Rev Bras Anestesiol. 2019;69(5):521–526

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
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CLINICAL INFORMATION

Postoperative angioedema induced by angiotensin-converting enzyme inhibitor: case report

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Received 8 December 2018; accepted 14 January 2019
Available online 20 October 2019

KEYWORDS
Angioedema;
Bradykinin;
Enalapril maleate;
Angiotensin-converting enzyme;
Angiotensin-converting enzyme inhibitors

Abstract
Background and objectives: Angioedema is a potentially fatal condition that may occur at any time in the perioperative period. It may result from histamine release, hypersensitivity reaction to drugs, or be triggered by bradykinin, in non-allergic reactions of hereditary or acquired etiology. The aim of this report is to report a case of angioedema in the early postoperative period in a patient on antihypertensive medication involving angiotensin-converting enzyme inhibitors.
Case report: A 67-year-old male, Afro-descendant, hypertensive, and taken enalapril maleate underwent orthopedic shoulder surgery under general anesthesia combined with brachial plexus block. The procedure lasted 3 hours uneventfully. After discharge from the post-anesthesia care unit, the patient presented with angioedema and severe airway impairment. Tracheal intubation was attempted but it was impossible due to edema affecting the lips, tongue, and oropharyngeal region Emergency cricothyroidotomy was performed. The onset of angioedema had no causal relationship with the administration of any medication; there were no cutaneous manifestations and also not response to therapy for hypersensitivity reaction to drugs, such as antihistamines, corticoid, and adrenaline. It was considered to be mediated by bradykinin, as the patient had already had two similar episodes and was on regular medication (enalapril). The evolution was satisfactory.
Conclusion: Angioedema is a potentially fatal condition when it affects the airway, and should be recognized by anesthesiologists and physicians working in the emergency departments.

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https://doi.org/10.1016/j.bjane.2019.09.002

PALAVRAS-CHAVE
Angioedema;
Bradicinina;
Maleato de enalapril;
Enzima conversora da angiotensina;
Inibidoras da enzima conversora da angiotensina

Angioedema pós-operatório induzido por inibidor da enzima conversora da angiotensina: relato de caso

Resumo
Justificativa e objetivos: O angioedema é uma condição potencialmente fatal que pode surgir em qualquer momento no perioperatório. Pode decorrer da liberação de histamina, em uma reação de hipersensibilidade a drogas ou ser desencadeado pela bradicinina, em reações não alérgicas, de etiologia hereditária ou adquirida. O objetivo desse relato é descrever um caso de angioedema, no pós-operatório imediato, em um paciente em uso de medicação anti-hipertensiva da classe dos inibidores da enzima conversora da angiotensina.
Relato de caso: Paciente de 67 anos, masculino, negro, hipertenso e em uso do maleato de enalapril, foi submetido a cirurgia ortopédica de ombro sob anestesia geral associada a bloqueio do plexo braquial. O procedimento durou 3 horas, sem intercorrências. Após a alta da sala de recuperação pós-anestésica, apresentou angioedema com grave comprometimento das vias aéreas. Tentou-se fazer intubação traqueal, mas foi impossivel devido ao edema que acometia os lábios, a língua e região orofaringeana. Fez-se a cricotireoidostomia de emergência. O aparecimento do angioedema não apresentou relação causal com a administração de qualquer medicação, não houve manifestações cutâneas e também não respondeu à terapêutica para reação de hipersensibilidade a drogas, como anti-histamínicos, corticoide e adrenalina. Foi considerado como mediado pela bradicinina, pois o paciente já havia apresentado dois episódios semelhantes e estava em uso regular de medicação (enalapril). A evolução foi satisfatória.
Conclusão: O angioedema é uma condição potencialmente fatal quando atinge as vias aéreas e deve ser de conhecimento do anestesiologista e dos médicos que trabalham nos setores de emergência.

Introduction

Angioedema is characterized by abrupt episodes of edema affecting the deep dermal layer of the skin and subcutaneous tissue. It may involve the lips, face, neck, and extremities. It can also occur in the submucosal tissue of various organs, particularly small intestine.[1,2] Laryngeal involvement may be fatal, while intestinal angioedema may be very painful and mimic an acute abdomen. Edema is not depressible and there is no erythema, it prefers areas where the skin is looser (especially the face and genitalia) and rarely itches. Subcutaneous or submucosal capillaries and postcapillary venules are believed to develop increased permeability as a result of the presence of vasoactive mediators, such as histamine, bradykinin, prostaglandins, and proteases.[2] This increased permeability is rapid and causes local plasma leakage resulting in edema. Bradykinin-mediated angioedema may occur in patients with hereditary angioedema (HAE) or acquired angioedema (AAE), as in patients on angiotensin-converting enzyme inhibitors (ACE inhibitors).[1–6]

Angioedema is of particular importance to anesthesiologists because it can appear at any time in the perioperative period and quickly become life threatening, as it may involve and compromise the upper airway mucosa leading to asphyxia.[1]

The aim of the present study is to report the case of a patient who presented with airway angioedema due to the use of ACE inhibitors, which resulted in serious consequences.

Consent to publication: The patient gave written informed consent for this case publication.

Case report

A 67-year-old male patient, 80 kg, black ethnicity, scheduled for emergency surgery on the right shoulder. He had a history of comorbid hypertension under treatment with enalapril maleate (20 mg/twice daily), smoking, and alcoholism; denied allergy and previous surgical procedure. On physical examination, he was clinically stable—airways without predictive tests for difficult intubation. Laboratory tests showed anemia with hemoglobin equal to 7.9 $g.dL^{-1}$. Blood transfusion was performed with two units of packed red blood cells, under the medical clinic discipline guidance. The electrocardiogram showed no significant changes and chest X-ray was normal. His physical status was classified as ASA 2, according to the American Society of Anesthesiologists (ASA). The patient was treated with enalapril maleate (20 mg) at standard time; there was a 4 h interval

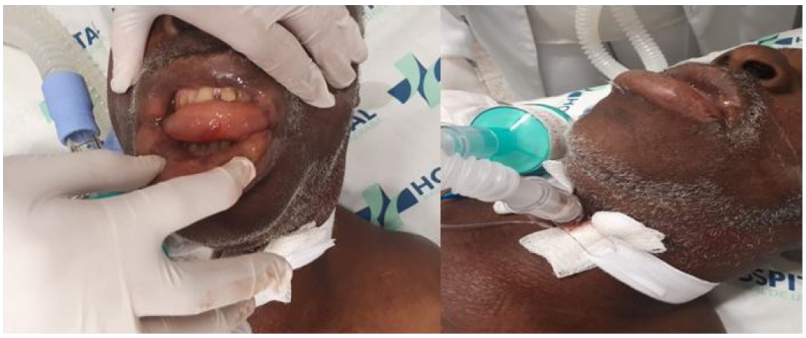

Figure 1 Picture of the patient 18 hours after emergency cricothyrotomy, presenting with macroglossia and lip edema.

before surgery. He received no pre-anesthetic medication and was admitted to the operating room with blood pressure (BP) equal to 152/72 mmHg and heart rate (HR) equal to 77 beats per minute (bpm). The patient was also monitored by means of a cardioscope, pulse oximetry, and capnography. General anesthesia with tracheal intubation was performed, combined with ultrasound-guided supraclavicular brachial plexus block. General anesthesia was induced with midazolam (5 mg), fentanyl (200 mcg), lidocaine (60 mg), propofol (120 mg), and rocuronium (40 mg). Brachial plexus block was performed with 0.375% ropivacaine (150 mg), and cefazolin (2 g) was given prior to surgical incision. Anesthesia was maintained with sevoflurane via a calibrated vaporizer, with inspired fractions ranging from 2% to 2.5%. The duration of the anesthetic-surgical procedure was 210 minutes. At the beginning of anesthesia, he had episodes of hypotension treated with low doses of metaraminol. And 20 minutes before the end the procedure, there was an increase in blood pressure, which was not related to the change in inhalation anesthetic concentration or presence of any other stimulus outside the surgical field. Blood pressure reached 180/120 mmHg. During this period, dipyrone (2 g), ondansetrone (8 mg), and hydrocortisone (500 mg) were administered. After surgery, he received atropine (1 mg) and neostigmine (2 mg). Hypertension was treated with slow administration of intravenous clonidine (75 g diluted in 100 mL 0.9% saline). Still on this medication, the patient was taken to the Post-Anesthesia Care Unit (PACU). Blood pressure (BP) remained around 160 $\times$ 100 mmHg and heart rate (HR) at 60 bpm during the 2-h PACU stay, where he received only oxygen via face mask. With an Aldrete and Kroulik Scale score of 9 and no complaints, the patient was discharged to the ward. About 30 minutes after admission, the nurse requested the presence of the doctor on duty in the ward because the patient presented with lip edema, macroglossia, difficulty breathing, and presence of laryngeal stridor and difficulty articulating words. No medication had been given after the patient arrived at the ward, but the on-duty doctor began treatment for anaphylaxis with oxygen via nasal catheter, intravenous hydrocortisone, and intramuscular promethazine. Physical examination showed diffuse pulmonary snoring, BP 170/100 mmHg, HR 88 bpm, and peripheral oxygen saturation (SpO_2) equal to 98%. His condition evolved with worsening of snoring and absence of speech, but maintained the hemodynamic stability and normal SpO_2. He received a sequence of medications that included intravenous diphenhydramine, ranitidine, and adrenaline without any improvement with either drug. The on-duty doctor then opted for tracheal intubation after fentanyl (100 μg) and etomidate (20 mg) administration. But due to airway edema, he was unable to intubate and opted for an emergency bedside cricothyrotomy with insertion of a cannula number 7.0. Without further complications, the patient was taken to the Intensive Care Unit (ICU) and maintained on mechanical controlled ventilation under sedation. The anesthesiologists were informed of the episode only on the following day, when the patient was taken to the definitive surgical tracheostomy. The patient still had significant tongue and lip edema (Fig. 1). He remained hospitalized for another seven days and was discharged. In contact with the patient's relatives, his daughter reported that he had had a similar condition twice after starting treatment for hypertension and had been admitted to a hospital until the problem was resolved. Since the patient (father) was addicted to alcohol, she did not know more details. Upon return to the orthopedics outpatient clinic, the patient was referred to the cardiologist, with a recommendation to change the antihypertensive medication to another class of medication other than ACE inhibitors.

Discussion

The present case illustrates the emergence of an angioedema after discharge from PACU, which resulted in a risk of hypoxia due to severe airway involvement. An emergency surgical approach was required to ensure patient oxygenation, which resulted in increased morbidity with ICU admission and need for new procedures, such as central venous puncture and surgical tracheostomy, in addition to prolonged hospital stay.

After emergency care, the next question was to elucidate the event etiology and pathophysiology. Since the patient had undergone general anesthesia combined with brachial plexus block, and thus received several medications, the first hypothesis to be considered was that it would be a drug hypersensitivity reaction (DHR). However, in this case it was difficult to detect the possible drugs responsible for the reaction, since at the time of angioedema manifestation no drug was administered and the last one received by the patient was about 3 hours earlier. Thus, elucidating the cause of the reaction became difficult. Causal diagnosis is necessary for the patient to be informed, not become vulnerable and risk his life in another situation. For such, some knowledge is important.

Acute episodes of angioedema are mostly mediated by histamine or bradykinin.[1,4,6] Histaminergics are of allergic origin and usually occur in DHR, called immediate reactions.[6–8] These reactions usually occur within 1 hour of taking a triggering drug and involve mast cells and/or basophils. Usually, clinical manifestations are isolated urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, intestinal symptoms (nausea, vomiting and diarrhea) or anaphylaxis, with or without cardiovascular collapse (anaphylactic shock). In retrospective reviews of intraoperative DHR, the most commonly identified causal agents were antibiotics, neuromuscular blockers, opioids, and latex.[9] However, in 53% of anaphylaxis cases in a single large institution, no causative agent was found in the postoperative allergy skin test. Most patients present with onset of symptoms within minutes of antigen exposure, and these symptoms usually subside after taking drugs, such as antihistamines, corticosteroids, and adrenaline.[2,7,8]

A secondary response, or late phase, may occur after 1 hour of allergen exposure and results from the synthesis of leukotrienes, prostaglandins, and platelet activating factor. These late reactions are associated with variable skin symptoms and their mechanism is heterogeneous, although they are predominantly mediated by T cells.[7,8] Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly related to these late manifestations.[7] Our patient did not receive NSAIDs and also had no history of allergic reaction to these drugs. No drugs were given for a period of 3 hours. Thus, the DHR diagnosis, both immediate and late, was ruled out, due to the absence of temporal relationship of angioedema onset and drug administration during anesthesia. Also due to the absence of skin allergic reaction and lack of response to the instituted therapy (corticosteroids and antihistamines), the condition persisted for more than 24 hours.

Thus, the patient did not have a histaminergic angioedema, but a bradykinin-mediated angioedema, which is characterized by absence of pruritus and rash and has a gradual onset. High plasma bradykinin levels may be the result of marked production caused by the activation of kinin-kallikrein system or inhibition of its degradation,[2,6] either inherited (HAE) or acquired (AAE). In HAE there is a suggestive clinical history. In the present case, the diagnosis considered was AAE related to ACE inhibitors, since the patient was on regular use of enalapril maleate and had had two previous episodes after starting treatment for hypertension. Non-steroidal anti-inflammatory drugs, especially aspirin,[7] may also be implicated in the genesis of bradykinin-mediated AAE, but the patient received only dipyrone and brachial plexus block for analgesia.

Many events triggered by kinins are related to the use of drugs acting through the angiotensin system, such as ACE inhibitors.[1,3,6] Kinins (bradykinin, calidin, and Met-Lys-bradykinin) are oligopeptides synthesized in plasma and/or interstitial fluid from the activation of kininogens by the action of kallikreins. They are involved in a number of biological events, including vasodilation, increased vascular permeability, pain modulation, smooth muscle contraction/relaxation, and effects on cell proliferation. Bradykinin, a potent vasodilator, is produced from the cleavage of high molecular weight kininogen by the enzyme kallikrein. Angiotensin converting enzyme (ACE), also known as kinase II, converts angiotensin I to angiotensin II and inactivates bradykinin. Angiotensin II has several physiological effects contributing to the genesis of hypertension, such as increased vascular resistance, release of aldosterone from the adrenal cortex, norepinephrine from sympathetic nerve endings, and antidiuretic hormone from the posterior pituitary. ACE inhibitors are commonly used to treat heart failure, hypertension, and other conditions by reducing angiotensin II concentrations, although they also lead to increased bradykinin levels. Of the three enzymes called metalloproteinases, which are primarily involved in bradykinin degradation, ACE (kinase II) is the most effective compared to the other two, aminopeptidase P and neutral endopeptidase. Bradykinin is metabolized to N-Arg-bradykinin, the metabolite of active bradykinin, by ACE/kininase II. Approximately half of the patients with ACE-induced angioedema were found to have an enzymatic defect in the degradation of this active metabolite, which in the presence of ACE inhibitors may result in increased bradykinin activity.[10] The exact mechanism by which ACE inhibitors cause angioedema is not fully understood, but bradykinin has shown to play a role in the pathogenesis of this adverse event due to stimulation of vascular receptors called B2. The binding of bradykinin to these receptors results in vasodilation and increased vascular permeability, leading to accumulation of interstitial fluid and angioedema.[2,3,6] Although other vascular mediators may also be involved.

Since captopril approval to treat high blood pressure in the early 80s, ACE inhibitors, along with angiotensin receptor blockers (ARBs), have been widely prescribed and used in about one third of surgical patients. However, only a small portion of patients develop angioedema. A randomized study[11] involving 12,557 patients treated with enalapril maleate showed an angioedema incidence of 0.68%. Makani et al.[5] reported a 0.3% incidence of ACE inhibitor-induced angioedema in a meta-analysis of 26 randomized studies with 74,875 patients. Although it is an uncommon adverse

event of ACE inhibitors, when analyzing the large number of patients treated with ACE inhibitors, it was found that ACE inhibitors are responsible for one third of the angioedema cases treated at emergency services.[12,13] Patients with an ACE inhibitor-related angioedema will typically have it with all other ACE inhibitors, because angioedema is an adverse event of these drugs and not a hypersensitivity reaction. Therefore, another type of antihypertensive drug should be used in patients with a history of ACE inhibitor-induced angioedema due to its contraindication. Our patient was advised about this conduct. Although several studies have reported angioedema in patients after switching from an ACE inhibitor to an ARB, there is no formal contraindication to prescribing these drugs after the interruption of an ACE inhibitor responsible for this complication.

ACE inhibitor-induced angioedema is more prevalent in African descent patients, secondary to a polymorphism found in the gene encoding aminopeptide P, which plays an essential role in the metabolism of these drugs.[6] It is also found in individuals over 65 years of age and in smokers, characteristics found in our patient. The time interval between initiation of treatment and development of angioedema is variable. Some patients may develop angioedema within one day, 50% within the first week of treatment, while in others it may take eight to 10 years to develop.[3,6,13] There is nothing to suggest a relationship with dosage, type or time of ACE inhibitor administration.[6] In the clinical case reported here, it was not possible to chronologically identify the onset of angioedema outbreaks presented by the patient, in relation to the beginning of treatment with enalapril maleate, as the onset was after the beginning of treatment for hypertension. One study[11] showed a significantly higher incidence of angioedema soon after the start of therapy (3.6/1000 patients in the first month of treatment vs. 0.4/1000 patients after 24 weeks of treatment), with an average period of 10.2 months after the start.

When oral cavity and larynx are affected, edema may progress rapidly to oropharyngeal obstruction with risk of asphyxiation, as was the case reported here. As mentioned in the study[11] involving 12,557 patients treated with enalapril maleate, 0.68% had angioedema, but none was affected severely enough to require tracheal intubation and no deaths were reported either. Other studies, however, reported that 10% of patients with ACE inhibitor-induced angioedema affecting the oral cavity required tracheal intubation, with death reported in seven Afro-descendent patients.

Currently, there are no laboratory tests for ACE inhibitor-induced angioedema diagnosis (in contrast to the low levels of C2, C4, and C1 esterase inhibitors observed in HAE).[1,2,4,6] Instead, a clinical diagnosis is made based on previous use of these drugs and disappearance of angioedema after their discontinuation. The triggers for angioedema onset vary between patients, and also within the same patient, so that predicting complications is not possible. It may be unprovoked or triggered by innocuous stimulation, such as device vibrations, snoring or minor trauma from dental procedures. The frequency of attacks seems to be increased by stress.[14] The perioperative scenario also represents a risk for developing angioedema due to airway manipulation and potential trauma, in addition to psychological and physiological stress.[14] In the present case, surgical stress and airway manipulation by tracheal intubation may be considered as possible causes of angioedema onset. Intuitively, trauma should be avoided during airway manipulation, although there is no clear relationship between the presence of trauma and development of angioedema. Therefore, even if airway manipulation is atraumatic, physicians should be aware of the possibility of developing airway edema. To date, no routine anesthetic has been considered contraindicated in patients with bradykinin-mediated angioedema.

We conclude that, although ACE inhibitor-related angioedema is a rare event, it is a potentially fatal disorder when airway is involved, so this condition should be known to anesthesiologists and physicians involved in emergency care. An in-depth understanding of the angioedema pathophysiology and various etiologies is essential to reduce the frequency and severity of these events.

Conflicts of interest

The authors declare no conflicts of interest.

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