

CASE REPORT

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Angiotensin Converting Enzyme Inhibitor-related Angioedema: A Case of an Unexpected Death

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ABSTRACT

Angioedema is an asymmetric non-pitting oedema on face, lips, tongue and mucous membranes; any delay in diagnosis and treatment can be fatal. Treatment with lisinopril as an angiotensin converting enzyme (ACE) inhibitor, can be a reason of angioedema.

Here we report a case who developed oral-facial edema four years after using lisinopril/hydrochlorothiazide. Laryngeal oedema is a main cause of death in angioedema. The treatment of choice in angioedema including fresh frozen plasma, C1 inhibitor concentrations and BRK-2 antagonists (bradykinin B2 receptor antagonists) were used.

In this case; a 77 years old female patient suffering from hypertension was considered. This patient was suffering two days from swelling on her face and neck. Non- allergic angioedema was distinguished in five major forms; acquired (AAO), hereditary (HAE), renin-angiotensin-aldosterone system (RAAS) blocker-dependent, pseudoallergic angioedema (PAS) and an idiopathic angioedema (IAO). She was admitted to our clinic with the diagnosis of hereditary angioedema. Patient had skin edema and life threatening laryngeal edema.

In emergency department treatment was started using intravenous methylprednisolone, diphenhydramine as well as inhaled and subcutaneous epinephrine simultaneously. Despite the initial treatment, the patient died due to the insufficient respiration and cardiac arrest. The patient has no history of kidney disease.

Keywords: Angioedema; Angiotensin converting enzyme inhibitor; Lisinopril

INTRODUCTION

Angioedema is known as a disease with various

clinical manifestations.^{1, 2} It is about four decades that ACE inhibitors (ACEI) are used for treatment of cardiovascular diseases like hypertension, heart failure, myocardial infarction and in diabetic patients (for its nephroprotective benefits).³ Angioedema is a rare but potentially serious complication in ACE-inhibitor treatment. The incidence of ACEI-induced angioedema

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is estimated to occur between 0.1%- 0.5 %.⁴ ACEI are generally well tolerated.⁴ Angioedema is an asymmetrically localized edema involving the skin and deep subcutaneous tissues. Lesions may develop in single or multiple places in the body including face, lips, tongue, hands and feet and probably in genital and gastrointestinal mucous membranes. Involvement of the respiratory tract can be fatal.⁵ Unlike the histamine pathway in allergic angioedema, ACEI-induced angioedema is mediated by bradykinin. Releasing bradykinin in angioneurotic edema attacks leads to increase in vascular permeability, development of swelling and ascites, hypotension as a result of vasodilation as well as development of spasm due to contraction in nonvascular smooth muscles.⁶ There is no published algorithm in ACE associated secondary angioedema treatment. ACEI-induced angioedema sometimes can be treated by termination of using ACEI and then with the administration of corticosteroids, antihistamines and epinephrine.

In this report, we introduce a case who has died because of late diagnosed ACEI associated angio neurotic edema and delayed treatment. We also review the treatment protocol used for her according to the literatures.

CASE REPORT

Our patient was a 77 years old female suffering from hypertension. She was hospitalized in a state hospital due to swelling on her face and neck that had begun 2 days earlier. The patient referred to our clinic

from the state hospital because of her shortness of breath and continuing complaints of dysphagia and hoarseness. Patient has been using lisinopril/hydrochlorothiazide 20 mg/12.5 mg once daily for four years. According to the literatures, this treatment may induce angioedema.⁷ There was no history of additional drug use, allergy, diabetes and kidney disease in this case. Physical examination of the patient showed bilateral orbital edema, but left orbit edema was greater. She had edema at left half of the face, left submental region and left half of the tongue. patient had skin edema without pruritus (Figure 1). On the flexible endoscopic examination severe oedema was observed on the base of the tongue, laryngeal face of the epiglottis, the left Aryepiglottic fold and the left arytenoid. No pathological findings was determined in hematological and biochemical examinations. C3, C4 and C1 esterase inhibitor levels were normal. Patient was admitted for diagnosis of angioedema and lisinopril treatment was terminated one day prior to being admitted to other clinic. Antihypertensive treatment was replaced with amlodipine 10mg/day. The therapy began with intravenous methylprednisolone and diphenhydramine along with inhaled and subcutaneous epinephrine in the emergency room. No icatibant treatment was possible in our clinic. Despite the first treatment, her condition worsened. Patient was taken to intensive care unit due to respiratory distress. Tracheotomy was opened and fresh frozen plasma infusion was started but before the completion of the plasma infusion cardiac arrest occurred.



Figure 1. Severe angioedema on the left side of the face and the orofacial area in the woman due to angiotensin- converting enzyme inhibitor treatment. The permission of the patient has been taken for publication of this photo.

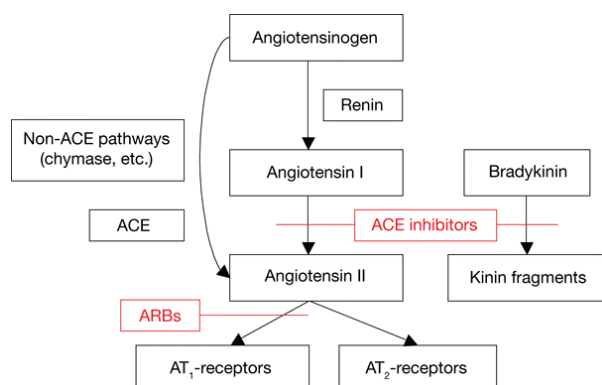


Figure 2. ACE inhibitory mechanism

DISCUSSION

ACE inhibitors are used for four decades, especially in the treatment of cardiovascular diseases like hypertension, heart failure, myocardial infarction and in diabetic patients due to its nephroprotective benefit.¹ ACE inhibitors block the activity of ACE which converts the angiotensin I into angiotensin II (Figure 2).

In our case, the patient has been using lisinopril for four years. There is no published algorithm in ACE associated secondary angioedema treatment. ACEI associated mild clinical cases often recovers within 24 to 48 hours after cessation of the drug. Steroids and antihistamines are used for treatment of these cases. Particularly, in moderate to severe ACEI related angioedema, conventional treatments of epinephrine, corticosteroids and antihistamines are often ineffective.

This patient was admitted in another hospital where antihistamine, epinephrine treatment was applied for 58 hours. Then she was transferred to our clinic due to progress of angioedema. C1 inhibitor levels were normal and the optimal approach has not been yet known in the diagnosis of type 3 HAE.⁸

In these conditions, it is necessary to firstly terminate the ACE inhibitors. It is usually resulted in stopping the signs and symptoms within 24-48 hours, although in some cases it may take longer. After the first episode of healing, due to the risk of the recurrence, at least one night close monitoring should be applied. In case of emergency condition, acute approach should be considered including a clear air passage and/or even intubation and mechanical ventilation in the case of life threatening respiratory failure. In this case, commonly used antihistamines,

anticholinergics and non-histamine-mediated corticosteroids were not very likely to be effective. Similarly, although epinephrine is recommended in patients with airway obstruction, but it could not rescue the patient. This treatment may be ineffective in severe cases.⁹ The ACEI-related angioedema symptoms can occur without activation of complement components. Fresh frozen plasma (FFP) and recombinant C1 inhibitor are available in most hospitals, but they are costly compared to other treatments such as ecallantide and icatibant.¹⁰

In our case, epinephrine was administered to the patient due to respiratory distress following tracheotomy. However in the treatment of acute attacks, fresh frozen plasma can be useful in the absence of C1 inhibitor replacement and C1 inhibitor concentrate. Severe cases of angioedema are generally unresponsive to systemic corticosteroid and antihistamine treatment. In prophylaxis, few patients have reported with a benefit from danazol and tranexamic acid treatment.¹¹

C1 inhibitor was not available for treatment of our patient. Fresh frozen plasma infusion was started. However, before completion of the infusion, the patient died due to asphyxia. There are some reports that FFP has a curable effect on a few cases of ACEI-related angioedema.^{12,13} Fresh frozen plasma was applied to replace the missing C1 inhibitor mostly within first 45 minutes of the attack. FFP usage often provides an improvement of clinical table. But a plasma substrate, quinine can cause deterioration of angioedema clinic after infusion of FFP and this effect of quinine should not be ignored. FFP usage can cause excessive volume load at congestive heart failure (CHF) and elderly patients. There is also a risk of viral transmission such as HIV and hepatitis after FFP infusion.¹⁴ In our case, the effective treatment was not provided for 58 hours after beginning the signs and symptoms.

In 1980's usage of purified C1 inhibitor preparations obtained from blood donors has been reported successful at treatment of angioedema episodes.¹⁵ In our country C1 inhibitor preparations of 1000U are available for treatment of acute attacks. Effectiveness of icatibant treatment in ACEI induced angioedema is clearly demonstrated at case series.¹⁶ BRK-2 are used successfully in these cases. Unfortunately BRK-2 antagonists are not available at our country. C1 inhibitor concentration is known to be effective if it is given in the first hour of the

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angioedema episode. When the C1 inhibitor concentration is not available, fresh frozen plasma can be used for treatment. Early diagnosis and treatment can prevent further complications. However, any delay of the treatment can be fatal as seen in our case.

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