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CASE REPORT

Angiotensin-converting enzyme inhibitors-induced angioedema treated by C1 esterase inhibitor concentrate (Berinert®): about one case and review of the therapeutic arsenal

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Key Clinical Message

C1 esterase inhibitor (Berinert®) is generally used to treat severe attack of hereditary angioedema. We describe here the case of a patient who presented with a severe angioedema induced by angiotensin-converting enzyme inhibitors (ACEIs) endangering her life. It could be successfully treated with that medicine.

Keywords

Angioedema, angiotensin-converting enzyme inhibitors, C1 esterase inhibitor, treatment, upper airways.

Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) are the main cause of angioedema (AE) induced by drugs. They are widely prescribed in Western countries and are ranked fourth of the most frequently prescribed drugs in the United States [1]. Seven percent of the Belgian population uses chronically a drug of this family or an angiotensin receptor blocker (ARB) [2]. The incidence of AE in the group of patients receiving ACEIs is rather low: it is estimated between 0.1% and 2.2% [3–5]. AE induced by ACEIs is characterized by a sudden and transient swelling of the subcutaneous and submucosal tissues. This local swelling is sometimes asymmetrical and painful. There is neither pruritus nor urticaria. A localized affection of the intestines is possible, but it usually affects the face, the tongue, and the rest of the ear, nose, and throat (ENT) region. Ignorance of this disease can have fatal consequences especially since it does not respond to treatments that are typically administered in this emergency situation, such as antihistamines, corticosteroids, and epinephrine [6]. In this article, we describe the case of a patient who presented an AE endangering her life. We discuss the diagnostic, therapeutic, and pathophysiological aspects of this disease.

Case Description

A 77-year-old woman is brought by ambulance to the emergency room at 11 AM for an edema of the tongue that started 2–3 h earlier. During the transfer in the ambulance, she was administered 125 mg of methylprednisolone and 0.5 mg of epinephrine subcutaneously. She said she never presented such symptoms. The apparition of the edema was brutal and it progressed rapidly. She had not eaten anything unusual. Her medical history revealed occasional and severe events of abdominal pain. She had recently been hospitalized to elucidate the origin of this pain but no etiology had been found. The woman had a morbid obesity (BMI = 38). Complete history

included anxiety, depression, reflux esophagitis, ancient esophageal fungus, sigmoid diverticulosis, diabetes type 2, hypertension, hypercholesterolemia, left subacromial bursitis, and cholecystectomy (several years ago). Daily treatment of the patient was composed of gliclazide 60 mg, esomeprazole 20 mg, atenolol 100 mg, altizide 15 mg + spironolactone 25 mg, attapulgite 3 g, bromide otilonium 120 mg, acetylsalycilic acid 80 mg, rosuvastatin 20 mg, bromazepam 6 mg, and lisinopril 20 mg (she has been taking it since 2007). She had no known allergies. She did not smoke and she consumed liquor only on occasional circumstances. On the family level, we noted that her daughter suffered from a minor oropharyngeal edema which did not need medical treatment. Physical examination on admission revealed, in addition to edema, a blood pressure of 190/100 mmHg and a regular heart rate of 104 bpm. These parameters were related at least partly to the administration of epinephrine. She was afebrile and her saturation was 96%. She was polypneic (about 30 breaths per minute) and dysarthric. Her parameters were monitored regularly. The ear nose throat (ENT) specialist on duty was called because of the possibility of a difficult intubation or tracheotomy. Upon the ENT specialist's arrival, the patient had a lower blood pressure: 147/60 mmHg. The edema of the tongue was very important and slightly asymmetrical with a right predominance. The lips and mouth were also affected as well as the neck. The pharynx was not visible and palpation of the neck did not allow localizing the different osteochondral structures. The swelling was not itching and the symptoms were not relieved by the corticosteroids and adrenaline previously administered in the ambulance. Histamine-induced AE was then ruled out and a bradykinin-induced AE either drug induced or hereditary was diagnosed. A blood test containing chemistry, enzymology, glucose, hematology, coagulation, etc., was asked, with addition of the dosage of tryptase, complement, and C1 esterase inhibitor (quantity and activity). We did not perform flexible endoscopy for fear of increasing the swelling. Fresh frozen plasma was administered but there was no improvement after 4 h. Berinert® (manufactured by CSL Behring GmbH, King of Prussia, Pennsylvania, USA) was ordered at the pharmacy and subsequently administered after discussion with the family because of the uncertainty of reimbursement of the drug by medical insurance. According to the patient's weight (102 kg) four ampoules were injected (20 UI/Kg). In less than an hour, the swelling was absorbed and the patient remained in hospital for 48 h observation. The administration of corticosteroids resulted in hyperglycemia which justified the instauration of a temporary insulin regimen. ACEIs were prohibited (and even sartans because of the severity of the symptoms) and 40 mg omeprazole and tranexamic acid 1 g twice a day were added to the treatment. The patient was followed up in the outpatient department. We got the results of the blood tests a few days later. They were as follows: C3 complement was slightly increased (158 mg/dL), C4 complement was normal, and the antigen and the activity of C1 esterase inhibitor were normal (31 mg/dL and 130%). Allergy skin tests were negative and tranexamic acid was stopped since hereditary AE was excluded. A contact with the patient's former cardiologist revealed that the patient had experienced a chronic cough a few years before with another ACEI medicine (ramipril). The patient was lost to follow up.

Discussion

In this case, allergic histamine-induced edema was rapidly excluded. Indeed the patient had no history of allergy (food or drug), she had not been eating for several hours, the edema was not itchy, and the epinephrine and antihistamines she received in the ambulance did not treat the symptoms. A bradykinin-induced AE can be either due to a deficiency (acquired or hereditary) in C1-esterase inhibitor or it can be drug induced. In this case, the recurrent abdominal pain of unknown etiology was an additional argument in this direction and the edema experienced by the patient's daughter a few years before was possibly a hereditary AE crisis. The patient took ACEIs (lisinopril) on a daily basis, which are the first cause of AE induced by drugs. Certain drugs can induce AE by three main mechanisms [7]. First, an allergic IgE-mediated reaction, mainly to beta-lactam constitutes the most frequent drug-induced AE. It is accompanied with urticaria. The second mechanism is involved in AE induced by aspirin and NSAID (NonSteroidal anti-inflammatory drugs). It is a nonallergic reaction in which an inhibition of cyclooxygenase results in major alternations in the arachidonic acid metabolism such as cysteinyl leukotriene overproduction. The third mechanism is the inhibition of bradykinin degradation. This inhibition is induced by ACEI. The bradykinin accumulation results in an increased vascular permeability and causes AE. This type of AE is never associated with urticaria. The diagnosis of ACEI-induced AE should always be put forward as early as possible in case of a compatible clinical image. In fact, 20–40% of the patients admitted to the emergency room for a suspicion of AE are suffering from an AE induced by these drugs [6, 8, 9]. Affection of the ENT sphere is very common and it may, in the absence of specific treatment, lead to suffocation in 25% of cases [5]. The diagnosis of this disease in the acute phase is clinical and anamnestic. The determination of the quality and the activity of C1 esterase inhibitor in the blood and the dosage of C4 aim to exclude a hereditary or acquired AE. In

fact, it is not uncommon that an edematous reaction due to ACEI reveals a deficit more or less important in C1 esterase inhibitor. The dosage of tryptase, which has not been performed, would have orientated the diagnosis toward an anaphylactic mechanism, if it had been increased, although this is unlikely given the clinical image. Endoscopy of the upper airway should be avoided because of the risk of worsening the symptoms and because of the swelling it can cause. Remember that there is no specific test for the diagnosis of AE on ACEI and that there is no means to predict the risk that a patient will develop an AE after taking it. The chronology of AE due to ACEI is fairly typical: the swelling appears in minutes or hours and fades within 24–72 h. It can, however, be life-threatening. The complete resolution of symptoms may take several days. The swelling disappears even if the ACEIs is not discontinued. However, there is a tendency for recurrences of increased importance. In most cases, the AE occurs during the first week of treatment with ACEIs [10]. However, the delay may be much longer and cases of patients treated for several years before the onset of the first attack are described, as in the case reported above [11, 12]. Moreover, although the majority of patients will see their symptoms disappear within weeks after stopping the ACEIs, some may have seizures up to 6 months after discontinuation of the drug. After such period, one should however consider another cause for the AE. Patients taking ACEI are not equal concerning the risk of developing AE. Among the described risk factors we find, in addition to C1 inhibitor deficiency and a history of AE whether hereditary or not, the African origin, female gender, trauma, smoking, age over 65 years, a history of other allergies, and various drugs use such as mTOR (mammalian target of rapamycin) inhibitors (sirolimus, everolimus, tacrolimus), estramustine, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, lidocaine, and oral anti-diabetic drugs of the gliptines family [13–15]. Furthermore, there is an increased incidence of AE in the group of patients with chronic cough induced by ACEI [16]. The mechanism linking these two side effects has not yet been precisely elucidated. Before discussing the therapeutic possibilities of AE induced by ACEI, let us consider its pathophysiology. ACEI are prescribed to treat hypertension and heart failure, and also for secondary prevention after acute myocardial infarction. They act on the renin–angiotensin–aldosterone system which plays an essential role in the regulation of renal blood flow and blood pressure. Its mechanism of action is: first, angiotensinogen, which is produced in the liver, is converted to angiotensin I by renin, which is produced in the kidney. Angiotensin I is then converted to angiotensin II by the angiotensin-converting enzyme (ACE) (also known as kininase II) produced substantially in the pulmonary endothelium. Angiotensin II is a vasoconstrictor through a mechanism that we will not detail here. In parallel, bradykinin results from the degradation of kininogen by kallikrein. Kallikrein requires complement factor XIIa for its activation. Angiotensin II is responsible for the inactivation of bradykinin, whereas ACE is involved in its degradation. In this way, the use of ACEI results in the accumulation of bradykinin. The metabolism of bradykinin does not depend on ACE. Indeed, several other enzymes are involved in the degradation especially when ACE is inhibited. A deficiency of any of these enzymes, for example, due to a genetic polymorphism, will therefore increase the risk of developing AE. Such polymorphism is observed in African populations, which probably explains the higher incidence of AE in these populations [7]. AE occurs when excess bradykinin and its metabolites causes vasodilation with increased permeability of venules and plasma extravasation in tissue submucosa. The therapeutic management of AE on ACEIs starts by stopping the suspected drug once the diagnosis is suspected. The patient is advised not to take any drug of the ACEI family ever again. Sartans (angiotensin II antagonists at the level of the AT1 receptor of angiotensin II) also have to be avoided, but to a lesser extent as they may exceptionally be responsible for the same side effects [17]. A patient who developed an AE during treatment with ACEI has a 10% risk of developing one again if taking sartans [18, 19]. Aliskiren (direct renin inhibitor) appeared to be an alternative for patients who have suffered from AE with the two classes of drugs mentioned above. Unfortunately, a recent analysis of pharmacovigilance has implicated aliskiren in cases of AE and renal failure [20]. When a patient presents with AE, a monitoring in hospital for at least 6 h is advised [5]. The main criterion of severity is the localization of the swelling. When the neck, tongue, or face are involved, a close monitoring is indicated, if possible in an intensive care unit. The development of edema and affection of the upper respiratory tract is unpredictable. The staff should prepare for a possible intubation and tracheotomy even though this may be very difficult and dangerous in a patient with edema of the ENT sphere. Any action, more or less traumatic, may indeed aggravate the phenomenon of infiltration. Antihistamines, corticosteroids, and epinephrine, which are commonly used to treat histamine-induced AE of allergic origin, are ineffective or have very limited effect on bradykinin-induced AE. When the patient's airway is compromised, it is necessary to use other therapeutic agents to accelerate the resolution of edema. The indications for the use of these drugs are often based on case reports and small series of patients and the choice of these molecules depend primarily on their availability. Their mechanism of action is shown in

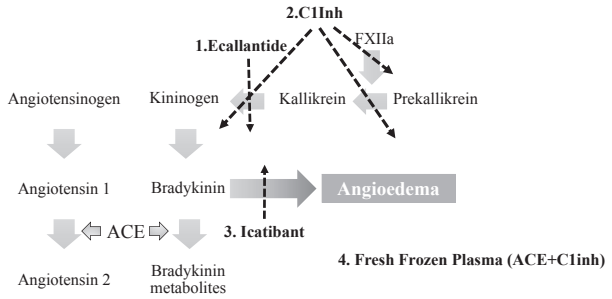

Figure 1. New drugs targeting the bradykinin pathway.

Figure 1. Considering the pathophysiological phenomenon of AE, the molecule that seems to be the treatment of choice is icatibant (Firazyr® manufactured by Shire Orphan Therapies Inc., St Helier, Jersey, USA). This is a blocker of bradykinin B2 receptors. According to recent studies, this treatment appears to be effective in the first hour after administration [21]. Its dose is 30 mg administered subcutaneously at a rate of up to three injections per 24 h. It should be administered as soon as possible. The C1 esterase inhibitor concentrate (Berinert®) is essentially the treatment of choice for hereditary or acquired AE due to a qualitative or quantitative deficiency of this enzyme. Its effectiveness in AE on ACEI has so far only been demonstrated in case reports [22, 23]. Its treating property in this situation seems to be due to the inhibition of kininogen activation at several levels which causes a decrease in the synthesis of bradykinin. The drug is administered at 20 IU/kg intravenously. Ecallantide, an inhibitor of plasma kallikrein, could also be effective but has not been studied yet. Fresh frozen plasma contains natural ACE and C1 esterase inhibitor. It has been shown that it effectively and rapidly treats AE due to ACEI [24, 25]. It is the treatment of choice when the molecules that are mentioned above are unavailable or while waiting for their administration as in the case described above. Tranexamic acid that is often used for prevention of hereditary AE attacks has not been evaluated for this indication. In many countries, Berinert® and Firazyr® are reimbursed in case of acute attack of hereditary AE type 1 or 2 documented by a family history and disturbed blood tests (C4 level lowered and functional and/or quantitative dosage of the C1 esterase inhibitor disturbed) while their effectiveness in cases of AE due to ACEI has been clearly demonstrated. In the case described above, for example, we had to explain to the family of the patient that according to the blood tests, the drug would not be reimbursed by the national medical insurance. The Berinert® was administered with the consent of the family and may have saved the life of the patient. Eventually she has been reimbursed by her private insurance. This last point deserves an epidemiological consideration. It is estimated that the incidence of hereditary AE is 1:50,000. The incidence of AE due to ACEI is probably higher although there are no official statistics. Indeed, as mentioned above, at least 0.1% of the patients that take ACEI will develop an AE and we know that in western countries about 4–5% of the population regularly consume these medications [2, 4, 5, 23]. Therefore, it is expected that thousands of people suffer from ACEI-induced AE every year with varying degrees of severity. Reimbursement of the appropriate medicine in case of serious AE due to ACEIs intake seems therefore justified.

Conclusion

The incidence of AE in patients taking ACEIs is low. However, these drugs are frequently prescribed in our population and it is estimated that there are hundreds of victims in Belgium each year. The ignorance of this disease and of its diagnosis and therapeutic features can have dramatic consequences. This diagnosis should be put forward in any patient with a nonpruritic AE who is treated by ACEIs and especially if he presents risk factors. While it is clear that studies using large cohorts are lacking, it still seems that new drugs such as C1 esterase inhibitor (Berinert®) and icatibant (Firazyr®) are effective and can be lifesaving in severe crises involving the vital prognosis of the patient.

Conflict of Interest

None declared.

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