Angiotensin converting enzyme inhibitors and delayed onset, recurrent angioedema of the head and neck

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IN BRIEF

- This paper highlights a possible serious cause of facial swelling presenting in a dental context.
- Increases the reader's knowledge of an important side-effect of a common medication.
- Informs the reader of the causes and treatment of angioedema.

PRACTICE

VERIFIABLE CPD PAPER

Angiotensin converting enzyme (ACE) inhibitors are a commonly prescribed, effective medication in the treatment of hypertension and heart failure. Several side-effects of dental relevance can occur including angioedema of the lips, mouth and throat. This adverse effect is well reported and can be fatal, but it is not always recognised by clinicians, as the angioedema does not always have a clear relationship with the commencement of the medication. The cases of angioedema reported here all presented in a dental setting and highlight both the delayed onset and the chronic recurrent nature of ACE inhibitor induced angioedema.

INTRODUCTION

Angioedema describes a well-defined non-pitting oedema of the subcutaneous tissues which can affect any area of the body but frequently presents as a transient swelling of the face and mucous membranes.[1-3] The swelling is usually of acute onset and subsides after a couple of days. The clinical picture can vary and ranges from mild localised symptoms to extensive upper airway obstruction, which can be fatal.[4-6] Although allergy is sometimes the cause, many patients develop the problem for non-allergic reasons and it is a well described complication of angiotensin converting enzyme (ACE) inhibitors.[1-6]

It is estimated that 35-40 million patients worldwide are currently prescribed ACE inhibitors for treatment of hypertension, heart failure and post-myocardial infarction.[7] In this population group 0.1-0.2% are affected by angioedema.[8,9] The use of ACE inhibitors in the UK is set to increase following the publication of NICE Clinical Guideline 34, which recommends that this group of drugs should be the first choice initial pharmacological intervention for hypertension in patients under 55 years of age (excluding patients of African and Caribbean descent).[10] Where angioedema secondary to ACE inhibitors occurs, in approximately 25% of patients the first episode of angioedema will occur within one month of the commencement of taking the ACE inhibitor.[11] However, it is not uncommon for a patient to be taking ACE inhibitors for many years before any side-effects become apparent.[4,5,12] Because of this frequent lack of temporal association between commencing the ACE inhibitor and angioedema occurring, many clinicians are unaware of the causative relationship.

We here report five cases of delayed onset angioedema that have presented to us in a dental setting over the last few years, to help raise awareness of both this relationship and the chronic recurrent nature of ACE inhibitor induced angioedema.

CASE REPORTS

Case 1

An 81-year-old Caucasian male patient was referred by his general dental practitioner (GDP) with a sore mouth. The patient gave a 20 year history of recalcitrant lichen planus affecting both his skin and mouth and was currently experiencing ulceration of his right buccal mucosa and lips, finding that topical steroids were of little help. The patient also complained of frequent attacks of spontaneously swollen lips occurring over the previous two years. These attacks were of sudden onset with an increase in size over minutes subsiding over the next two days. The swellings were painless but of concern. The patient had sought the opinion of a dermatologist without success. He had a medical history of hypertension, hypercholesterolaemia, angina, gout, osteoarthritis, gastric ulcer, petit mal and impaired renal function. He had previously suffered a myocardial infarction and pulmonary embolism. In addition a carcinoma had been excised from his right ethmoid sinus. He had no known allergies. The patient's medication was lamotrigine, clopidogrel, levetiracetam, atenolol, co-proxamol, frusemide, pravastatin and ramipril. The patient had been taking the ACE inhibitor ramipril 5 mg once a day for five years.

The patient was diagnosed with angioedema secondary to ACE inhibitors and ulcerative lichen planus. With respect to the angioedema, his general medical practitioner (GMP) was contacted

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with a view to changing his ACE inhibitor to an alternative class of medication. For the treatment of his ulcerative lichen planus the patient was prescribed topical tacrolimus in orabase 0.1% and advised to apply sparingly to the affected areas of oral mucosa twice daily.

At the review appointments the patient had not experienced any further episodes of angioedema following a change of his ramipril to an angiotensin II receptor antagonist. The patient also reported that his lichen planus had dramatically cleared up following use of tacrolimus.

Case 2

A 64-year-old Caucasian male was referred by his GDP with recurrent episodes of facial swelling. The patient gave a two year history of frequent recurrent transient swelling of the right side of his tongue, lips and face. The swellings were painless, appeared over 3-4 hrs and lasted for 6-24 hrs. The patient had spent several thousand pounds on private consultations with various medical specialists in an attempt to identify the cause without success. He had no known allergies, although an allergic cause to his swelling had been postulated. He had been prescribed an antihistamine for the episodes of swelling, which had made very little difference. The patient's medical history consisted of hypertension, type II diabetes and mild asthma for which he was taking glibenclamide, aspirin, enalapril and a salbutamol inhaler to use when needed. The patient had been taking the ACE inhibitor enalapril 10 mg once a day for five years.

A diagnosis of angioedema secondary to ACE inhibitors was made. The GMP was informed of the diagnosis, and changed the patient's enalapril to an angiotensin II receptor antagonist. At review the patient reported a sustained resolution in symptoms following his medication change.

Case 3

A 78-year-old Caucasian male was referred by his GDP with a three month history of recurrent episodes of acute swellings of his tongue and throat. The swellings had a rapid onset and reached a maximum in size after an hour. On each episode the patient had needed to attend an accident and emergency department and was treated with steroids and antihistamines. The swelling had decreased over a period of several hours each time. The patient's medical history consisted of angina, a previous myocardial infarction and bronchiectasis. He had no known allergies. The patient was taking aspirin, lisinopril (an ACE inhibitor), bisoprolol, frusemide and isosorbide mononitrate.

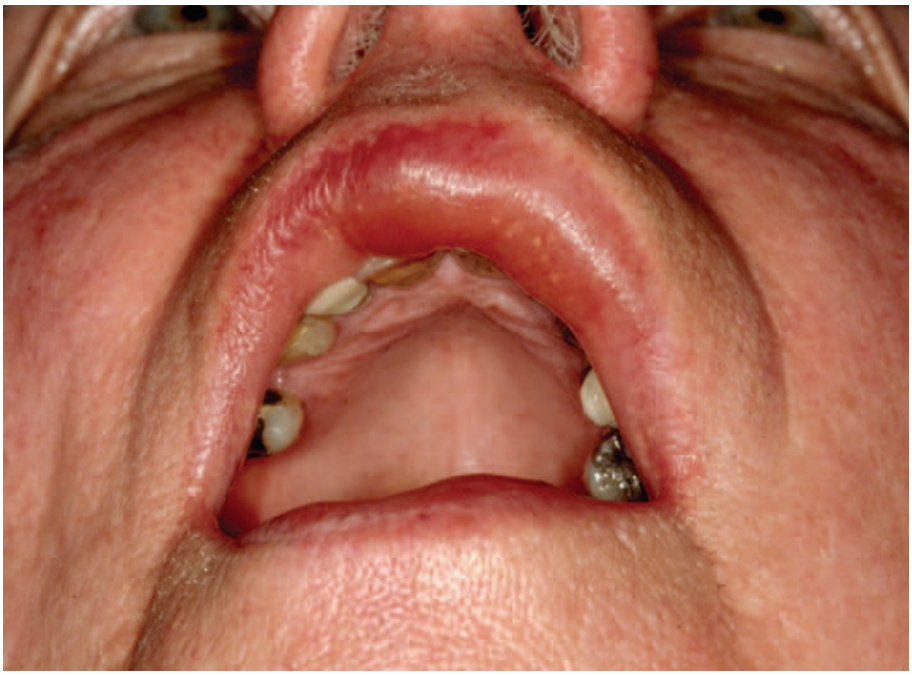

Fig. 1 Swelling of upper lip due to angioedema

The patient was diagnosed with angioedema secondary to ACE inhibitors. The patient subsequently had his lisinopril changed to an angiotensin II receptor antagonist and at his review appointment reported no further episodes of angioedema.

Case 4

A 77-year-old Caucasian male was referred on an urgent basis by his GDP with a swollen upper lip (Fig. 1). He gave a history of recurrent swelling of his lips. The swellings were painless, of rapid onset and usually resolved within a day. The patient's medical history consisted of asthma, hypertension and mitral valve prolapse for which he was taking bendrofluazide, lisinopril and a flixotide inhaler. He had been taking the ACE inhibitor lisinopril 10 mg once daily for six years. He had no known allergies.

A diagnosis of angioedema secondary to ACE inhibitors was made and his GMP informed. After changing his lisinopril to an angiotensin II receptor antagonist no further episodes of angioedema were reported.

Case 5

An 86-year-old Afro-Caribbean male was referred by his GDP with a 21 month history of intermittent episodes of swelling affecting his upper and lower lips. These painless swellings occurred once or twice each month, taking about an hour to develop fully and resolving slowly over the following two days. The patient's medical history revealed that he suffered from hypertension and had undergone resection of an abdominal tumour some five years ago. He had no known allergies. His medication comprised amlodipine, bendroflumethiazide, doxazosin, aspirin and enalapril.

A diagnosis of angioedema secondary to ACE inhibitors was made and the patient's GMP informed. The GMP was initially reluctant to change the patient's medication until the potential serious consequences of upper aero-digestive tract angioedema were emphasised in a further letter, following which the patient was commenced on the angiotensin II receptor antagonist losartan. At review five months later there had been no recurrence of the patient's angioedema.

DISCUSSION

Since ACE inhibitors were first introduced, the most common reported side-effect is a non-productive cough which is thought to occur in 5-25% of patients.[13] Other frequently reported side-effects are angioedema and dizziness.[13] There are several less common side-effects reported that affect the oral cavity, including dysgeusia, scalded mouth syndrome and oral ulceration.[8]

Angioedema secondary to ACE inhibitors is frequently recurrent, its severity is variable and may fluctuate. Deaths have been reported.[6] ACE inhibitor induced angioedema has a predilection for the head and neck. It is reported to be responsible for 25-35% of cases of angioedema in these sites[2] with the tongue and lips being most commonly involved.[11] While the prevalence of ACE inhibitor induced angioedema is highest in the head and neck, other parts of the body can be affected. Recurrent gastrointestinal angioedema is not uncommon and in these cases patients present with abdominal pain, nausea and vomiting.[14] Such patients often undergo multiple unnecessary investigations in an attempt to find the cause for their symptoms before the correct diagnosis is made.

The pathophysiology of angioedema secondary to ACE inhibitors is unclear, however it is thought to be a biochemical rather than an immunological response. The principle cause is thought to be related to bradykinin. In addition to blocking the conversion of angiotensin I to angiotensin II, ACE inhibitors also block the metabolism of bradykinin, therefore increasing its levels within tissues.[1] Bradykinin is an important inflammatory mediator and increased tissue levels result in vasodilatation, increased vascular permeability and interstitial oedema, thereby leading to angioedema.[1]

Angioedema is usually reported in patients on standard doses of ACE inhibitors and there is no clear evidence of a dose-response relationship. It has been suggested that individuals susceptible to developing angioedema secondary to ACE inhibitors may have a genetic deficiency of other bradykinin metabolising enzymes.[12] These patients would therefore naturally have a raised level of bradykinin, which would predispose the patient to episodes of angioedema as the effect of the ACE inhibitor would further raise the levels of bradykinin. This could explain why only a proportion of patients taking ACE inhibitors are affected by angioedema.

Black patients of African origin may be at greater risk than other patients. Patients in this ethnic group who are taking ACE inhibitors have been found to have an increased incidence of angioedema.[5,15,16] There is some evidence that there is a racial difference in the kallikrein-kinin system which leaves patients of African origin with an increased sensitivity to bradykinin, thereby offering an explanation to this apparent racial difference.[15,16]

The recommended management for patients who experience angioedema secondary to ACE inhibitors is to change medication to an alternative class of drug.[7,9] Angiotensin II receptor antagonists are a popular choice as they are well tolerated and decrease cardiovascular mortality and morbidity.[17] As angiotensin II receptor antagonists do not block bradykinin metabolism, it was thought that the unwanted side-effect of increased bradykinin would be avoided. However, it has been reported that angioedema can also be associated with this medication.[11,18] The pathophysiology of angiotensin II receptor antagonists causing angioedema is unclear but may relate to angiotensin II receptors being stimulated by increased levels of angiotensin II, which may activate the bradykinin-prostaglandin-nitric oxide cascade leading to bradykinin mediated adverse effects.[17] Unfortunately it has been reported that all classes of antihypertensives can be associated with angioedema to some extent and hence arrangements should be made for the patient's treatment for hypertension or heart failure to be reviewed by their physician when angioedema is thought to be ACE inhibitor related.[19]

Angioedema in the head and neck can occur for other non-allergic reasons as well as being ACE inhibitor induced. Other non-allergic causes include pressure urticaria, hereditary angioedema, acquired angioedema and idiopathic angioedema. Both hereditary and acquired angioedema are caused by C1 esterase inhibitor deficiency or dysfunction.[20,21] Angioedema in these cases is frequently precipitated by trauma or surgical procedures, but patients may give a history of spontaneous abdominal pain or pharyngeal swelling for no reason. Hereditary angioedema is usually due to an autosomal dominant condition, whereas acquired angioedema may be the result of lymphoproliferative disease.

The management of acute episodes of angioedema is partly dependent on the underlying cause. In all cases, should the patient's breathing be compromised, then transfer to hospital to allow securing of the airway should be arranged as soon as possible. For hereditary and acquired angioedema, an infusion of C1 esterase inhibitor will be the hospital treatment of choice. For ACE inhibitor associated angioedema, there is no standardised treatment for the acute attack other than discontinuation of the ACE inhibitor.[22] Other emergency procedures are essentially the same as would be clinically warranted for an attack of acute allergic angioedema, including epinephrine, antihistamines and systemic steroids. There is, however, little evidence of their effectiveness in this situation and recent interest has centred on treatment with C1 esterase inhibitor concentrate infusion. Preliminary reports have been encouraging.[23,24]

Angioedema of the head and neck is a serious and potentially fatal medical problem for which patients may initially present to their dental practitioner. Dentists should be aware of the potential causes of angioedema, including the causative relationship of angioedema with ACE inhibitors. Dentists should ensure that the patient's GMP is alerted should a patient on ACE inhibitors present with a history of angioedema of the head and neck.

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