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Antihypertensive Drug-induced Orofacial Angioedema: Case Reports

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Antihypertensive Drug-induced Orofacial Angioedema

Case Reports

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ABSTRACT

The antihypertensive medications, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can cause orofacial angioedema (AE). Because the AE can result in serious complications, the dental practitioner must be prepared to make a prompt diagnosis.

Knowledge of a patient's medications is an inherent and vital aspect of any dental examination. Many medications cause adverse reactions whose head and neck manifestations are often first seen by the dental practitioner. The dentist must become aware of the orofacial signs and symptoms that may be caused by these agents. Recognition can prevent serious and/or fatal outcomes. Unfortunately, diagnosis and treatment are frequently delayed because the problem is often misdiagnosed and attributed to other causes, some of which are mistakenly thought to be dental-related.

A not-infrequent adverse reaction from the commonly prescribed antihypertensives, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is orofacial angioedema (AE). The authors wish to call the dental profession's attention to this untoward reaction, and simultaneously emphasize the importance of making a prompt diagnosis.

The AE caused by ACE inhibitors or ARBs usually involves the head and neck, and is defined as a painless, non-inflammatory, non-pitting, non-pruritic, asymmetric edema that can involve the skin, subcutaneous tissues and mucous membranes. The AE may become fatal if it progresses to airway obstruction.[1-11] The incidence of AE with ACE inhibitors has been reported to range from .1% to .7%,[1,8,12-16] but appears to be somewhat lower when ARBs are prescribed.[5,10,16-18] The onset of AE may begin within a few hours or weeks following either medication's ingestion, or its appearance may be delayed for many years following prolonged medication use.[14-21] Dosage does not seem to be a factor in the development of the AE.[5]

The areas of swelling caused by these drugs, in order of frequency, are the oral mucosa, tongue, lips, facial cheek and neck.[7,12] Initially, the edema is mild and resolves rapidly. Multiple transient recurrences can develop, and there is some tendency to increase in severity as time progresses.[2,16] Even a slight swelling should be recognized as an early sign of a potentially serious problem. The average age of AE onset has been reported to be 52 to 62 years, with 65% of the patients being female.[16-21] African-Americans are thought to be more susceptible than Caucasians to the condition.[8,22]

From Columbia University College of Dental Medicine, New York, NY

Case reports of three patients are presented to illustrate the signs and symptoms of orofacial AE associated with the use of ACE inhibitors or ARBs.

Case Reports

Case #1

A 62-year-old male was seen in the hospital's emergency room because of the 24-hour presence of a painless edematous tongue swelling (Figure 1). There was some difficulty with speech and deglutition.

The patient's medical history indicated that he was being medicated for reflux disease (omeprazole), an enlarged prostate (tamsulosin), elevated cholesterol (atorvastatin) and hypertension. He stated that he had no allergies. Because of his elevated blood pressure, lisinopril (20 mg daily), an ACE inhibitor, has been prescribed for the past 10 years. According to the patient, there have been no previous episodes of orofacial edema despite his long-term use of lisinopril.

Because of a concern regarding airway blockage, intravenous steroid therapy was administered and the patient was observed for 12 hours, during which time significant resolution of the tongue swelling occurred. An oral prednisone taper was prescribed and the patient was allowed to go home. The next day, he reported that the tongue swelling had totally resolved. He was told to discuss the use of alternative antihypertensives with his internist.

Case #2

A 59-year-old male was seen in Columbia University College of Dental Medicine with a one-day painless swelling of the lower lip (Figure 2). Palpation revealed that the lower lip was edematous and not indurated. Pruritis was not present. Intraorally, no dental pathology was evident.

A medical history indicated that other than a history of hypertension and elevated cholesterol, there were no medical issues or history of any allergies. To address the patient's hypertension, the ARB irbesartan (150 mgm twice a day) has been used as a medication for the past seven years. His other medications included rosuvastatin because of an elevated cholesterol level and the diuretic hydrochlorothiazide. No other medications have been used by the patient.

During the seven years of ARB therapy, there were no previous episodes of orofacial AE. Because the AE was limited to the lip and had stabilized, no therapeutic intervention was advised. The swelling resolved spontaneously within 36 hours. The patient was referred to his internist for further evaluation.

Case #3

A 62-year-old female was referred by her dentist to the Columbia University College of Dental Medicine in May 2017 regarding a right facial swelling present for three days. By the time the patient was seen, no swelling was evident. She did state that during

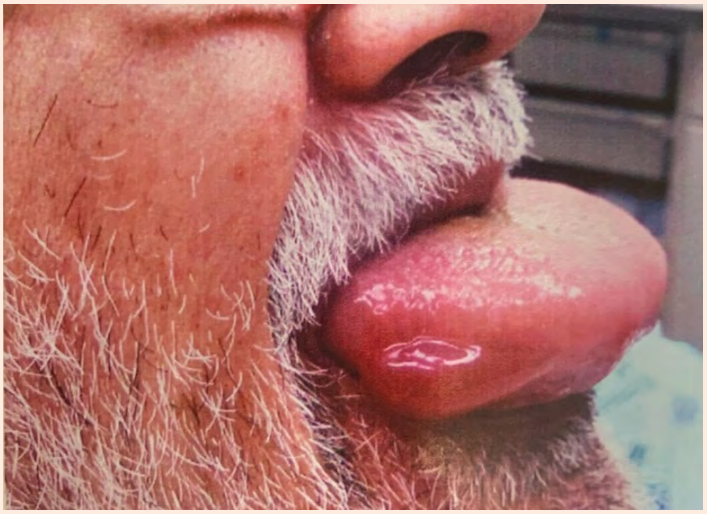

Figure 1. Case 1: Angioedema of tongue.

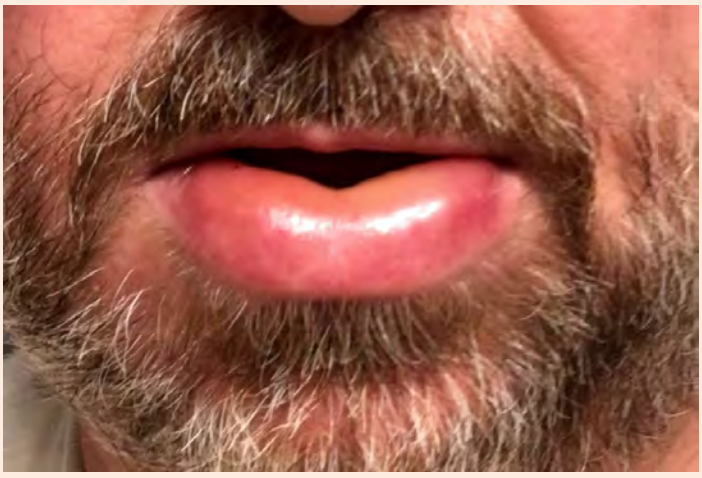

Figure 2. Case 2: Angioedema of lower lip.

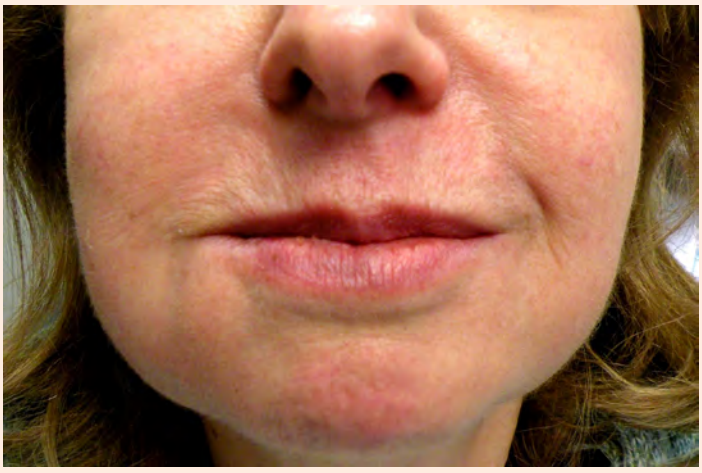

Figure 3. Case 3: Right facial swelling extends to inferior border of mandible. There is significant obliteration of right nasolabial fold.

the previous year, a similar transient (two days) swelling had occurred on the left side.

Her medications included the ARB valsartan (160 mg daily), which was first prescribed in 2012 for her hypertension. Montelukast for asthma and atorvastatin for an elevated serum cholesterol level have also been prescribed. No other medications were being used. The patient stated that the swelling had disappeared 48 hours prior to her visit. Extraorally, palpation of the facial tissues revealed them to be normal in tone and painless. No cervical lymphadenopathy was evident. Intraorally, the mucosa was normal in appearance and no dental pathology was noted. Because no definitive diagnosis could be made, she was advised to return immediately if the swelling recurred. In the presence of a visible swelling, a more accurate evaluation could be made.

In September 2017, the patient phoned to say the right facial swelling had returned. She was seen the next day when, according to her, the swelling had now subsided significantly. Nevertheless, a moderate swelling was still apparent (Figure 3). The extraoral examination revealed a visible swelling of the right facial buccal soft tissues that extended from the right infraorbital area to involve the soft tissues over the inferior border of the body of the right mandible. The right nasolabial fold was mostly obliterated. Visibly, no erythema was seen and pruritis was absent. Palpation of the distended right buccal tissues caused no pain, and there was no induration. The tissues did feel edematous, but pitting was not evident. A diagnosis of AE caused by the ARB was made.

The patient was referred to her physician who prescribed an alternative antihypertensive. Subsequent contact with the patient (nine months later) indicated that the facial swelling had subsided one day after her visit and that there had been no recurrences.

Discussion

Facial edema associated with the angiotensin-related antihypertensives was first reported by Jett in 1984.[23] The causation of the AE from an ACE inhibitor differs from that caused by an ARB. An ACE inhibitor blocks the activation of ACE, otherwise known as kinase II. Kinase II stimulates the conversion of angiotensin I to II, a vasoconstrictor that serves to inactivate bradykinin.[6-8,14,16,18] The chemical mediator bradykinin encourages vasodilation and increases capillary permeability. Because bradykinin is not inactivated, its ability to favor tissue edema from a vasodilation and an increase in capillary permeability is significantly enhanced. The resulting AE is not allergic in origin, as determined by the absences of eosinophilia and/or an elevated serum IgE.[16]

ARBs were introduced as alternatives to the ACE inhibitor. It was falsely thought that the change would avoid the AE encoun-

tered with an ACE inhibitor. Nevertheless, the ARB has also been shown to cause AE.[5,10,16-18] The exact role of the ARB in producing AE is not fully understood. It has been suggested that ARBs selectively block vascular AT1 receptors. Consequently, the unopposed AT2 receptors are activated. This process results in an elevated level of tissue bradykinin that then causes AE from the increase in vasodilation and vascular permeability. [14,18,24,25] Regardless of the mechanism of action, the signs and symptoms of ARB edema are essentially the same as those caused by the ACE inhibitors.

Our patients represent classic examples of orofacial AE associated with an ACE inhibitor or an ARB. Specifically, the ARBs irbesartan and valsartan have been reported as causative agents.[5,11,14,26-28] The ACE inhibitor lisinopril has been similarly cited.[29,30] Over a five-year span, our third patient had three mild and transient episodes of facial edema. The left side was involved once, while there were two episodes involving the right buccal tissues. All episodes resolved rapidly with no treatment.

Our first and second patients each had only one episode of AE, despite their long use of the inciting medication. The tongue (Case 1), lip (Case 2) and cheek (Case 3) swellings rapidly resolved. Nevertheless, there is a tendency for AE episodes to intensify in time and even become life-threatening. Progression to airway compromise, with its need for intubation or tracheostomy, is a threatening possibility.

AE has varied origins and a differential diagnosis is required. Many AEs are related to allergies from food that may contain substances that encourage mast cell degradation with the resulting release of the edema-causing mediator histamine.[7,18,20,22] Other acquired causes of AE include temperature extremes, some other medications and trauma.[8] Hereditary AE is an autosomal dominant defect of C-1 esterase inhibitor, whose absence can readily be detected through serologic testing.[7,18,22] Of interest is the fact that edema that involves areas other than the head and neck is rarely seen in association with an ARB or an ACE inhibitor.[16]

Treatment

The orofacial AE symptomatology associated with an ACE inhibitor or ARB can be mild or severe. Mild transient episodes of edema not only require reassurance, but also demand medical referral for medication re-evaluation. In severe cases, the treatment protocol involves the use of intravenous steroids, diphenhydramine and intramuscular epinephrine. This approach has proven to be the therapeutic standard. A need for intubation or tracheostomy is dependent upon the existence and severity of airway obstruction, combined with the patient's response to the administered therapeutic agents.

Queries about this article can be sent to Dr. Mandel at lm7@cumc.columbia.edu.

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REFERENCES

1. Peacock ME, Park DS, Swiec GD, Erley JK. Perioral angioedema associated with angiotensin-converting enzyme inhibitor. J Periodontol 2005;76:651-654.
2. Forslund T, Tohmo H, Weckstrom G, Stenborg M, Jarvinen S. Angio-oedema-induced by enalapril. J Int Med 1995;238:179-181.
3. Shionoiri H, Takasaki I, Hirawa N, et al. A case report of angioedema during long-term (66 months) angiotensin-converting enzyme inhibition therapy with enalapril. Jpn irc J 1996;60:166-170.
4. Gaboriau HP, Solomon JW. Angioneurotic edema. J La State Med Soc 1997;149;50-52.
5. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. Ann Pharmacother 2000;34:526-528.
6. Chiu AG, Krowiak EJ, Deeb ZE. Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology. Laryngoscope 2001;111:1729-1731.
7. Tisch M, Lampl L, Groh A, Maier H. Angioneurotic edema of the upper aerodigestive tract after ACE-inhibitor therapy. Eur Arch Otorhinolarynhol 2002;259:419-421.
8. Zanoletti E, Bertino G, Malvezzi L, Benazzo M, Mira E. Angioedema of the upper airways and antihypertensive therapy. Acta Otolaryngol 2003; 123:960-964.
9. Elinav E. Rabinowitz Y, Lorberbaum M, Nisanewitz V. Episodic macroglossia as the sole manifestation of angiotensin-converting enzyme inhibitor-induced angioedema. Ann Otol Rhinol Laryngol 2004;113:223-224.
10. Ciaccio CE. Angioedema: an overview and update. Mo Med 2011;108:354-357.
11. Kalra A, Cooley C, Palaniswamy C, Karla A, Zanotti-Cavazzoni SL. Am J Ther 2012; 19: e189-92.
12. Thompson T, Frable MAS. Drug-induced life-threatening angioedema revisited. Laryngoscope 1993;103:10-12.
13. Nielsen EW, Stenberg PA, Einarsen E, Johansen HT, Molines TE. Angioedema associated with ACE inhibitors. Tidsskr Nor Laegforen 1994;114:804-806.
14. Irons BK, Kumar A. Valsartan-induced angioedema. Ann Pharmacother 2003;27:1024-1027.
15. Moss JR, Zanation AM, Shores CJ. Ace inhibitor-associated recurrent intermittent parotid gland swelling. Otolaryngol Head Neck Surg 2005;133; 992-994.
16. Grant NN, Deeb ZE, Chia SH. Clinical experience with angiotensin-converting enzyme inhibitor-induced angioedema. Otolaryngol Heck Neck Surg 2007;137:931-935.
17. Duerr M, Glander P, Diekmann F, Dragun D, Neumayer H-H, Budde K. Increased incidence of angioedema with ACE inhibitors in combination with mTor inhibitors in kidney transplant recipients. Clin J Am Soc Nephrol 2010;5:703-708.
18. Nykamp D, Winter EE. Olmesartan medoxomil-induced angioedema. Ann Pharmacother 2007;41:518-520.
19. Kazim SF, Shahid M. Losartan-associated anaphylaxis and angioneurotic edema. J Pak Med Assoc 2010;60:685-686.
20. Kanani A, Schellenberg R, Warrington R. Urticaria and angioedema. Allergy, Asthma Clin Immunol 2011;7 (Suppl l):59.
21. Wahbe L, Schultz-Coulon H-J. Angioneurotische odeme des Kopf-Hals-Bereiches unter der Therapie mit ACE-Hemmen. HNO 2007;55:709-715.
22. Tai S, Mascaro M, Goldstein NA. Angioedema: a review of 367 episodes presenting to three tertiary care hospitals. Ann Otol Rhinol Laryngol 2010;119: 836-841.
23. Jett GK. Captopril-induced angioedema. Ann Emerg Med 1984;13:489-490.
24. Griendling KK, Lasseque B, Alexander RW. Angiotensin receptors and their therapeutic implications. Annu Rev Pharmacol Toxicol 1996;36:281-306.
25. Volpe M, DePaolis P. Angiotensin II AT2 subtype receptors: an emerging target for cardiovascular therapy. Ital Heart 2000;1:96-103.
26. Conesa AR, Fernandez M, Reques G. Angioedema due to irbesartan. Rev Esp Cardiol 2010;54:532.
27. Nielsen EW, Hypotensive shock and angio-oedema from angiotensin ll receptor blocker: a class effect in spite of tripled tryptase values. J Intern Med 2005;258:385-7.
28. Tan CH, Tang SC, Lin RJ, Jeng JS. Neurologic picture. Orolingual angio-oedema after altepase therapy in a stroke patient concurrently using angiotensin ll receptor blocker. J Neurol Neuro surg Pyschiatry 2010;81:1079.
29. Gutman I. Acutely swollen tongue in a middle-aged woman. Am Fam Physician 2010; 82:279.
30. Ducote A, Kesterke MJ, Bhattacharjee R, Reed-Fuller A, Reddy LV. Macroglossia secondary to lisinopril-induced acute angioedema. Proc (Bayl Univ Med Cent) 2019; 32:70-72.