Clinical Practice Statement

What is the Emergency Department Management of Patients with Angioedema Secondary to an ACE-inhibitor? (11/12/2020) Update to the 2011 CPC statement.

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Recommendations:

1. The primary focus of emergency treatment is airway evaluation and stabilization.
2. A careful history and physical exam must be performed to differentiate ACE inhibitor-induced angioedema (ACE-I-AE) from acute allergic angioedema, idiopathic angioedema (IAE), or hereditary angioedema (HAE).
3. There is insufficient data to support the routine use of epinephrine, antihistamines, and steroids in ACE-I-AE.
4. There is insufficient data to support the use of icatibant, ecallantide, C1-INH concentrate, tranexamic acid, or fresh frozen plasma (FFP) in ACE-I-AE.
5. No laboratory tests confirm the diagnosis of ACE-I-AE.
6. Patients with ACE-I-AE should be advised to stop the medication and that ACE-I-AE is a class effect, therefore, all types of ACE-Is should be avoided.

Discussion

ACE inhibitors (ACE-I) are a frequent cause of angioedema seen in the emergency department (ED). The current paper is an update to our 2011 CPC Statement and focuses only on the management of ACE-I-AE.

Angioedema occurs in approximately 0.1-0.7% of patients taking ACE-Is. ACE-I-AE can occur within hours after medication administration or even after a period of years from its first use. A careful history and physical exam must be performed to differentiate patients with ACE-I-AE from those with acute allergic angioedema, IAE, or HAE. By doing so, unnecessary, ineffective, and often costly treatments can be avoided.

Angioedema is characterized by swelling of the subcutaneous or submucosal tissue of the skin, oropharynx, upper respiratory tract, gastrointestinal (GI) tract. Patients with angioedema have asymmetric swelling of the lips, tongue, floor of the mouth, face, neck or eyelids, and/or combined with respiratory distress, stridor, muffled voice, or drooling. Patients may also present with isolated swelling of the extremities or GI tract. ACE-I-AE is thought to be primarily due to an excess of bradykinin that results from inhibition of ACE, an enzyme that also functions to metabolize bradykinin. The diagnosis of ACE-I-AE should be considered in any ED patient presenting with angioedema who has been taking an ACE-I recently or has taken that class of drug in the past.

The primary management of patients with any form of angioedema is maintenance of airway patency. The presence of any signs or symptoms that suggests laryngeal or posterior pharyngeal involvement (e.g. dysphagia, dysphonia, globus sensation, hoarseness, stridor, drooling), or any evidence of respiratory distress warrants careful consideration for emergent airway management. Patients who are not in extremis but have symptoms concerning for

airway involvement, or swelling of the tongue, soft palate, or floor of the mouth should have fiber-optic nasopharyngoscopy performed, provided the equipment is available and the provider has the necessary skill. It is important to recognize that manipulation of the airway may cause increased swelling leading to the need for immediate intubation or a surgical airway. Therefore, intubation and cricothyrotomy equipment should be at the bedside, prior to performing any invasive exam.

There are no laboratory studies that confirm or exclude the diagnosis of ACE-I-AE. Some experts recommend that a C4 complement level be obtained during the acute presentation to determine if hereditary or acquired C1-INH deficiency is present. A low C4 level during an acute attack is a good screening test for these forms of angioedema.

Since the physiologic pathways leading to ACE-I-AE are different from acute allergic reactions, AE, and IAE, medications commonly used in those conditions (e.g., corticosteroids, antihistamines) have not been found to be effective in the treatment of ACE-I-AE. Despite no proven benefit for the treatment of ACE-I-AE, a trial of steroids and antihistamines can be considered due to the low likelihood of harm. Additionally, epinephrine has not been shown to benefit patients with ACE-I-AE but may be considered for patients with more severe presentations. In mild cases of AE, it is unlikely that any potential unproven benefit would outweigh the risk of epinephrine administration.

No high-quality randomized controlled trials have demonstrated a benefit of icatibant, ecallantide, pooled plasma C1-INH concentrate, or recombinant C1-INH in the treatment of ACE-I-AE. Tranexamic acid (TXA) has been proposed for the treatment of ACE-I-AE, but the evidence is limited to retrospective chart reviews and case reports. Evidence for the use of FFP in ACE-I-AE is limited to case reports and case series. FFP contains the enzymes required to break down bradykinin but also has substrates required to form bradykinin. Additionally, treatment with FFP usually involves the administration of 2 or more units of plasma, which may be poorly tolerated in some patients.

Patients who are intubated or have other critical care needs should be admitted to the intensive care unit. Patients with less concerning exams should be admitted to an observation unit or watched in the ED until they are stable for discharge. There is currently no well-defined time period for observation that can be recommended. Repeat fiber-optic examination can be performed to monitor for improvement or progression of swelling.

Conclusion

The primary focus for a patient with ACE-I-AE is airway management. Patients not requiring immediate intubation but who have signs or symptoms concerning for airway involvement should undergo fiber-optic examination, if available. If there is diagnostic uncertainty regarding the etiology of a patient presenting with angioedema, it may be appropriate to initiate medication treatment for an acute allergic reaction or anaphylaxis.

Since our last CPC Statement, new medications have been utilized for the treatment of ACE-I-AE without validation in well-designed, randomized controlled studies. Due to their lack of demonstrated efficacy and high cost, icatibant, ecallantide, and C1-INH cannot be recommended. Without additional evidence, the use of TXA and FFP should be considered investigational.

Intubated patients should be admitted to an intensive care unit. The disposition of patients who are not intubated should be based on clinical condition and concern for progression of swelling. Regardless of patient disposition, any patient presenting with suspected ACE-I-AE should be counseled to immediately discontinue the medication and to avoid the ACE inhibitor class altogether.