Use of Tranexamic Acid Prevents Intubation in ACE Inhibitor-Induced Angioedema

Ramzan Judge, Stephanie Kolaski and Farhan Qadeer

1Shore Medical Center, USA
2Thomas Jefferson University, USA

*Corresponding author: Ramzan Judge, Shore Medical Center, 100 Medical Center Way, Somers Point, NJ 08244, USA

Abstract

Angiotensin-converting enzyme inhibitors (ACE-I) are medications within the antihypertensive class that are used by nearly 108 million patients worldwide [1]. A rare but possibly life-threatening adverse effect of ACE-I is angioedema, which occurs due to elevated levels of bradykinin [2]. In this case report, we discuss a patient case where the use of tranexamic acid (TXA), an antifibrinolytic agent, prevented impending intubation due to ACE-I induced angioedema.

Introduction

ACE-I, a common antihypertensive medication, regulates blood pressure by inhibiting angiotensin-converting enzyme (ACE). This inhibition prevents the formation of angiotensin II from angiotensin I, a peptide hormone that causes vasoconstriction [3]. ACE is also involved in the degradation of bradykinin, a potent mediator of vasodilation. When ACE is inhibited, the arteriolar smooth muscle relaxes and increases blood flow, leading to increased vasodilation of blood vessels, vascular permeability, and possible development of angioedema with or without the need for intubation. The development of ACE-I induced angioedema (ACE-AE) originates with kallikrein, which cleaves high molecular weight kininogen to generate bradykinin [4,5]. The initial production of bradykinin can be decreased by a known antifibrinolytic agent, TXA. TXA has been shown to improve ACE-AE and prevent impending intubation by reducing the amount of bradykinin needed to be degraded by ACE (Figure 1).
ACE which can catalyze the degradation of excessive bradykinin [8]. Icatibant, a selective antagonist of the bradykinin β2 receptor, was shown in a phase II trial to decrease the time of complete resolution of ACE-AE when compared to antihistamine and corticosteroid therapy [9]. Ecallantide, a plasma kallikrein inhibitor, was studied in another phase II trial where it was thought to decrease ACE-AE by inhibiting kallikrein, the enzyme responsible for converting kininogen to bradykinin [10]. Both icatibant and ecallantide are well studied in the treatment of hereditary angioedema (HAE), which are associated with C1esterase inhibitor deficiency [5]. However, the uses of these bradykinin targeted therapies are limited in ACE-AE due to cost and efficacy [11].

A more novel approach in the acute management of ACE-AE involves TXA. As seen in Figure 1, TXA inhibits the conversion of plasminogen to plasmin, an important enzyme for kallikrein-activation and bradykinin formation.

Discussion

While ACE-AE is rare, unfortunately, it is estimated that between 0.1 to 0.7% of patients on ACE-I develop angioedema [2]. This arises most commonly within the first year of treatment. However, it may also develop after years of use. Angioedema presents as asymmetric swelling of the face, lips, larynx, genitalia, or extremities. It occurs due to elevated levels of bradykinin, leading to vasodilation of blood vessels, increased vascular permeability, and plasma extravasation into the submucosal tissue. The most severe cases include failure to secure the airway requiring intubation [4]. There are also some genetic and environmental risk factors for development of ACE-AE. These include age over 65, African American decent, smoking, and history of ACE-I induced dry cough [6,7].

Currently, there is no standard treatment for ACE-AE. Typical first line management includes a combination of histamine targeted therapies (e.g. epinephrine, antihistamines, and corticosteroids), which are likely ineffective. Intubation is also considered as swelling of the mucosa can lead to airway obstruction with concomitant hypoxia and potentially death. Fresh frozen plasma (FFP), icatibant, and ecallantide have all been explored in the use of ACE-AE. FFP contains ACE which can catalyze the degradation of excessive bradykinin [8]. Icatibant, a selective antagonist of the bradykinin β2 receptor, was shown in a phase II trial to decrease the time of complete resolution of ACE-AE when compared to antihistamine and corticosteroid therapy [9]. Ecallantide, a plasma kallikrein inhibitor, was studied in another phase II trial where it was thought to decrease ACE-AE by inhibiting kallikrein, the enzyme responsible for converting kininogen to bradykinin [10]. Both icatibant and ecallantide are well studied in the treatment of hereditary angioedema (HAE), which are associated with C1esterase inhibitor deficiency [5]. However, the uses of these bradykinin targeted therapies are limited in ACE-AE due to cost and efficacy [11].
Currently, there are no large, randomized, controlled trials published regarding the use of TXA in ACE-AE. However, there are limited retrospective studies and case reports justifying its role in. In 2010, a retrospective study analyzed the treatment of TXA given to 25 patients for sporadic idiopathic bradykinin angioedema. It was found that 18 patients had complete remission of symptoms, corresponding to 72%, after administration of TXA [13]. Another retrospective observational study in 2014, which included 37 patients who had either HAE or idiopathic non-histaminergic angioedema, reported that an average of 2.5g of tranexamic acid taken for six months was able to reduce the number of angioedema attacks by 75% [14]. Lastly, a 2018 retrospective review reported improvement in 27 of the 33 patients studied with ACE-AE after receiving 1 gram of TXA within 1 hour of symptom onset. In this review, none of the patients required intubation [15].

Our case report shows that TXA is a cost effective antifibrinolytic agent that reduces the symptoms of ACE-AE. The effect seen in our case is confounded by the concomitant use of histamine targeted therapies. However, TXA was considered only after the patient failed to show improvements with the aforementioned therapies.

Conclusion

The accessibility and affordability of TXA makes it a viable option for patients presenting to the ED with ACE-AE. Our case supports the need for further investigation to assess the role of TXA in ACE-AE.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors state no conflicts of interest.

Funding Statement

The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Facts about Hypertension (2021) Centers of disease control and prevention website.
2. Montinaro V, Cicardi M (2020) ACE inhibitor-mediated angioedema. Int Immunopharmacol 78: 106081.
3. (2021) ACE Inhibitor-Induced Angioedema. UpToDate. Wolters Kluwer Health, Inc. Riverwoods, IL.
4. Wang K, Geiger H, McMahon A (2021) Tranexamic acid for ACE inhibitor induced angioedema. Am J Emerg Med 43: 292.e5-292.e7.
5. Kostis WJ, Shetty M, Chowdhury YS, Kostis JB (2018) ACE inhibitor-induced angioedema: A review. Curr Hypertens Rep 20: 55.
6. (2021) Tranexamic Acid. Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.
7. Morimoto T, Gandhi TK, Fiskio JM, Seger AC, So JW, et al. (2004) An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract 10: 499-509.
8. Warrier MR, Copilevitz CA, Dykewicz MS, Slavin RG (2004) Fresh frozen plasma in the treatment of resistant angiotensin-converting enzyme inhibitor angioedema. Ann Allergy Asthma Immunol 92: 573-575.
9. Baş M, Greve J, Stelter K, Havel M, Strassen U, et al. (2014) A randomized trial of icatibant in ACE-inhibitor-induced angioedema. N Engl J Med 372: 418-425.
10. MacGinnitie AJ, Campion M, Stolz LE, Pullman WE (2012) Ecallantide for treatment of acute hereditary angioedema attacks: analysis of efficacy by patient characteristics. Allergy Asthma Proc 33: 178-185.
11. Bernstein JA, Tyson C, Relan A, Adams P, Magar R (2020) Modeling cost-effectiveness of on-demand treatment for hereditary angioedema attacks. J Manag Care Spec Pharm 26: 203-210.
12. Mudd PA, Hooker EA, Stolz U, Hart KW, Bernstein JA, et al. (2020) Emergency department evaluation of patients with angiotensin converting enzyme inhibitor associated angioedema. Am J Emerg Med 38: 2596-2601.
13. Du-Thanh A, Raison-Peyron N, Droket C (2010) Efficacy of tranexamic acid in sporadic idiopathic bradykinin angioedema. Allergy 65: 793-795.
14. Wintenberger C, Boccon-Gibod I, Launay D, Fain O, Kanny G, et al. (2014) Tranexamic acid as maintenance treatment for non-histaminergic angioedema: Analysis of efficacy and safety in 37 patients. Clin Exp Immunol 178: 112-117.
15. Beauchêne C, Martins-Héricher J, Denis D, Martin L, Maillard H (2018) Tranexamic acid as first-line emergency treatment for episodes of bradykinin-mediated angioedema induced by ACE inhibitors. Rev Med Interne 39: 772.