Angiotensin-Converting Enzyme Inhibitor-Induced Oropharyngeal Angioedema Following Cystoscopy Using Proseal LMA: A Case Report.

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Oropharyngeal angioedema is a potentially disastrous perioperative airway complication. The anesthesiologist must efficiently diagnose and treat progressive airway obstruction, a process that involves differentiating between mechanical, pathologic, and reactive causes. Angioedema developing from angiotensin-converting enzyme inhibitor (ACEi) therapy is a relatively rare but perhaps under-diagnosed complication of this common therapeutic class. This report details a case of oropharyngeal angioedema following an otherwise uneventful cystoscopy.

Case Report

A 75 year old caucasian male was scheduled for cystourethroscopy with bilateral replacement of ureteral stents and possible retrograde pyelogram and ureteroscopy. His medical history included metastatic prostate cancer and new onset hypertension; his surgical history was limited to prior cystourethroscopy with stent placement. The patient's only known medical allergy was penicillin.

The patient was prepared for anesthesia by preoperative interview and chart review, his questions were answered and a brief physical exam was conducted. He was transported to the operating suite where, using standard monitors, general anesthesia was induced with 1.8 mg/kg Propofol and 1 µg/kg Fentanyl. A staff CRNA placed a #4 proseal laryngeal mask airway (PSLMA) atraumatically under supervision by an attending physician, followed by placement of a commercially produced plastic molar bite guard. Placement of the LMA was confirmed by positive pressure ventilation, breath sounds, and end tidal CO₂. A Salem sump was easily passed via PSLMA, aspirating a minimal volume of fluid. Anesthesia was maintained using Sevoflurane in .50 FiO₂ at 3.5 L/min, and an additional 25 µg fentanyl and 4 mg ondansetron were administered. Respiration remained spontaneous with pressure assistance throughout the case; no difficulty with PSLMA function was documented for the remainder of the 60 minute case. Finally, sevoflurane was discontinued, monitors were removed, and the patient was transported to PACU while respiring spontaneously via #4 PSLMA. Fluid volume administered was 500 ml lactated ringer's.

Following an uneventful PACU course, the patient was transferred to a surgical step-down floor without complaint or distress. Approximately 2 hours following PACU discharge, the on-call resident was notified of the patient's new-onset odynophagia secondary to lingual swelling. Though the patient demonstrated no respiratory distress, physical exam revealed a painless sublingual/lingual evanescent, pruritic, non-pitting edema. No mucosal trauma was evident except a small soft palate abrasion. Lab values were unchanged from prior to the surgery. A list of medications included atenolol 12.5 mg P.O. Q.D., and a new lisinopril 5 mg P.O. Q.D. prescription. Further questioning revealed the patient had taken his 4th ACEi dose the morning of his surgery.

The patient was placed on pulse oximetry and given diphenhydramine, solu-medrol, and ranitidine while his lisinopril was discontinued. The hospitalist service was consulted and replaced lisinopril with losartan 50 mg P.O. Q.D. No further complications developed, and the patient was discharged the following day with instructions to follow up with both urology and his primary care physician.

Discussion

ACEi are a mainstay of monotherapy for both congestive heart failure and for hypertension. While their side effect profile remains favorable, this class is not without complications ranging from
bothersome to life-threatening (5,11,14). Angioedema represents one of the most ominous side effects of ACEi therapy, but is reported to be relatively rare. A published incidence of 0.1-0.2% may fall shy of actual occurrence, as these numbers were derived only from reported cases in a primarily Caucasian population (9-12). Actual cases may be more common, and some estimates suggest that up to 25% of angioedema cases can be attributed to ACEi therapy (12-14). Angioedema secondary to ACEi is independent of concurrent medications and dosage, and is more common and severe in black males (1,12,13). 60-70% of cases will arise within the first week of therapy, though some cases present months or years after treatment initiation (2,6,10). Angioedema presents as painless, non-pitting, circumscribed edema of varying size, and often effects the gastrointestinal tract and genitalia, but more commonly involves orofacial tissues in ACEi associated cases, with a noted predilection for the lips, tongue, uvula, or upper respiratory tract (3-6,12-14).

Multiple theories exist on the etiology of ACEi induced angioedema, though exact mechanisms remain undefined. Antibody formation of tissue-specific, antinuclear, and IgG varieties have been demonstrated following long-term administration of ACEi in 8-53% of this group. While cutaneous reactions secondary to other drug classes are thought to be immune-mediated, the variable time frame following ACEi administration seems to discredit this theory (12). Additionally, the angioedema observed in association with ACEi therapy is histo-logically confined to the subcutaneous and deeper dermal layers, while many immunologically mediated cutaneous reactions (urticaria, rash, pemphigus reactions) affect more superficial tissues (8,11-13).

ACEi interfere with the enzyme cascade of the complement system, and may result in elevated kallikrein activation and ensuing bradykinin production, which in combination with a plasmin-produced C2 kinin has been proven to provoke angioedema. Nonetheless, reactions are reported to the entire ACEi class rather than specific chemical molecules, suggesting the mechanism may be related to their pharmacologic action rather than an immunologic response (9-13).

Inflammatory mediators leading to histamine release are potential players in ACEi angioedema development. ACE inhibitors limit kinase II activity inhibiting bradykinin degradation, and the above mentioned complement cascade interference serves to amplify circulating bradykinin levels. Bradykinin can lead to increased vascular permeability and vasodilation, as well as mast cell degranulation liberating histamine and potentiating vasodilation and cutaneous flushing associated with wheal and flare reactions (3,6,14). Local tissue injury may initiate a cycle of events leading to angioedema development due to vasoactive substances either recruited to or liberated by injured tissues. The result is a multi-factorial event of concurrent tissue injury (airway instrumentation or head and neck procedures), genetic predisposition (complement, carboxypeptidase N, α-1 antitrypsin, and ACE deficiencies) and the described complication associated with ACEi agents (7,11,12).

Most cases of ACEi related angioedema are mild, self-limited and responsive to treatment (2,9,11,12). Occasionally swelling can persist or resume following proper treatment, and it is difficult to predict which cases represent the greatest risk in this regard. The location of angioedema relates to the degree of airway risk, with the majority of cases confined to the anterior tongue and fewer patients complaining of dysphagia or demonstrating posterior oropharyngeal involvement (8,12). An oropharyngeal predilection combined with the potential for rapid swelling lends itself to obvious airway concerns, occasionally necessitating emergent tracheal intubation or tracheostomy. 22% of angioedema cases were considered life threatening due to respiratory distress in one retrospective study, and reports of mortality due to ACEi related angioedema exist (3,5,11).

Management of ACEi related angioedema hinges on discontinuation of the offending agent. Therapeutic alternatives exist, and are best selected by those specializing in long-term management of the patient’s condition (2,4,12). Additional care is supportive with frequent airway assessment and respiratory monitoring. Appropriate management involves a team approach between anesthesiologist and otolaryngologist as progressive swelling can create difficult intubating conditions (4,9). Mild cases confined to the tongue commonly respond to discontinuation of the ACEi as well as intravenous diphenhydramine, corticosteroid, and H2 antagonist therapy. Rarely, .01 mg/kg subcutaneous epinephrine may be required by the stridorous, failing patient, as well as definitive airway maneuvers best accomplished in a surgical environment (5,6,8,11-13).
Summary

This case report highlights a relatively rare but potentially fatal reaction to a commonly prescribed agent. Mechanisms of ACEi angioedema are poorly understood, though it appears a combination of recent ACEi therapy initiation with a gender, racial or undiagnosed genetic condition, along with airway instrumentation and/or head and neck procedures increases the likelihood of this reaction. Prompt, repetitive airway observation is of paramount importance in management, and difficult airways may rapidly develop despite apparent resolution. Surgical airway consultation must be considered depending on progression and severity. ACEi agents must be discontinued if suspected, and antihistamine/antiinflammatory agents may be helpful with epinephrine reserved for emergent measures.

References