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Use of Tranexamic Acid for The Treatment of ACE Inhibitor Induced Angioedema

Ramzan Judge[1]*, Matthew Freidel[2], Farhan Qadeer[1]

[1]Department of Pharmacy, Shore Medical Center, New Jersey, United States
[2]Department of Medicine, Thomas Jefferson University, Philadelphia, United States

Case Report

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***For Correspondence:**
Ramzan Judge, Department of Pharmacy, Shore Medical Center, New Jersey, United States
E-mail: ramzanjudge@gmail.com

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ABSTRACT

Angiotensin Converting Enzyme Inhibitors (ACEI) is commonly prescribed antihypertensive agents in the United States and is generally safe and effective. However, in a small subset of the population, potentially fatal complications may arise as a result of their incidental effect of increasing bradykinin leading to angioedema. While there is no approved treatment, Tranexamic Acid (TXA) can decrease recovery time and improve outcomes by reducing the production of bradykinin. In this paper we discuss a patient case at our facility whose ACEI-Angioedema (ACEI-AE) improved after administration of TXA.

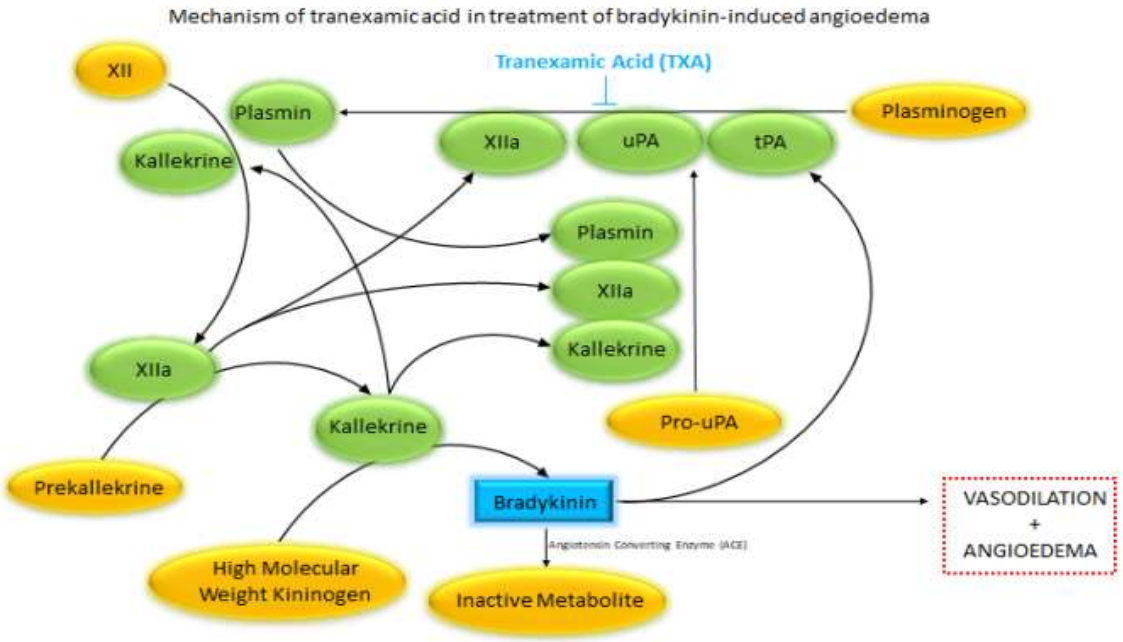
INTRODUCTION

ACEIs are the most commonly prescribed class of antihypertensive pharmacotherapy used in the United States [1]. Unfortunately, 0.1%-0.7% of patients experience side effects such as chronic dry cough, and angioedema [2,3]. ACEI irreversibly inhibits Angiotensin-Converting Enzyme (ACE), which leads to lower blood pressure by preventing the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor. Additionally, ACE is also responsible for the degradation of bradykinin, which is a potent mediator of arteriolar smooth muscle vasodilation and vascular permeability *via* activation of β2 bradykinin receptors.

This results in increased circulating bradykinin causing edema of the subcutaneous and submucosal tissue [4-6]. ACEI-AE can often be clinically differentiated from hereditary angioedema in that ACEI-AE typically affects the face and airways, potentially resulting in fatal airway restriction. Conversely, hereditary angioedema can be identified *via* levels of C1 esterase inhibitor, as well as C2 and C3 levels [7].

The underlying etiology of ACEI-AE is the result of increased circulating bradykinin due to an either increased synthesis or decreased elimination. Therefore, it is theoretically possible to decrease the circulating supply by reducing the initial production of bradykinin. One potential agent that affects this pathway is TXA (Figure 1).

Figure 1. Overview of the mechanism of action of TXA in reducing bradykinin production in the setting of ACEI-AE.



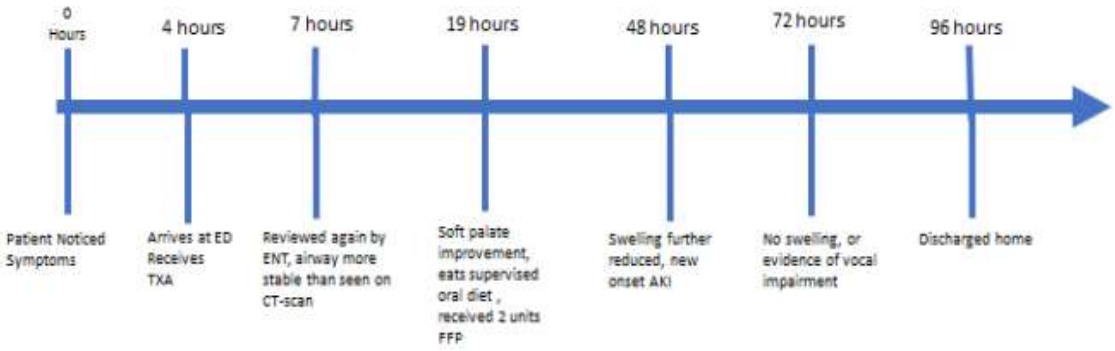
CASE PRESENTATION

Our Patient had a past medical history positive for hypertension, and other comorbidities. The patient was prescribed hydrochlorothiazide-lisinopril, which he began taking 5 months prior. He presented to a local urgent care complaining of a swollen throat and difficulty swallowing where he was given methylprednisolone 125 mg IV push, diphenhydramine 25 mg IV push, and transferred to the emergency department. Upon presentation at the emergency department, the patient had an O2 saturation of 99%, Temperature of 36°C, respiratory rate of 16 bpm, heart rate of 80 bpm, and a blood pressure of 161/101. In the ER, the patient was treated with an additional dose of diphenhydramine 25 mg, dexamethasone 20 mg, famotidine 20 mg , epinephrine 0.3 mg IM, and TXA 1 g IV. One hour after the medication was administered, the CT scan showed significant hypertrophy of the palatine tonsils, lingual tonsils, and swelling of the base of the tongue and associated moderate thickening of the epiglottis and a moderate amount of retropharyngeal edema. Resulting effacement of a 1.2 cm length segment of the

oropharyngeal airway consistent with suspected angioedema, it was recommended to consider intubation. However, this was ultimately not necessary. Three hours after the administration of TXA, the ENT specialist noted the airway was more stable than what was seen on the CT-scan, the majority of the swelling had been confined to the soft palate, and it was stable without any striders.

The following day the patient received 2 units of FFP. Patient was talking without difficulty or drooling. He had complete resolution of symptoms of ACEI-AE, however remained inpatient for observation of new onset acute kidney injury. At the time of discharge, on day 4, no additional interventions were required, the patient was counseled, and ACE-I allergy was documented on electronic medical records (Figure 2).

Figure 2. Timeline of events. Progression of events from symptoms presentation to patient discharge.



RESULTS AND DISCUSSION

ACEI-AE is uncommon, but it is believed that there are genetic and environmental risk factors that play a role in developing ACEI-AE. Groups such as African Americans, women, those with a history of drug rash, smoking, age over 65, use of NSAIDs or immunosuppressive agents are more likely to develop ACEI-AE [7].

Currently ACEI-AE is challenging for the clinician as there is no effective treatment. Oftentimes, patients are treated with antihistamines, corticosteroids, and epinephrine, as these are effective in histamine-dependent angioedema cases 5. Intubation is also frequently performed to secure the airway. Trials have been performed for using medications for hereditary angioedema in the setting of ACEI-AE, including of icatibant, a competitive antagonist of the bradykinin β2 receptor. Phase III trial found no appreciable benefit of icatibant in ACEI-AE [8]. Fresh Frozen Plasma (FFP) may also be used, and is recommended when no specific treatment options are available [9]. FFP contains ACE, and reintroducing it back into the patient may help break down the bradykinin. FFP may cause a transient exacerbation of ACEI-AE due to the presence of the bradykinin precursor's kininogen and high molecular weight kallikrein. Other possible drawbacks for the use of FFP include volume overload, allergic reactions, and the potential for infusion related reactions [5].

Another therapeutic option that has been used in the management and prevention of HAE flares is TXA. It is a readily available antifibrinolytic agent that costs about $4 per dose [10]. TXA inhibits the conversion of plasminogen to plasmin, which prevents the activation of factor XII into factor XIIa. XIIa is required to activate kallikrein to cleave

high molecular weight kininogen, which ultimately is converted into bradykinin [11]. The reduced production of bradykinin restores a patient to a homeostatic level of bradykinin, thereby lessening the edema.

TXA was shown in a retrospective study to reduce the number of non-histaminergic angioedema attacks by 75%, with the greatest effect noticed in idiopathic non-histaminergic angioedema patients [12]. It has also been demonstrated that doses up to 3 g per day of TXA induced complete prevention of idiopathic nonhistaminergic angioedema in 11/15 patients, and partial prevention in 4/15 patients [13]. TXA, therefore, offers a promising pharmacotherapy for ACEI-AE. While there are no randomized controlled trials, there is a growing body of case reports which may provide a justification for further research. A recent case report describes the use of TXA in conjunction with diphenhydramine, famotidine, and corticosteroid in ACEI-AE. The clinicians noted improvement within 30 minutes, with complete resolution within 2 hours after presentation [13]. Furthermore, in 2018, a retrospective analysis of 33 ACEI-AE patients who were given TXA found that 81.8% had improved compared to standard treatment without requiring mechanical ventilation, or experiencing any adverse events [14].

CONCLUSION

Our single-patient case report is confounded with the administration of FFP and histamine directed medications. However, improvements were only seen after the administration of TXA. Despite this, the promise of TXA as a treatment for ACEI-AE should be investigated further. Given the ubiquity of TXA and its low cost compared to other drugs of interest such as icabitrant, further studies are warranted.

This case report, along with available supporting literature indicates a promising role of TXA in managing ACEI-AE. The potential benefit, combined with the low cost of TXA warrants further research.

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