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Angiotensin converting enzyme related angioedema

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Introduction

A 54 year old female patient arrives to the emergency department (ED) via squad complaining that 2 days ago her lips were tingling and her face felt a little swollen but it subsided. Today she woke up with her tongue protruding out of her mouth, her lips, face and eyes are swollen. She does not present with itching or urticaria. Squad personnel established an IV, gave her intravenous (IV) Benadryl 50 mg, and 0.3 mg subcutaneous epinephrine without any change in her condition. The emergency medical service (EMS) also applied oxygen at 2 liters per minute (lpm). She denies taking any new medications or being around any possible new allergens. She has a list of her medications and it includes aspirin, Metformin, Simvastatin, and Lisinopril, all of which she has been on for over a year. Vital signs are BP 184/110 mm/hg, HR 116 bpm, RR 16/min, temporal temperature 98.2 F., and SPO2 96% on 2 lpm of oxygen. Perplexed, the ED staff begins their care of this anaphylactic appearing reaction.

This presentation to the emergency department has become more common and is classic for the diagnosis of ace-inhibitor (ACEi) related angioedema. Although it looks like a histamine mediated response, it does not respond to typical emergency treatments and is thought to be a bradykinin mediated response. Angioedema is a well recognized adverse effect of ACEi and is drug class specific, not dose specific, with symptoms appearing from initial dosing to 10 years post initiation. The incidence of ACEi angioedema is 0.1% to 1% with 40% of those patients presenting months to years after initial dosing (Winters, Rosenbaum, Vilke, & Almazroua, 2013). Tai et al. cite a female predominance of 65.7% of retrospective reviews, the mean age was 51.8, and racial composition was 10.9% Caucasian, 62.4% African American, and 14.7% Hispanic (Tai, Mascaro, & Goldstein, 2010). It is prudent that this diagnosis is recognized, the pathophysiology understood, and treatment measures taken to control life threatening symptoms and prevent future reactions.

Signs and symptoms

Angioedema (AE) is characterized by nonpitting edema of the dermis and subcutaneous layers. The most common sites of involvement are the tongue, lips, face, and throat. Airway compromise is rare but drooling, stridor, dysphagia, are symptoms that may require primary or advanced airway control (see appendix B). Swelling can occur in the extremities, genitalia, and viscera of the abdomen causing abdominal pain that may be unexplained or misdiagnosed with the routine testing performed in the ED (Lewis, 2013). A careful history and physical exam can help the practitioner differentiate between a histamine mediated reaction from a bradykinin mediated angioedema reaction.

Known recent exposure to triggers such as certain foods, insect stings, sulfa drugs, penicillins, or other drug classes can lead a differential diagnosis as histamine mediated response. Rapid onset of the swelling accompanied by hives and itching are key indicators of an allergic reaction. Bradykinin mediated angioedema is not typically accompanied by urticaria (Cicardi, et al., 2014).

(Rasmussen,Mey,& Byg, 2014, p. 1)

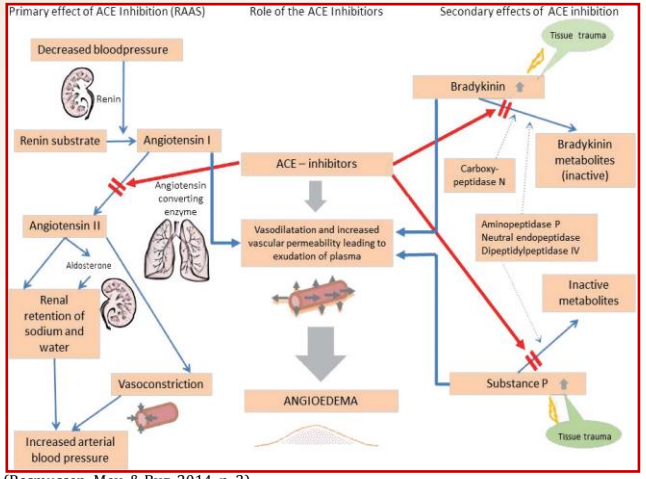
Pathophysiological process

Angiotensin converting enzyme (ACE) is activated by the negative feedback loop of the renin-angiotensin-aldosterone system (RAAS). Renin is stimulated in the kidneys by decreased circulating blood pressure, serum sodium concentrations, or sensing low renal perfusion; in hypertensive patients this could be from renal artery stenosis. Renin stimulates creation of angiotensinogen I. Angiotension I is then converted to angiotensin II (a potent vasoconstrictor) by ACE in the lungs. Angiotension II causes vasoconstriction and the aldosterone system to stimulate sodium and water retention in the tubules of the kidneys that contributes to the increase in blood pressure (Appendix A). Another function of ACE is that it breaks down the proteins bradykinin, aminopeptidase P (which helps inactivate bradykinin among its other functions), and carboxypeptidase (Rasmussen, Mey, & Byg, 2014).

Bradykinin is produced in the kidney from kininogen and functions as potent endothelial vasodialator. It releases nitric oxide and prostaglandins, can cause contraction of non-vascular smooth muscle in the bronchus (bronchoconstriction), increases vascular permeability, and causes natriuresis contributing to the drop in blood pressure (Busse & Buckland, 2012).

ACE inhibitors interfere with the RAAS by blocking the conversion of angiotensin I to angiotension II by inhibiting ACE. The effect of lower blood pressure is that the vasoconstriction of angiotensin II is blocked and the lack of degredation of bradykinin by ACE allows vasodialation. Eventually angiotensin II levels return to near normal as alternative pathways are used for activation and hypertension control is maintained by bradykinin mediated vasodialation (Lewis, 2013).

"Excess bradykinin can act on bradykinin B2 receptors, leading to a change in vascular integrity and subsequent edema" (Norman & Holmes, 2012, p. 384). Substance P, or aminopeptidase P, also accumulates when ACE is blocked which causes increased vascular permeability, possible activation of inflammatory processes, and edema. The adaption or maladaption in conjunction with the increased levels of bradykinin and substance P are thought to be the pathophysiology involved in ACEi angioedema. Histamine release may be involved in the pathophysiology of ACEi angioedema but common treatment regimines such as antihistamines, histamine blockers, steroids, and adrenaline do not markedly improve swelling, therefore, it is unlikely that histamine plays a significant role in this form of angioedema (Rasmussen, Mey, & Byg, 2014).



(Rasmussen, Mey, & Byg, 2014, p. 3)

Implications for nursing care

The most important implication for nursing care is to recognize the life threatening airway compromise that can accompany ACEi AE, although rare. Observation of the patient for 12 to 24 hours in the ED or via an admission to the hospital (Rasmussen, Mey, & Byg, 2014) will depend on the severity of the edema and potential for airway deterioration. The practitioner will need to recognize that the patient needs taken off of the offending medication, and because this type of reaction is drug class specific, the patient cannot be put on any other ACE inhibitors. Current research shows that patients can usually tolerate angiotension receptor blockers (ARB's) but there have been some reports of a small percentage of patients developing AE from these medications also. ARB's are not prescribed as much as ACEi's which may explain the higher rates of AE with ACEi's.

Current recommended treatment for ACEi AE is that the patient needs to be monitored until the swelling resolves. A retrospective analysis by Tai et al. states that "90% of episodes were treated with IV steroids and histamine blockers, although not evidence-based and ineffective" (Tai, Mascaro, & Goldstein, 2010). They also cite that new therapies are being evaluated with kallikrein inhibitors and bradykinin receptor antagonists but are not approved yet in the United States for ACEi AE. An additional treatment option that has been used with some success is fresh frozen plasma which contains ACE to break down bradykinin but also contains kininogen, a bradykinin substrate (Lewis, 2013).

Many studies have tried to correlate risk factors such as African American (AA) ethnicity, female sex, diabetes, smoking, and alcohol use to give the practitioner information to consider about the risk to benefit ratio for prescribing ACEi (Lin, Levine, & Lin, 2013). AA's show a propensity for bradykinin sensitivity related to polymorphisms that call for additional studies (Moholisa, et al., 2013). Conflicting studies through this research was that initially diabetics were thought to show some protection against this phenomena but other meta-analysis' showed maybe this was not accurate, and would also need further investigation.

Conclusion

Ace inhibitors are the number one prescribed drug class for hypertension. Since the mid 80's when they started gaining popularity there has been an increase in reported ACEi AE. Patients may be on an ACEi for one week to ten years before developing the possibly life threatening reaction. The practitioner must be able to recognize the signs and symptoms, understand the pathophysiology of this bradykinin mediated edema, and know the current recommended treatments. There continues to be discussion about the risk factors and increased susceptibility to develop ACEi AE and a risk to benefit analysis for each patient. The practitioner should provide anticipatory guidence about these risks, even though currently <1% of patients will develop AE, so the patient can also recognize an AE episode before it is life threatening.

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