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ACEI associated angioedema

A case study and review

Background
Angioedema is an infrequent but potentially serious adverse effect of angiotensin converting enzyme inhibitors (ACEIs).

Objective
This article describes a case of ACEI associated angioedema and reviews important clinical features of the condition.

Discussion
The mechanism of ACEI associated angioedema is not allergic (histamine mediated), but rather due to an alteration of the balance of bradykinin and other vasodilator mediators. Onset may be delayed for weeks, months or years and episodes may be recurrent. Occasionally, airway obstruction may occur. Diagnosis is from history and physical examination; there is no specific diagnostic test. In contrast to allergic angioedema, ACEI associated angioedema is generally unresponsive to corticosteroids and antihistamines, although these agents are often used by convention. In the longer term, cessation of the ACEI is necessary to reduce the risk of recurrent episodes.

Keywords: angiotensin-converting enzyme inhibitors; angioedema; drug toxicity

Case study

A woman, 78 years of age, from a psychiatric hostel, presented to a general practitioner at 8 o'clock in the morning complaining of a 'swollen tongue' associated with a tingling sensation of her lips and oral mucosa. She had not eaten that morning. Examination was unremarkable. She was reassured and sent back to the hostel.

The woman presented again 6 hours later complaining of difficulty swallowing. Her tongue was now markedly swollen and protruding from her mouth. There was no stridor, however, auscultation of her chest revealed transmitted turbulent sounds from the pharynx. The patient was still able to speak, and denied difficulty breathing or voice change. She was given 100 mg hydrocortisone and 25 mg promethazine intramuscularly. An ambulance was called and she was transferred to the emergency department of the local hospital with 'macroglossus of uncertain aetiology'.

The patient's past medical history included bipolar affective disorder, hypertension, hyperlipidaemia, ischaemic heart disease, peptic ulcer disease, primary hyperparathyroidism (treated surgically), and chronic renal impairment. She had experienced one less severe episode of tongue swelling 6 months prior, which resolved spontaneously. She did not seek a medical opinion regarding this previous episode.

The patient was taking the following regular medications:

- lithium 125 mg/day
- trifluoperazine 5 mg/day
- felodipine 10 mg/day
- trandolapril 4 mg/day
- atorvastatin 80 mg/day
- clopidogrel 75 mg/day
- pantoprazole 40 mg/day
- budesonide/eformoterol (200/6) twice daily
- alendronate 70 mg weekly
- annual influenza vaccination.

The only recent medication change had been a switch from aspirin to clopidogrel 2 months prior; all other medications had been prescribed long term with no recent dose adjustments. She had been taking trandolapril for 4 years and had no known drug allergies.

Upon arrival at the hospital her vital signs were: Glasgow Coma Scale (GCS) 15, temperature 36.7°C, blood pressure 194/100, heart rate 100 bpm, respiratory rate 18 breaths/min, and oxygen saturation 100% on 6L oxygen via a CIG mask. She had a large protruding tongue that completely obscured the view of the posterior pharynx, but

no lip or facial oedema. There was bilateral submandibular swelling, but full and pain free neck range of motion and the larynx and cricoids were readily palpable. She was nose breathing, but without stridor or signs of respiratory distress. Examination of her chest, abdomen, cardiovascular system and neurological system was unremarkable.

The patient was given four doses of intravenous adrenaline 0.3 mg, as well as intravenous hydrocortisone and ranitidine. An urgent awake fibre optic nasotracheal intubation was performed in theatre and the patient was then managed in the intensive care unit under sedation. Moderate glottic oedema was noted during intubation.

Serum biochemistry revealed acute-on-chronic renal dysfunction with a trough lithium concentration of 1.0 mmol/L (<0.8 mmol/L). Complete blood picture, coagulation studies, a vasculitic screen, thyroid function tests, complement levels, and C1 inhibitor level were all normal. A lateral cervical spine X-ray showed complete obliteration of the oropharynx by the patient's tongue, but was otherwise unremarkable (*Figure 1*). Plain chest X-ray was normal.

The tongue swelling peaked on day two of admission and had largely resolved by day six. Unfortunately by this time the patient had developed a ventilator associated pneumonia and was requiring haemodialysis for her acute renal dysfunction. On day eight, the patient suffered an ST elevation acute coronary syndrome, which was then complicated by pulmonary haemorrhage while on a therapeutic heparin infusion. In consultation with the woman's family, the decision was made to palliate the patient. She died on day nine of admission following extubation.

Discussion

This case outlines multiple characteristics that are typical for angiotensin converting enzyme inhibitor (ACEI) associated angioedema. These include the distribution and evolution of swelling, the presence of a preceding episode, and the poor response to conventional therapies. For this reason, the case serves as a useful learning tool for clinicians wishing to better understand the phenomenon. It should be noted however, that the severity of this case was unusual.

Angioedema or transient and localised swelling of the deeper layers of the dermis, subcutaneous or submucosal tissues was first described by the German physician Quincke in 1882[1] and may be due to inherited or acquired C1 inhibitor deficiency, environmental exposures (eg. bee stings) or medicines.[2] A range of medicines have been associated with angioedema, but ACEIs appear to be by far the most frequent single cause.[2] The first case of ACEI associated angioedema was described in 1980 due to captopril.[3] Initially this was thought to be a rare adverse effect;[4] however recent studies have found that approximately 30% of angioedema cases may be associated with an ACEI.[5]

Unlike allergic angioedema, which is mediated by mast cell degranulation and histamine release, ACEI associated angioedema is thought to be mediated by increased bradykinin and substance P,[6,7] as these molecules are normally metabolised by ACEIs (*Table 1*). Binding of bradykinin and substance P to their vascular receptors (BK2 and NK1, respectively) causes vasodilatation and increased vascular permeability leading to interstitial fluid accumulation.[2]

As occurred in this case, ACEI associated angioedema usually presents with localised, nonpitting oedema around the head and neck.[2] It is morphologically identical to angioedema from other causes and most commonly involves the lips, tongue, cheek and pharynx[5,8,9] (*Table 2*). As ACEI associated angioedema is due to elevated levels of vasodilators caused by ACEI inhibition,[2,6,10] rather than immune mechanisms, it occurs typically without urticaria.[2,11,12] Swelling develops over about 4–6 hours and usually takes 24–48 hours to resolve,[5,13] although it may persist for longer. As occurred in this case, there may be a history of preceding episodes, with long symptom free intervals.[14,15] Severity varies between cases and ranges from very mild to life threatening. In approximately 10% of cases airway obstruction occurs.[5,9] Fatalities from ACEI associated angioedema are extremely rare, with only isolated case reports in the literature.[5] To the authors' knowledge, the case presented here is the first documented fatality with ACEI associated angioedema caused by trandolapril.

Occasionally, angioedema of the intestine may occur.[16] This should be considered in the differential diagnosis for patients with otherwise unexplained episodic abdominal pain who are taking an ACEI.[17,18]

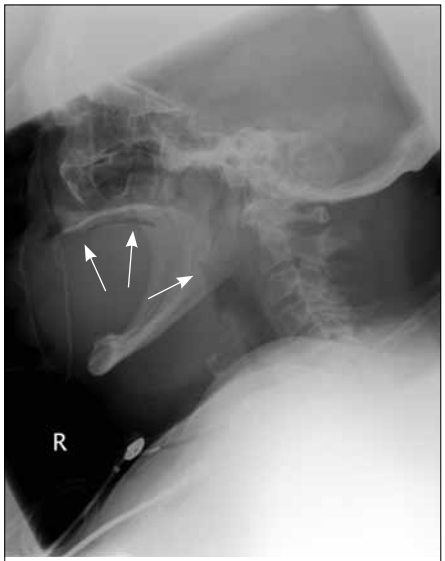

Figure 1. Lateral cervical spine X-ray showing the edentulous woman with gross tongue swelling completely filling the oropharynx. The superior-posterior margin of the tongue is indicated by arrows

Incidence

The best estimate of incidence of angioedema with ACEIs comes from the OCTAVE trial, a large 6 month study in the hypertensive population using enalapril.[19] Angioedema was specifically looked for prospectively and occurred at a rate 0.68% over 6 months in subjects on enalapril. As there is an ongoing risk of angioedema,[15] this suggests that annual incidence may be greater than 1%. Considering that ACEIs are usually continued for many years, the cumulative risk to a patient during their lifetime may be significant. Many other studies have not looked specifically for angioedema, therefore its incidence is possibly underestimated.[4,15,20]

The time lag between initiation of an ACEI and onset of ACEI associated angioedema is variable. In the late 1980s to early 1990s there were a number of publications from national drug regulatory authorities suggesting that most cases occurred early (within the first week) of commencement of an ACEI.[21,22] However, this conclusion was based on the trend shown by spontaneous case reports, which are inherently biased for reporting early onset adverse effects, as delayed effects are less likely to be recognised. More recently, audits of angioedema[15,23] suggest that late onset of ACEI associated angioedema is more common and may occur months or

Table 1. The pathophysiological basis of angioedema

	C1 inhibitor deficiency (inherited* or acquired)	Allergic angioedema	ACEI associated angioedema
Mechanism	Increased kinins due to increased production	Mast cell degranulation	Increased kinins due to decreased degradation
Urticaria	Typically absent	Present	Typically absent

* Also known as hereditary angioedema

Table 2. Frequency with which ACEI associated angioedema affects different anatomical sites

	Banerji et al, 2008[5]* (n=220)	Grant et al, 2007[9]* (n=228)
Lip	70%	54%
Tongue	52%	• Anterior tongue 40% • Base of tongue 11%
Laryngeal	59%	• Larynx 4% • Supraglottis 12% • Pharynx 9%
Cheek	20%	Data not recorded
Periorbital	10%	Data not recorded
Hand	0%	<1%
Genitals	0%	<1%

* Both these studies were retrospective chart reviews of patients presenting to emergency departments with ACEI associated angioedema. The study by Grant et al was undertaken by a department of otolaryngology head and neck surgery, which may explain the more precise characterisation of airway swelling

years after commencement of treatment.[15,23] An average duration of prior exposure of 12–14 months has been suggested.[9,11] The delayed onset of the reaction makes the association difficult to recognise.

Risk factors

Recognition of ACEI angioedema has improved over time from approximately 10–25% of cases in the early 1990s[23] to about 80% in a recent audit.[24] However, perhaps because of delayed onset, infrequent occurrence and inadequate physician awareness,[25] some cases remain unrecognised. Misdiagnosing the event as a food or drug allergy has been cited as the most common physician error resulting in failure to diagnose, and thus correctly treat, ACEI associated angioedema.[26] In the case study patient, symptoms were unlikely to be attributable to food allergy, as it would be unusual for this to present late in life, with isolated tongue swelling and without urticaria.[27] Furthermore, the patient had not eaten that day.

It is not possible to predict which patients will develop angioedema with an ACEI, although there are a number of recognised risk factors. The most significant of these are a previous episode of angioedema and African ancestry.[2,14] Smoking, older age and being female also increase risk, although less dramatically.[2,19] There is a reduced risk in people with diabetes.[7,19] Pharmacogenetic studies are currently investigating genetic factors associated with increased risk.[28] There is no clearly identifiable relationship with dose, or whether risk varies between different ACEIs.[2] Concomitant medications as a potential precipitant for ACEI associated angioedema have not been studied extensively as many studies have been retrospective case note audits of emergency department attendance where medication use is not well documented. However, a possible increased risk with aspirin, nonsteroidal anti-inflammatories and immunosuppressive agents has recently been suggested.[2] The patient presented here was not documented to be taking any of these.

The rise in drug interactions

Drug interactions may become more important in the future. The 'gliptins' are a new class of orally active hypoglycaemics. They exert their effect via inhibition of dipeptidyl peptidase 4 (DPP-4) activity, potentiating the action of 'incretins'.[29] Dipeptidyl peptidase-4 is also involved in the breakdown of other peptides such as bradykinin. As it is now appreciated that bradykinin plays a central role in the pathophysiology of ACEI associated angioedema, the relationship between the use of a gliptin, ACEI exposure, and occurrence of angioedema has been investigated as part of the premarketing surveillance of vildagliptin.[30] Among patients taking an ACEI, vildagliptin use was associated with an increased risk of angioedema (OR: 4.57, CI: 1.57–13.28), although there was no increased risk with vildagliptin alone.[30] Vildagliptin (and potentially sitagliptin) use may be associated with increased risk of angioedema among patients taking ACEIs.[30,31] Given the widespread and long term use of ACEIs, and the potential for long term use of the gliptins, awareness of the potential for this interaction is important. Importantly, the patient presented here was not documented to be taking a gliptin.

For an individual patient the question that arises is, was the angioedema due to the ACEI or was it just a chance occurrence? Epidemiological studies suggest that there is an attributable risk of 50–80%.[7,15] Attributable risk is defined here as the proportion of the incidence of angioedema in those exposed to ACEIs that can be attributed to the exposure.[7,15] That is, about 50–80% of new cases of angioedema in patients taking an ACEI would be eliminated if the ACEI was avoided.

Treatment

There have been no trials of antihistamines or corticosteroids for ACEI associated angioedema and these treatments are of unproven efficacy and may be ineffective.

Bradykinin receptor antagonists are currently in development, although these do not yet have an established role or regulatory approval for use in ACEI associated angioedema.[32] In the longer term, cessation of the ACEI is important to reduce the probability of further episodes, as with ongoing ACEI therapy, recurrent events are likely and may be more severe.[26,33,34]

Summary

- Awareness of the possibility of ACEI angioedema is essential for timely recognition of the problem.
- The mechanism of ACEI associated angioedema is not immune.
- Swelling develops gradually over several hours, a period of observation may be appropriate to ensure the airway is not threatened.
- Marked base of tongue and floor of mouth oedema are the most reliable indicators of the need for airway intervention.
- Antihistamines and corticosteroids are often used as standard therapy, however these medications are of unproven efficacy.
- In the long term, cessation of the ACEI is necessary to reduce the risk of recurrent episodes.

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