CASE REPORT

Severe migratory Angioedema due to ACE inhibitors use

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Abstract

Angioedema due to use of angiotensin-converting enzyme inhibitors (ACEIs) is a rare side-effect but is seen more often because of the increase in the use of these drugs due to their effectiveness and good tolerance in the treatment of hypertension and congestive heart failure. Other types of angioedema, which should be included in the differential diagnosis, are the hereditary type, which results from deficiency of C1 esterace inhibitor and the allergic angioedema. Angioedema is a potentially life-threatening condition when it is located to the mucosal and submucosal layers of the upper airway. Some times an angioedema case can be very severe, resistant to the usual treatment and even rarely fatal. The last eight months, six patients with angioedema due to ACEIs (5 cases) or angiotensin II receptor blockers (1 case), were examined and hospitalized at our department. We describe the case of a 65year old woman with severe migratory angioedema of the tongue, the floor of the mouth and the oropharynx, which was rather resistant to the usual treatment. Hippokratia 2009; 13 (2): 122-124

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Angioedema may be a life-threatening condition and is characterized by indurated, well demarcated, nonpruritic and often erythematous swelling which is located in one or more areas of the head and neck (face, lips, tongue, larynx). Milton, followed six years later by Quincke, described the first cases of angioedema in 1876[1,2].

Hereditary angioedema is a clinical entity which has been attributed to deficiency or dysfunction of the C1 esterase inhibitor[3]. Acquired angioedema could be a result of several factors. The use of ACEIs is considered the most common (35% of acquired angioedema is caused by these drugs)[1].

The ACE, metabolizes bradykinin, a potent vasodilating substance, and converts angiotensin I to angiotensin II, a powerful vasoconstrictive agent. ACE inhibitors decrease angiotensin II and aldosterone levels on the one hand and increase the level of bradykinin and prolong its action on the other hand. The combination of these mechanisms can cause fluid extravasation into the subcutaneous tissues, which produces angioedema[2,4].

Since the mid 80's ACE inhibitors have been more frequently used for the treatment of hypertension, congestive heart failure and diabetic nephropathy. As a result and due to their efficacy and rarity of serious side effects, the number of angioedema cases has increased over these years and is expected to increase further in the future. Another reason for the increase of ACE inhibitors use and the angioedema, is the rise of life expectancy in western societies, which has lead to more patients with hypertension and congestive heart failure who use these drugs[5,6].

Case report

A 65year old obese woman, weighting 105 kg, came to our emergency department complaining of dysphagia and severe edema of her tongue. There was no respiratory distress. During the ENT examination it was found an enlarged oedematous non-tender tongue, which protruded slightly from her lips. The floor of the mouth also had a symmetrical mild swelling. Under transnasal flexible endoscopy the visualization of the hypopharynx and larynx was normal. Auscultation of the neck was negative for stridor. Her blood pressure was 145/70 mmHg and her pulse rate was 96/min. The patient was given a dose of 0,5 mg of epinephrine sq (under monitoring of the circulatory system) and the same was repeated 20 minutes later. She was also given 500mg of methylprednisolone iv bolus. Oxygen, 4 L/min was administered. Two hours later there was no improvement. On contrary, the ENT examination showed severe deterioration of the mouth's floor swelling and extension of the angioedema in the soft palate and uvula. She was given two more doses of epinephrine IM with half an hour interval. A dose of 1000 mg methylprednisone plus 50 mg ranitidine and 1 amp dimetindene were also given iv.

After a detailed history was taken, it was found that the patient had started on Captopril 25mg tid for the treatment of hypertension ten months ago. She also mentioned that she had milder episodes of the same condition in the past few months for which she was treated in other hospitals.

The patient, after two hours, had tachypnea, tachy-

cardia, but no orthopnea. She had normal arterial blood gases. A new flexible fiberoptic examination revealed a watery edema of her tongue base. Due to this deterioration we prepared to secure the patency of the upper airway. The patient transferred to the operation room where instruments for intubation and tracheotomy were available and ready. Inhalation of racemic epinephrine was added, one last dose of epinephrine was given im and further doses of corticosteroids were administered (Dexamethasone 12mg tid). The patient appeared to be stabilized and eight hours later a mild improvement of the edema was noticed.

The patient was finally hospitalized in the ENT ward without any surgical intervention. She was given inhalations of racemic epinephrine, dexamethasone 12 mg iv, 3 times per day for the first 2 days and H1 plus H2 antihistamines. For the next 3 days dexamethasone dose was modified and tapered off. The patient was discharged with a complete resolution of her signs and symptoms and with instructions to quit the ACE inhibitor, and modify therapy after consulting her cardiologist. Methylprednisolone and ranitidine were continued orally for 6 more days.

Discussion

ACEIs are widely used for the treatment of hypertension and congestive heart failure. The most common side effects include hypotension (usually after the first dose), renal dysfunction, hyperkalemia and nonproductive cough. Rare side effects are angioedema (0.1-0.2%), hepatotoxicity, dysgeusia, teratogenesis if given during pregnancy, rash, proteinuria and neutropenia[1,2,4].

Two categories of angioedema are described: congenital and acquired. ACEIs are the most common cause of acquired angioedema, which is caused rather by biochemical than immunologic factors. ACEIs reduce the function of ACE which is produced in the lungs, converts angiotensin I to angiotensin II and inactivates bradykinin, a powerful vasoconstrictive agent. ACE, also known as kinase II, metabolizes bradykinin a potent vasodilatating substance. ACEIs increase bradykinin levels, prolong its action and also decrease angiotensin II and aldosterone levels. The combination of these mechanisms results to local or general vasodilatation followed by fluid extravasation into the subcutaneous tissues causing angioedema. The angioedema due to ACE inhibitors therapy may appear from several hours to 2 years after initiation of treatment[2,7].

Angiotensin II receptor blockers (ARBs) block the angiotensin II receptors, thus inhibiting the known actions of angiotensin II that are associated with hypertension. ARBs do not affect ACE, and theoretically bradykinin should remain unaffected[8]. In recent years, unexpectedly, isolated case reports of angioedema associated with ARBs have been published[9,10].

Head and neck are the most common area of angioedema. The usual presentation is a hard-demarcated extensive erythematous edema localized mainly at the face, lips and tongue. It could evolve into edema of the larynx, upper airway obstruction and death. Rarely angioedema can be localized at the hands, feet and abdominal viscera (and be presented with symptoms like abdominal pain, nausea, diarhoea)[1,2,4].

From March 2008 to November 2008, we managed, using proper medications, six patients with angioedema due to ACEIs (5 cases – 2 Captopril, 1 Lisinopril, 1 Enalapril, 1 Quinapril) and ARBs (1 case – Losartan Potassium). The harder to be controlled patient was the case report, which was presented previously.

A detailed history is the most important tool in diagnosis angioedema secondary to ACE inhibitors or ARBs. Other diagnostic procedures, especially when there is suspicion of hereditary or allergic angioedema, include measurement of C1 esterace inhibitor, C4, total and specific IgE, and specific skin tests[11].

The first therapeutic step is to secure the patency of the upper airway. The next step can be use of medications, standard intubation, intubation with use of a flexible bronchoscope, cricothyroidotomy, or tracheotomy. This depends on the severity of the obstruction and the physician's experience. Patients should be carefully monitored as they usually have hypertension, heart disease and other internal illnesses that make the use of epinephrine or high doses of corticosteroids hazardous. It should be emphasized that the mechanism causing angioedema secondary to ACEIs is not the same causing allergic angioedema and that ACEIs have a prolonged half-life. As a consequence the standard treatment for allergic reactions (epinephrine, corticosteroids and antihistamines) may not be as effective and corticosteroids should also be used for a longer period to avoid recurrence. A comprehensive emergency management of acute angioneurotic edema is depicted on Table 1[2,10,12].

Table 1: Emergency Management of Acute Angioneurotic Edema of the Upper Aerodigestive Tract.

1. Secure patency of the upper airway
2. Discontinue medication and perform clinical observation and examination
3. Monitor circulatory system; perform electrocardiography and pulse oximetry
4. Administer subcutaneous epinephrine (be aware of tachycardia, arrhythmia, or use of beta-blockers)
5. Administer oxygen, 3-6 L/min, depending on pulse oximetrical saturation
6. Perform emergency blood tests
7. Administer corticosteroids
8. Administer antihistamine drugs
9. Administer inhaled racemic epinephrine (be aware of tachycardia, arrhythmia, or use of beta-blockers)
10. Administer intravenous C1 esterase inhibitor in rare cases of a known lack of C1 esterase inhibitor

The immediate discontinuation of ACEIs or/and ARBs following an episode of angioedema is mandatory, as continuing therapy dramatically increases the risk of recurrent angioedema with serious morbidity. ACEIs, ARBs and Moxonidine like drugs, should not be prescribed to patients who have a history of hereditary or acquired angioneurotic edema[10,12].

In everyday practice angioedema secondary to these drugs is usually diagnosed after several episodes because the first episode is often underestimated and the involved physicians may not be aware of the association. The patient is usually treated symptomatically while continuing to take the ACEIs or ARBs, risking a more severe (and potentially lethal) episode in the future. The suspected medication should be removed and replaced by alternative drugs for the treatment of hypertension or congestive heart failure. It should also be noticed that diuretics, Ca^{++} channel blockers, or beta-blockers could also, very rarely, cause angioedema[1-2,10-12].

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