Recurrent Severe Angioedema Associated with Imidapril and Diclofenac

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ABSTRACT

Background: Angioedema due to angiotensin-converting enzyme inhibitors (ACEIs) therapy occurs not infrequently and is sometimes associated with life-threatening conditions.

Case Summary: A 59-year-old woman presented with recurrent angioedema of the tongue complicated by upper airway obstruction which required endotracheal intubation. Laboratory tests including complement levels were normal. ACEI-associated angioedema precipitated by NSAIDs was suspected. Her condition improved after discontinuation of imidapril and diclofenac without other specific treatment.

Discussion: ACEIs, and in particular concomitant use with NSAIDs, should be avoided in patients with a history of angioedema because continuing administration tends to lead to more severe attacks.

KEY WORDS

angioedema, angiotensin-converting enzyme inhibitors (ACEIs), diclofenac, imidapril, NSAIDs

INTRODUCTION

Angioedema is a self-limited, localized swelling that involves subcutaneous tissue or mucosa, most commonly in the periocular area, perioral area, tongue, genital area and extremities. Angioedema may be classified as hereditary or, more commonly, acquired, which is usually allergic or idiopathic in origin. However, several drugs have been described as causing acquired angioedema particularly angiotensin converting enzyme inhibitors.

Angiotensin converting enzyme inhibitors (ACEIs) are a widely used class of pharmacologic agents indicated in the treatment of hypertension, congestive heart failure, diabetic nephropathy and have been widely recognized as a cause of angioedema. Imidapril is one of the most commonly prescribed ACEIs in Japan and is believed to produce least adverse effects among ACEIs. The author reports a case of a patient with severe recurrent angioedema resulting in upper airway obstruction in association with imidapril and diclofenac.

CLINICAL SUMMARY

A 59-year-old female patient with a medical history of type 2 diabetes, hyperlipidemia, hypertension and obesity presented with swelling of the tongue and difficulty in breathing after taking diclofenac to relieve her knee pain for 2 days. She had no urticaria, fever, abdominal pain, vomiting or diarrhea.

There was a history of a similar episode which occurred 2 years prior, without concomitant use of NSAIDs, which required prophylactic nasotracheal intubation. Her previous medication included enalapril (which she was administered for a period of 7 years) was discontinued and the symptoms spontaneously resolved in a few days without any specific treatment.

She was later switched to therapy with imidapril for approximately 2 years. Her other current medications consisted of glipizide, metformin, fenofibrate, atenolol, hydrochlorothiazide and nifedipine. She denied any history of smoking, drug rash, seasonal allergies, or previous upper airway surgery.

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**PATHOLOGICAL FINDINGS**

Laboratory tests including complete blood count, blood chemistries, and tryptase levels were within normal limits. Complement levels included the following: CH50 41.1 mg/dL (19–40), C3 146 mg/dL (76–171) and C4 26.9 mg/dL (10–40). Unfortunately, C1 inhibitor (C1-INH) and C1q level could not be measured. However, their levels are expected to be in the normal range due to sufficient C4 and CH50 levels. Therefore, the diagnosis of ACEI-associated angioedema due to imidapril was made by exclusion of other possible causes including allergic angioedema, hereditary and acquired angioedema associated with C1-INH deficiency.

She was prophylactically intubated via the nasotracheal approach due to the fact that her symptoms worsened concomitant with the treatment of intravenous chlorpheniramine, ranitidine and hydrocortisone. Her condition improved within the next 48 hours after discontinuation of imidapril and diclofenac without other specific treatment. Due to potentially serious adverse reactions, oral challenge test with diclofenac was not performed. However, she was subsequently treated with other NSAIDs, including aspirin was well tolerated.

**DISCUSSION**

The reported incidence of ACEI-associated angioedema varies from 0.1–2.2%,1 to as great as 2.8–6% when ascertained prospectively in some clinical trials.5 ACEI-induced angioedema is the most common cause of acute angioedema in accidents and emergency hospital departments and up to 20% may be life-threatening.5 Among the 776 cases of recurrent angioedema unaccompanied by urticaria in a large clinical survey in Italy, 85 (11%) were related to treatment with ACEIs.7 Given that 35–40 million people worldwide are currently taking ACEIs, the number of people at risk for this side effect is substantial.3

The mechanism of ACEI-induced angioedema is not yet fully understood because angioedema only develops in a minority of patients with ACEIs therapy and its effect is idiosyncratic, not dose-related and can occur with any ACEIs.2

The mechanism most likely involves increased local levels of bradykinin from ACE blockage and decreased aminopeptidase P activity in the bradykinin degradation pathway, in which diminished activity of dipeptidyl peptidase IV in the substance P degradation pathway also appears to contribute.1,2,5,8

Of cases of ACEI-related angioedema, 47–72% present within the first week of treatment.1 However, recent reports found that less than 25% of patients developed angioedema within 1 month of starting ACEIs therapy.1 Onset may be delayed by up to 10 years of treatment,1,5 which could be one reason why physicians fail to recognize this association. In the presented patient, the adverse events occurred after a 7 and 2 year period of treatments with enalapril and imidapril, respectively.

ACEI-induced angioedema has a predilection for the head and neck and most frequently involves the tongue and lips, which may lead to life-threatening airway compromise.1,2,5 Rarely, ACEI-associated angioedema may involve visceral organs including bowel walls, which usually leads to delay in diagnosis because of confusion with other gastroenterological pathology.2,5 Pruritus and urticaria also rarely coexist.

Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) is frequently seen in patients with a history of ACEI-associated angioedema.1 NSAIDs themselves can cause angioedema by either immunological (IgE-mediated) or non-immunological (pseudoallergic) reactions, which in the latter are likely a result of increased leukotriene production due to cyclooxygenase blockage.6 Therefore, concurrent use of NSAIDs may precipitate or worsen angioedema in patients with ACEI therapy.

NSAIDs-induced angioedema is usually accompanied by urticaria and occurs soon after taking the drugs, contrary to the presented patient, suggesting that the main cause of these adverse events could be due to ACEI therapy. However, the role of NSAIDs in the precipitation of ACEI-induced angioedema in this patient can not be excluded.

It is generally accepted that ACEIs are contraindicated in patients with a pre-existing history of hereditary or acquired angioedema.2 The rate of angioedema was much higher in ACEI-continued exposure (18.7 per 100 patient-years) than in those whose use of the drug was discontinued (1.8 per 100 patient-years).2 Black Americans have an incidence of ACEI-associated angioedema 4–5 times higher than that of white Americans.1,2,5 No sex predominance has been noted except for patients with gastrointestinal involvement which occurred exclusively in women.10 Smoking, increasing age (>65 years), female gender, history of drug rash and seasonal allergies are also associated with increase risk, where as diabetes appear to be protected from ACEI-associated angioedema.5,11 However, there is no tight association between ACEI-associated cough and angioedema.5 Pre-existing narrowing of the oropharyngeal space due to obesity, previous upper airway surgery or trauma and patients with sleep apnea may represent a risk factor for developing upper airway obstruction secondary to ACEI-related angioedema.2,11

Early recognition and discontinuation of the ACEIs remain the primary therapy for ACEI-associated angioedema. Immediate treatment depends on the severity of the episode. Primary supportive therapy includes airway management, with a minority of cases requiring intubation or cricothyroidotomy. Although many physicians treat patients with antihistamines,
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steroids and in more severe cases, epinephrine, no clinical trial has addressed the efficacy of these treatments. Patients presenting with angioedema should be tested for C1 inhibitor function as well as C4, C3, C1q levels to exclude the possibility of hereditary angioedema or acquired C1-INH deficiency. Angioedema generally resolved after 24–48 hours and does not seem to recur if the ACEIs are withdrawn. Administration of FFP has also been effective in the treatment of resistant cases.

Patients who have experienced angioedema while taking one ACEI should not be treated with another. The rate of angioedema in patients taking angiotensin II receptor blockers (ARBs) is significantly lower than the rate of angioedema observed during ACEIs therapy, as a report showed that only 8% of patients who previously experienced angioedema from ACEIs, developed angioedema from ARBs. Nevertheless, physicians should use ARBs with caution in patients who have experienced ACEI-induced angioedema.

In conclusion, ACEIs, particularly, in concomitant use with NSAIDs should be avoided in patients with a history of angioedema because continuing administration tends to lead to more severe attacks.

REFERENCES