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ANGIOEDEMA OF THE LIPS AND TONGUE AFTER PERINDOPRIL TREATMENT: A CASE REPORT

Yamile Sierra-Gordillo, MD, MSc[1,2]*, Mario Francisco Guerrero Pabón MD, MSc[2], Juan David Lozano-Rincón, MD, MSc[1], Vanessa Figueroa, MD[1]

[1]Clínica Los Nogales, Bogotá, Colombia.
[2]Universidad Nacional de Colombia.

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***Corresponding Author: Yamile Sierra-Gordillo**
Clínica Los Nogales, Bogotá, Colombia.
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ABSTRACT

Background: Angioedema is potentially life-threatening clinical syndrome of sudden and transient onset. It can be hereditary or acquired. Angioedema secondary to angiotensin-converting enzyme inhibitor drugs is a known adverse reaction involving bradykinin and does not respond to conventional treatments. Angiotensin-converting enzyme inhibitor drugs are frequently prescribed for the treatment of arterial hypertension. We report the first case of angioedema in our institution and country**. Case presentation:** An 84-year-old Colombian man attended the emergency department for diffuse abdominal pain, with subsequent appearance of lip edema and sensation of a foreign body in the throat. He had no history of allergies to medications, foods, or previous similar episodes. History of arterial hypertension, for which he had been prescribed perindopril 5 mg every 12 hours, four days before the emergency consultation. Trade name, Coversyl A, contains perindopril arginate 5 mg corresponding to Perindopril 3.395 mg. Physical examination with edema of the lips and tongue. The tests performed were normal. A diagnosis of angioedema induced by perindopril was made, this medication was withdrawn. The patient was hospitalized for two days and was treated with corticosteroids and tranexamic acid with complete recovery and improvement. **Conclusión:** Angiotensin-converting enzyme inhibitors are drugs increasingly used in daily clinical practice, so adverse reactions such as angioedema are becoming more common in emergency medical services.

KEYWORDS: Angiotensin-converting enzyme inhibitor, ACE inhibitor-induced; Angioedema.

INTRODUCTION

Angioedema is a potentially fatal clinical syndrome of sudden and transient onset. It is defined as localized edema without pitting, involving dermal, subcutaneous or submucosal tissues. It can affect the face, lips, upper respiratory tract and gastrointestinal tract. It is secondary to increased vascular permeability due to the sudden release of different mediators such as histamine and tryptase or bradykinin. Angioedema can be hereditary or acquired, resulting from an allergic reaction to food, drugs, autoimmune disorders, inhalants or idiopathic. Acquired angioedema is characterized by acquired C1 esterase inhibitor deficiency, inappropriate activation of the contact kinin system and overactivation of the human complement system.[1]

The most frequent cause of drug-associated acquired angioedema is ACE inhibitors, which account for approximately 25-39% of cases. Angioedema secondary to ACEIs is a known adverse reaction of idiosyncratic presentation involving the bradykinin pathway and is unresponsive to conventional treatments.

The first available oral ACEI; captopril was introduced in 1980, and since then the prescription of this class of drugs frequently prescribed for the treatment of arterial hypertension; and heart failure particularly in patients with heart failure with a reduced ejection fraction and diabetic nephropathy, has increased worldwide, because of its undisputed protective benefits and impact on morbidity and mortality.[2,3] This increased use has led to a higher incidence of ACE inhibitor-induced acquired angioedema.[4]

In some countries such as Australia the Adverse Reaction Advisory Committee has issued a warning in its bulletin about the continued reporting of angioedema due to ACE inhibitors. Among the more than 7000 reports of angioedema since 1970, 13% have been attributed to ACE inhibitors.[5]

In this article we report the first case of ACE inhibitor-induced angioedema presented at our institution. This is a 84-year-old male patient who presented with lip and tongue edema induced by perindopril. This case report of an adverse reaction due to angioedema is the first case reported in our country according to the national pharmacovigilance program consulted as of 2024.

CASE REPORT

An 84-year-old Colombian man consulted the emergency department for three days of clinical symptoms consisting of diffuse colicky abdominal pain with subsequent swelling of the lips and sensation of a foreign body in the throat. He did not present fever, respiratory distress, urticaria, pruritus or other symptoms.

The patient reported that the symptoms started after the change in antihypertensive treatment, four days ago, the treating physician discontinued losartan and changed it to perindopril.

He had no history of allergies to medications, food or previous episodes of the same characteristics.

Histories of hypertension, hypothyroidism, prostate cancer in remission, chronic obstructive pulmonary disease, chronic sensory and motor polyneuropathy and obstructive sleep apnea were recorded.

He had been prescribed perindopril 5 mg every 12 hours, four days prior to the emergency consultation,and he had not ingested other medications, xenobiotics or food other than usual ones.

In the physical examination he presented vital signs within goals for the age group. He was oriented, and as the only finding he had edema of the subcutaneous cellular tissue of the lower hemiface, without other relevant alterations.

There were no signs of respiratory distress, and auscultation was normal. There was no inspiratory stridor or other abnormal sounds.

The abdomen was soft, and nonpainful with normal bowel sounds, and no masses or megaliths were palpable.
The skin was normal in appearance, and there were no dermal lesions or any type of rash.

Labs performed were CBCs with normal cell lines, especially those with no eosinophilia. Electrolytes and azotemia were normal. In addition a chest X-ray and ultrasound of the abdomen were performed without relevant findings.
A diagnosis of perindopril-induced angioedema was made, so this ACEI was withdrawn. The patient was given intravenous fluids, and antihypertensive therapy was adjusted with losartan and amlodipine. He received a single dose of hydrocortisone 100 mg, micronebulization with budesonide and a single intravenous dose of tranexamic acid 1 g.
He was hospitalized under surveillance for two days, presenting complete resolution of the inflammatory changes in the face, without involvement of any other organic system, and achieved adequate control of blood pressure. He was discharged with an allergology control order and a recommendation of no re-exposure to perindopril.

The causality of the adverse reactions secondary to perindopril was assessed via the Naranjo algorithm, with a probable result.

DISCUSSION

We report the case of an older Latino male born in Colombia who presented with perindopril-induced angioedema of the lower hemiface.

Angioedema is characterized by local, asymmetric swelling of the skin or mucous membranes. The pattern of swelling is an important diagnostic consideration, particularly if it occurs with or without urticaria. Recurrence of angioedema without urticaria mandates evaluation for C1INH deficiency.Cases of recurrent angioedema with associated urticaria or pruritus that are histamine-mediated may be considered to be on the spectrum of chronic urticaria.[6] Our patient presented for the first time with a clinical picture not associated with pruritus or urticaria.

The incidence of ACE inhibitor-induced angioedema has been investigated and it is estimated that between 0.1% and 0.7% of patients treated with these agents develop angioedema involving mainly lip and tongue edema. The incidence rate was 1.97 (1.77-2.18) cases per 1000 person-years. Although rare they can also involve other areas, such as the gut and extremities. Our patient presented with involvement limited to the lips and tongue, as described in most patients.[7,8]

The occurrence of ACEI-associated angioedema is variable in relation to the initiation of treatment. It can occur at any time after a patient starts taking an ACE inhibitor even within 1 day of starting an ACE inhibitor. Most cases were observed within the first 3 months. The risk is highest during the first month, with a relatively constant annual risk of 0.10-0.12 % observed in retrospective studies. In our patient this adverse reaction developed 4 days after the initiation of treatment. ACE inhibitor-induced angioedema can occur at any dose with in the therapeutic range.[8,9]

The mechanism by which ACE inhibitors cause angioedema is not fully understood. Hereditary angioedema and acquired angioedema are related to low levels or abnormal functions of the esterase inhibitor C1, which regulates the complement, fibrinolytic, and contact system pathways. However, in ACE inhibitor-associated angioedema, the inhibition of an enzyme related to bradykinin degradation does not involve proteins of the complement pathway. ACE inhibitors act on the renin angiotensin system, interfering with the conversion of angiotensin I to angiotensin II through the inhibition of ACE, also known as kininase II. ACE is a dipeptidyl carboxypeptidase, the main enzyme responsible for the degradation of 75% of bradykinin, a nanopeptide that is physiologically produced in the kallikrein-kinin system and converts substance P to active metabolites.

The half-life of bradykinin is very short; in the presence of ACE inhibitors it is prolonged by a 5-12-fold increase. Therefore, blockade increases the concentration of bradykinin, and could contribute to the resulting angioedema; however, it is not clear why angioedema affects only one group of treated patients.[10]

There is a population at increased risk for this complication. Reported risk factors for adverse effects of ACE inhibitors include female sex, older age, smoking status, history of seasonal allergies or drug exanthems, immunosuppression, and coronary artery disease. A recent meta-analysis reported three significant loci; 1q24.2 and 14q32.2, which were previously described, and 20q11.22 which is a new risk locus for ACEI adverse effects.[11]

In our patient we identified risk factors described in the literature for development of ACE inhibitor-induced angioedema such as advanced age.

There are no laboratory biomarkers to confirm the diagnosis of ACEI-induced angioedema.

Currently, there are no Food and Drug Administration-approved therapies for the treatment of ACE inhibitor-induced angioedema.(12) The treatment of ACE inhibitor-induced angioedema poses a challenge for clinicians.The evaluation of the suspected drugs and the discontinuation of ACE inhibitor therapy constitute the mainstays of medical management. Supportive measures should then be instituted. Most cases are self-limiting and resolve within 24-48 hours. Medications such as epinephrine, antihistamines and corticosteroids are generally ineffective.

Specific treatments, such as icatibant, a bradykinin receptor antagonist, and ecallantide, a kallikrein inhibitor, are not widely available and data on their clinical efficacy are still lacking.

Treatment options include fresh frozen plasma and tranexamic acid. Fresh frozen plasma, which includes ACE and C1-esterase inhibitors, was first employed for the treatment of angioedema in 1969 and acts by promoting the breakdown of excess bradykinin through its intrinsic enzymatic activity. Despite several years of use in hereditary angioedema, data on its efficacy are limited to clinical cases.

Tranexamic acid is an antifibrinolytic agent that inhibits the passage of plasminogen to plasmin. Plasmin plays a role in kallikrein production by converting factor XII to XIIa, which then promotes the conversion of prekallikrein to kallikrein. Kallikrein is involved in the production of bradykinin. Therefore, it indirectly decreases bradykinin production. Tranexamic acid is well tolerated and easy to administer. It has been reported in the literature as a treatment option but there is a lack of randomized controlled studies to determine whether tranexamic acid is an effective treatment for ACE angioedema.[13]

Finally, it is important to recognize ACE inhibitor-induced angioedema, especially when it involves the respiratory tract, due to the risk of asphyxia for patients. It is also important to recognize that it is not a type I hypersensitivity reaction and that to date there are no approved therapies for its treatment.

CONCLUSION

Angiotensin-converting enzyme inhibitors are drugs increasingly used in daily clinical practice, so adverse reactions such as angioedema are becoming more common in emergency medical services. Healthcare providers should be aware of these risks.

CONFLICTS OF INTEREST

None were declared

Written informed consent was obtained from the patient for publication of this case report.

AUTHOR CONTRIBUTIONS

Yamile Sierra-Gordillo: Conceptualización, writing – original draft ,Writing – review & editing. Juan David Lozano-Rincón: Writing – original draft. Vanessa Figueroa: Writing – original draft. Mario Francisco Guerrero Pabón :reviewing and editing.

REFERENCES

1. Cicardi M, Zanichelli A. Acquired angioedema. Allergy Asthma Clin Immunol, 2010 Jul 28; 6(1): 14. doi: 10.1186/1710-1492-6-14.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernández AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation, 2022 May 3; 145(18): e895-e1032. doi: 10.1161/CIR.0000000000001063. Epub 2022 Apr 1. Erratum in: Circulation, 2022 May 3; 145(18): e1033. doi: 10.1161/CIR.0000000000001073. Erratum in: Circulation, 2022 Sep 27; 146(13): e185. doi: 10.1161/CIR.0000000000001097.
3. Kazi D, Deswal A. Role and optimal dosing of angiotensin-converting enzyme inhibitors in heart failure. Cardiol Clin, 2008 Feb; 26(1): 1-14, v. doi: 10.1016/j.ccl.2007.12.001.
4. Sarkar P, Nicholson G, Hall G. Brief review: angiotensin converting enzyme inhibitors and angioedema: anesthetic implications. Can J Anaesth, 2006 Oct; 53(10): 994-1003. doi: 10.1007/BF03022528.
5. Adverse Drug Reactions Advisory Committee: ADRAC Angioedema—still a problem with ACE inhibitors. Aust Adv Drug React Bull, 2005; 24: pp. 7.
6. Zuraw BL, Bernstein JA, Lang DM, Craig T, Dreyfus D, Hsieh F, Khan D, Sheikh J, Weldon D, Bernstein DI, Blessing-Moore J, Cox L, Nicklas RA, Oppenheimer J, Portnoy JM, Randolph CR, Schuller DE, Spector SL, Tilles SA, Wallace D; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. J Allergy Clin Immunol, 2013 Jun; 131(6): 1491-3. doi: 10.1016/j.jaci.2013.03.034.

7. Moellman JJ, Bernstein JA, Lindsell C, Banerji A, Busse PJ, Camargo CA Jr, Collins SP, Craig TJ, Lumry WR, Nowak R, Pines JM, Raja AS, Riedl M, Ward MJ, Zuraw BL, Diercks D, Hiestand B, Campbell RL, Schneider S, Sinert R; American College of Allergy, Asthma & Immunology (ACAAI); Society for Academic Emergency Medicine (SAEM). A consensus parameter for the evaluation and management of angioedema in the emergency department. Acad Emerg Med, 2014 Apr; 21(4): 469-84. doi: 10.1111/acem.12341.
8. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology of ACE Inhibitor Angioedema Utilizing a Large Electronic Health Record. J Allergy Clin Immunol Pract, 2017 May-Jun; 5(3): 744-749. doi: 10.1016/j.jaip.2017.02.018
9. Desai C. Meyler's side effects of drugs: The international encyclopedia of adverse drug reactions and interactions. Indian J Pharmacol, 2016 Mar-Apr; 48(2): 224.
10. Wilkerson RG, Winters ME. Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema. Immunol Allergy Clin North Am, 2023 Aug; 43(3): 513-532. doi: 10.1016/j.iac.2022.10.013.
11. Mathey CM, Maj C, Eriksson N, Krebs K, Westmeier J, David FS, Koromina M, Scheer AB, Szabo N, Wedi B, Wieczorek D, Amann PM, Löffler H, Koch L, Schöffl C, Dickel H, Ganjuur N, Hornung T, Buhl T, Greve J, Wurpts G, Aygören-Pürsün E, Steffens M, Herms S, Heilmann-Heimbach S, Hoffmann P, Schmidt B, Mavarani L, Andresen T, Sørensen SB, Andersen V, Vogel U, Landén M, Bulik CM; Estonian Biobank Research Team; DBDS Genomic Consortium; Bygum A, Magnusson PKE, von Buchwald C, Hallberg P, Rye Ostrowski S, Sørensen E, Pedersen OB, Ullum H, Erikstrup C, Bundgaard H, Milani L, Rasmussen ER, Wadelius M, Ghouse J, Sachs B, Nöthen MM, Forstner AJ. Meta-analysis of ACE inhibitor-induced angioedema identifies novel risk locus. J Allergy Clin Immunol, 2024 Apr; 153(4): 1073-1082. doi: 10.1016/j.jaci.2023.11.921.
12. Pathak GN, Truong TM, Chakraborty A, Rao B, Monteleone C. Tranexamic acid for angiotensin-converting enzyme inhibitor-induced angioedema. Clin Exp Emerg Med, 2024 Mar; 11(1): 94-99. doi: 10.15441/ceem.23.051.
13. Hasara S, Wilson K, Amatea J, Anderson J. Tranexamic Acid for the Emergency Treatment of Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema. Cureus, 2021 Sep 20; 13(9): e18116. doi: 10.7759/cureus.18116.