



Role of Tranexamic acid in NSAIDs induced angioedema.

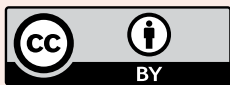
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ABSTRACT:

Tranexamic acid (TXA) is an antifibrinolytic agent that inhibits the conversion of plasminogen to plasmin, a key step in kallikrein activation and bradykinin formation. Tranexamic acid is used in the prophylactic management of hereditary angioedema; however, evidence for TXA in Non-Steroidal Anti-inflammatory drug-induced angioedema (NSAIDs-AE) is limited. We describe a patient who presented to the ICU department with NSAIDs-AE and was successfully treated with TXA. This case suggests that TXA may be a beneficial treatment modality in the management of NSAIDs-AE and warrants further investigation.

Keywords: Anaphylaxis, Non-allergic Anaphylaxis, Tranexamic acid, Angioedema



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INTRODUCTION:

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are widely utilized for their potent analgesic, anti-inflammatory, and antipyretic properties¹. However, despite their extensive use, NSAIDs have been linked to a range of adverse effects, some of which can pose significant risks to patients' well-being. One such infrequent but noteworthy adverse reaction is NSAID-induced non-allergic angioedema, characterized by localized swelling involving deep subcutaneous tissues and mucous membranes. The incidence of hypersensitivity reactions to NSAIDs, resulting in urticaria and angioedema, appears to be on the rise, with prevalence rates ranging from 0.1% to 0.3%². Although NSAID-associated angioedema is commonly assumed to be an allergic response mediated by immunoglobulin E (IgE), it is crucial to recognize that some cases manifest without any involvement of IgE. Instead, this subset of patients experiences angioedema due to a direct pharmacological effect of NSAIDs on the kinin-kallikrein system, leading to bradykinin-mediated vasodilation and increased vascular permeability³.

Tranexamic acid, a synthetic antifibrinolytic agent, has garnered attention as a potential therapeutic option for managing NSAID-induced angioedema, particularly the non-allergic variant. Its mechanism of action involves inhibiting plasmin, an enzyme responsible for fibrin breakdown and subsequent bradykinin release. By reducing bradykinin production, tranexamic acid offers a promising approach to alleviating the vascular leakage and edematous manifestations commonly seen in NSAID-induced angioedema⁴.

In this case report, we present a compelling account of an elderly patient who developed non-allergic angioedema following the administration of a commonly prescribed NSAID. This condition was effectively managed with the use of tranexamic acid, highlighting the potential benefits of this therapeutic intervention in such cases. By sharing this illustrative case, we aim to underscore the significance of recognizing and managing NSAID-induced non-allergic angioedema promptly and explore the potential role of tranexamic acid in achieving favorable patient outcomes.

CASE REPORT:

A 64-year-old female with lupus cerebritis and acalculous cholecystitis was admitted to the Intensive Care Unit (ICU) for the management of her lupus. During her stay, she received antibiotics, steroids, and tramadol for pain relief. The patient had no reported drug allergies and denied any previous adverse reactions to medications.

On Day 4, after being shifted to the ward, the patient complained of abdominal pain, and an injection of ketorolac was administered. Approximately two hours after receiving intravenous ketorolac, the patient experienced significant facial swelling, particularly around the lips, eyes, and tongue. Stridor was also observed, prompting the activation of the rapid response team, and the patient was swiftly transferred back to the ICU for further management.

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At the time of evaluation, the patient's vital signs indicated a blood pressure of 150/100 mmHg, a heart rate of 132 beats per minute, a respiratory rate of 32 breaths per minute, and an oxygen saturation of 90% on 3 L of oxygen. There were no signs of a skin rash, hives, or itching; however, airway examination was difficult due to submandibular edema and marked tongue swelling. Based on the clinical presentation, the patient was suspected to be suffering from angioedema.

Immediate treatment was initiated to manage the angioedema, which included intravenous epinephrine (100 mcg), intravenous corticosteroids (hydrocortisone 100mg), and antihistamines (Chlorpheniramine and ranitidine). Additionally, intravenous fluids were administered to maintain hydration, and oxygen was provided via a nasal cannula at a rate of 3 L/minute. Despite these interventions, the patient's symptoms did not improve, and her airway remained compromised. Consequently, a decision was made to proceed with awake fiberoptic intubation in the operating theater, with ENT surgeons on standby for a possible tracheostomy if securing the airway proved challenging.

After successful intubation, the patient was transferred back to the ICU. However, the angioedema did not subside even with conventional anaphylaxis treatment protocols in place. C1 esterase inhibitor level to confirm the diagnosis of non-allergic angioedema couldn't be sent due to the unavailability of the test in our centre.

Considering a potential bradykinin-mediated anaphylactic mechanism, the patient was administered 1 gm of intravenous Tranexamic acid. The resolution of angioedema was evident by a reduction in her peri-oral swelling. She remained on mechanical ventilation for one day, after which she was extubated. She remained in the ICU for one more day and was subsequently transferred to the ward.

DISCUSSION:

Angioedema is a potentially life-threatening condition characterized by localized swelling in the subcutaneous or submucosal tissues. It can be triggered by various factors, including medications. Among these, nonsteroidal anti-inflammatory drugs (NSAIDs), like ketorolac, have been infrequently reported to cause angioedema. While the exact mechanism of drug-induced angioedema remains uncertain, it is believed to involve the release of vasoactive substances, particularly bradykinin⁵.

Clinical manifestations of NSAID-related urticaria and angioedema reactions can be categorized into three types: NSAID-induced urticaria or angioedema (NIUA), NSAID-exacerbated cutaneous disease (NECD), and Single NSAID-induced Urticaria/Angioedema/Anaphylaxis (SNIUAA)³.

Angioedema can be classified into two types based on immune mechanisms: allergic (IgE-mediated) and non-allergic (Non-

IgE-mediated). Allergic angioedema involves immune-mediated reactions, while non-allergic angioedema mimics immune-mediated allergic reactions without underlying immunological evidence, making diagnosis challenging for clinicians. Distinguishing between immune-mediated and non-immune-mediated reactions requires careful evaluation. The patho-mechanism of NSAID-induced non-allergic angioedema is associated with cysteinyl leukotrienes and bradykinin pathways. NSAIDs inhibit the cyclooxygenase pathway, directing the lipoxygenase pathway and generating leukotrienes, leading to the development of angioedema. NSAID-induced allergic angioedema is relatively common, whereas NSAID-induced non-allergic angioedema is rare.

Bradykinin-mediated angioedema, such as laryngeal angioedema, can be life-threatening due to its resistance to corticosteroids and antihistamine drugs. For the treatment of hereditary angioedema (HAE) and acquired angioedema (AAE), C1-INH concentrates are the drugs of choice. Additionally, new drugs, such as the bradykinin B2-receptor antagonist icatibant and the kallikrein inhibitor ecallantide, have shown promise in improving treatment outcomes for bradykinin-mediated angioedema (figure 1)⁶.

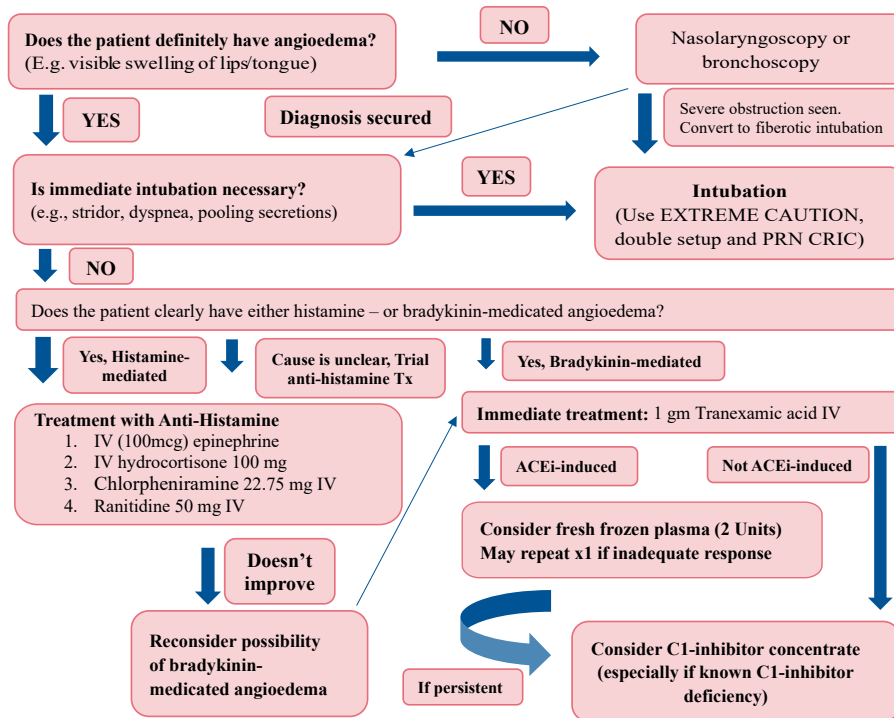
Tranexamic acid (TXA) has been explored as an alternative therapy for long-term prophylaxis in HAE by inhibiting plasminogen activation and thus reducing bradykinin production⁷. However, its role in the acute treatment of bradykinin-mediated angioedema is less well defined.

Hasara S et al. and Wang K et al. have shown that TXA may be beneficial in the management of angiotensin-converting enzyme inhibitor-induced angioedema (ACEI-AE)^{8,9}. Judge R et al. have also showed the effective management with 1g TXA administration for ACE-I induced angioedema. The patient was re-evaluated and noted with tongue swelling with improvement in speech¹⁰. In 2018, a retrospective review was done with the improvement in 27 of the 33 patients studied with ACE-AE after receiving 1 gram of TXA within an hour of symptoms onset⁷.

In this case, the patient developed angioedema shortly after receiving ketorolac therapy. While ketorolac is generally well tolerated, it is crucial to be aware of the potential for severe allergic reactions, including angioedema. Timely identification and management are vital to prevent airway compromise and ensure patient safety. Discontinuation of the offending medication and avoidance of related drugs in the future are typically advised.

Clinicians should be diligent in obtaining a detailed medication history and educating patients about the signs and symptoms of drug-induced angioedema. Referral to an allergist or immunologist is often warranted for further evaluation, including skin testing or laboratory studies, to identify the underlying cause and provide appropriate recommendations for future drug use.

Figure 1 Overall approach to the patient with angioedema



CONCLUSION

The article presents a life threatening case of NSAIDs-induced angioedema and its effective treatment with Tranexamic acid. Though allergic reactions to ketorolac are uncommon, they can occasionally result in life-threatening consequences such as angioedema, which can be treated with the readily accessible Tranexamic acid. This case report also highlights the need for further investigation in this area.

ETHICAL CONSIDERATIONS

This case report did not require the approval of any Ethical Committee. Written informed consent was obtained from the patient's visitors.

CONFLICT OF INTEREST : None

ABBREVIATIONS

NSAIDS: Non-Steroidal anti-inflammatory drugs

HAE: Hereditary angioedema

AAE: Acquired angioedema

TXA: Tranexamic acid

REFERENCES:

- Wallace JL, Soldato PD. The therapeutic potential of NO-NSAIDs. *Fundamental & clinical pharmacology*. 2003;17(1), 11-20.
- Thong B.Y.H & Tan TC. Epidemiology and risk factors for drug allergy. *British journal of clinical pharmacology*. 2011;71(5), 684-700.
- Doña I, Blanca-Lopez N, Torres MJ, Gomez F, Fernandez J, Zambonino MA & Cornejo-García, JA. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. *Allergy*. 2014;69(4), 438-444.
- Stoldt J, Cox C, Matusz E. Tranexamic acid use in the setting of ACE inhibitor induced angioedema. *Am J Emerg Med*. 2022 May;55:230.e3-230.e4. doi: 10.1016/j.ajem.2022.01.041. Epub 2022 Jan 21. PMID: 35105472.
- Bas M, Adams V, Suvorava T, Niehues T, Hoffmann T K & Kojda G. Nonallergic angioedema: role of bradykinin. *Allergy*. 2007;62(8), 842-856.
- Obtułowicz K. Bradykinin-mediated angioedema. *Pol Arch Med Wewn*. 2016; 126 (1-2): 76-85
- Beauchêne C, Martins-Héricher J, Denis D, Martin L & Maillard H. Tranexamic acid as first-line emergency treatment for episodes of bradykinin-mediated angioedema induced by ACE inhibitors. *La Revue de Médecine Interne*. 2018;39(10), 772-776.
- Wang K, Geiger H & McMahon A. Tranexamic acid for ACE inhibitor induced angioedema. *The American journal of emergency medicine*. 2021;43, 292-e5.
- Hasara S, Wilson K, Amatea J, Anderson J & Wilson KM. Tranexamic acid for the emergency treatment of angiotensin-converting enzyme inhibitor-induced angioedema. *Cureus*. 2021;13(9).
- Judge R, Kolaski S, Qadeer F (2021) Use of Tranexamic Acid Prevents Intubation in ACE Inhibitor-Induced Angioedema. *Int J Crit Care Emerg Med* 7:127. doi.org/10.23937/2474-3674/1510127