been taking regularly for 24 months.

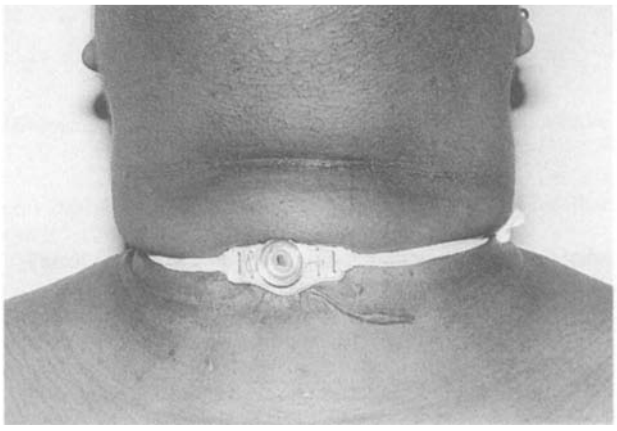

Fig. 1
Case 1 showing tracheostomy tube and previous tracheostomy scar.

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TABLE I
CAUSES OF ANGIOEDEMA

(A)	Congenital		
	Hereditary angioedema	(1)	C1 esterase inhibitor deficiency (85%)
		(2)	C1 esterase inhibitor dysfunction (15%) Normal/raised C1 low C4
(B)	Acquired		
	(1)	C1 esterase inhibitor deficiency	
		B Cell lymphoma	
		Connective tissue diseases	
		Development of C1 esterase inhibitor autoantibodies	
	(2)	Allergic type I hypersensitivity	
		Parasites, food additives, drugs	
	(3)	Chemical histamine releasers	
		Morphine, codeine, iodinated contrast media	
	(4)	Physical stimuli	
		Extremes of temperature, sunlight, vibration	
	(5)	Angiotensin converting enzyme inhibitors	
	(6)	Rare miscellaneous	
		Systemic capillary leak syndrome	
		Urticaria pigmentosa	
	(7)	Idiopathic	

Skin testing was negative for seafoods, and complement and C1 esterase inhibitor levels were normal. A diagnosis of ACE inhibitor induced angioedema was made following which her antihypertensive treatment was changed to allow for the withdrawal of the ACE inhibitor. After six months on this new regimen she has had no further episodes of angioedema.

Case 2

An 80-year-old woman presented to the Accident and Emergency Department with an eight-hour history of general malaise and a one-hour history of progressive swelling of the tongue and floor of the mouth. She did not have stridor and there were no predisposing factors for angioedema from the history elicited at that time.

She was given intravenous hydrocortisone and chlorpheniramine, but the swelling continued and her breathing became increasingly laboured. It was decided to transfer the patient to the operating theatre for intubation. She was successfully intubated using a microlarygoscopy tube guided over a bougie. Due to the continued swelling of the tongue it proved impossible to secure the tube in position and so a tracheostomy was performed. Endoscopy revealed massive oedema of the tongue, floor of mouth and vallecula. The larynx and hypopharynx were normal.

Post-operatively she was continued on intravenous hydrocortisone and chlorpheniramine, started on erythromycin and metronidazole, and transferred to the intensive care unit where she required ventilatory and inotropic support for six days. Of note in her past medical history were the facts that she had undergone an abdominal aortic aneurysm repair in 1989 and had recently had a myocardial infarct. The oedema gradually subsided over the 72 hours following tracheostomy. At this time it became known that she had been started on ramipril (Tritace) by her general practitioner for treatment of hypertension, three days prior to her admission. A provisional diagnosis of angiotensin-converting enzyme inhibitor induced angioedema was made.

She was transferred to the general medical ward on the sixth post-operative day where she continued to make a rapid recovery. She was decannulated on the 16th post-operative day and discharged home two days later having been started on alternative antihypertensive treatment.

Discussion

There are numerous causes of angioedema (Table I), however, in a recent review the single most common cause, where a cause could be identified, was ACE inhibitors (Megerian *et al.*, 1992). This side effect of ACE inhibitors was first reported in 1984 (Jett, 1984), and since then there has been a steady increase in reports. It has been estimated that the incidence of angioedema secondary to ACE inhibitors is 0.1–0.2 per cent (Slater *et al.*, 1988). The majority of these reactions begin soon after the first dose (60 per cent within the first week), symptoms are mild and relatively short lived (Slater *et al.*, 1988; Smith and Morgan, 1989).

Angioedema develops in the subcutaneous tissues and presents as a diffuse swelling. The microscopic appearance of the lesions is that of oedema with vascular dilatation and a moderate inflammatory cell infiltrate. The final mediators in this process are histamine and the vasoactive products of the complement cascade. In ACE inhibitor-induced angioedema the mechanism is thought to be biochemical rather than immunological. Activation of complement and the release of histamine from mast cells do not take place.

The cause of angioedema is usually apparent from the history. In those cases where there is doubt, measurement of C1 esterase inhibitor and C4 fraction of complement levels will confirm or exclude hereditary angioedema. Similarly skin tests and measurement of IgE levels may suggest the diagnosis of allergic angioedema.

ACE is produced in the lungs and is responsible for the conversion of angiotensin I to the powerful vasoconstrictor angiotensin II. ACE is also known as kininase II and as such is responsible for the metabolism of bradykinin, a powerful vasodilator (Figure 2). Following the administration of an ACE inhibitor, the patient's bradykinin levels are raised and its action prolonged (Regoli and Barabe, 1980). At the same time there is a reduction in plasma angiotensin II and aldosterone levels. The combined effect of these changes creates an environment in which angioedema is more likely to develop. A recent study (Anderson and de Shazo, 1990), in which the cutaneous response to intradermal bradykinin was measured in patients on ACE inhibitors, concluded that ACE inhibitor-induced angioedema may reflect a variation in the kinetics of bradykinin metabolism in susceptible patients. The response does not seem to be dose related (Roberts and Wuerz, 1991) and the reasons for individual susceptibility are not known. It should be emphasized that although the majority of reactions are seen early in the course of treatment, angioedema may develop at any time during the administration of ACE inhibitors. The longest recorded interval between start of treatment and presentation with angioedema was two years (Chin and Buchan, 1990). In addition, the more usual mild, self-limiting episodes may go unreported or unrecognized by medical staff, with the result that severe, life-threatening angioedema may present suddenly in a patient who had seemingly tolerated treatment for many months.

The management of these patients is for the most part medical; this being dependent on the severity of the symptoms. With all patients the first concern is for the airway and a nasopharyngeal airway may be all that is required as surgical intervention is

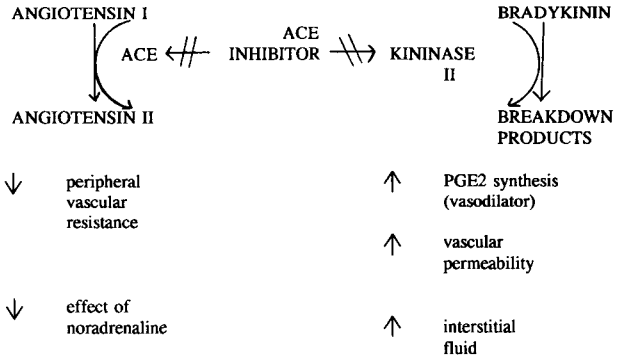

FIG. 2
Mode of action of ACE inhibitors in angioedema.

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rarely needed (Gannon and Eby, 1990). It is essential that medical staff with appropriate expertise and equipment are available should tracheostomy prove necessary. Intubation may be extremely difficult or impossible, as in the reported cases which are representative of the more severe reactions so far recognized.

Once the airway has been secured routine anti-allergic therapy should be instituted with intravenous antihistamines and steroids, together with subcutaneous adrenaline. It must be remembered that in the case of ACE inhibitor induced angioedema the mechanism is not allergic and this 'standard' regimen may not be effective. Due to the prolonged half lives of ACE inhibitors, any relief of symptoms may only be temporary. A deterioration in the patient's condition may follow, signalling the need for intervention to secure the airway via intubation or tracheostomy. This is of particular importance with the newer once daily agents such as, lisinopril, cilazapril, fosinopril and quinapril. All patients, even those who respond well to initial treatment, must be observed closely for at least 24 hours to ensure full resolution of symptoms. ACE inhibitors must be stopped, following which a full recovery may be expected.

While there is little evidence that previous episodes of angioedema due to other causes are indicative of an increased susceptibility to ACE inhibitor induced angioedema, some authors (Orfan *et al.*, 1990), have reported an association which seems unlikely to be purely coincidental. All patients starting treatment with ACE inhibitors should be made aware of the possibility of angioedema and told to inform their doctor of any lip swelling, difficulty in breathing or swallowing, or episodes of muffled voice. Where ACE inhibitors are thought to have been responsible for angioedema it is important to ensure that the patient never receives any similar drugs in the future or the angioedema will recur (Singer and MacGregor, 1986). Alternative antihypertensive treatment will be required, but it must be remembered that diuretics, calcium antagonists and beta blockers have all been reported as causing angioedema (Hedner *et al.*, 1991), though as yet no cross sensitivity has been documented.

The cases we report highlight several important aspects of ACE inhibitor induced angioedema. In *Case 1* there was a delay in onset of symptoms of 18 months followed by a six-month period of frequent, minor, self-limiting episodes of lip swelling which went unreported. It has been suggested (Orfan *et al.*, 1990), that the variability in the onset of symptoms 'may be explained by a spectrum of biochemical susceptibility, variation in dose and potency of the ACE inhibitor, and the waxing and waning of indeterminate cofactors'. In this case the failure to report the minor episodes, culminated in a life-threatening event. The length of time from initiation of treatment with ACE inhibitors and possible lack of awareness of the association between this group of drugs and angioedema led to an initial misdiagnosis of epiglottitis. This in turn resulted in a second serious event which could have been fatal. In *Case 2* an elderly patient with severe cardiovascular disease was put in a critical condition following the prescription of a routine antihypertensive.

Both cases illustrate the difficulties which may be experienced in the management of the upper airway obstruction following angioedema secondary to ACE inhibitors. This degree of severity is not the norm and tracheostomy is usually avoided due to the mild nature of the symptoms and their short duration. In spite of this it must be emphasized that it is better to err on the side of caution, complications may develop relatively late and it should not be assumed, even after an apparently good early response to subcutaneous adrenaline that intubation/tracheostomy will not be necessary.

With the increasing use of ACE inhibitors in the management of hypertension such episodes are likely to become more common. Only if there is greater awareness of angioedema as a side effect of ACE inhibitors on the part of patients, prescribing doctors, casualty staff and ENT surgeons will such episodes be managed appropriately.

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