



Ketorolac induced non allergic angioedema: A case report

Chinju¹, Mahesh P A^{2,3}, Shilpa Palaksha^{*1,3}

¹Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru – 570015, India

²Department of Pulmonary Medicine, JSS Medical College, JSS Academy of Higher Education & Research, Mysuru – 570015, India

³Special Interest Group, Quality & Safe use of Medicine, JSS Academy of Higher Education & Research, Mysuru – 570015, India



Article History:

Received on: 10 Feb 2020
Revised on: 12 Mar 2020
Accepted on: 14 Apr 2020

Keywords:

Angioedema,
Allergic,
Nonallergic,
NSAIDs

ABSTRACT

Non- Steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed category of drugs. NSAIDs are the main cause of allergic reactions both in adults and children. Hypersensitivity reactions due to NSAIDs involve 0.3% to 0.5% of the overall population. Among the different types of NSAIDs induced hypersensitivity reactions, urticaria and angioedema are the most common. Angioedema can be of two types, allergic (IgE) & Nonallergic (Non IgE) mediated. Allergic angioedema is immune mediated but non allergic angioedema mimic immune mediated allergic reaction without underlying evidence of immunological mechanism which can cause diagnostic difficulties for the clinician. Distinguishing immune-mediated and non-immune-mediated reactions can be difficult, so careful evaluation is needed. Pathomechanism of NSAIDs induced non allergic angioedema is based on cystenyl leukotrienes and bradykinin pathway in which NSAIDs block cyclo oxygenase pathway and directs the lipoxygenase pathway and generates leukotrienes which result in the development of angioedema. NSAIDs induced allergic angioedema is quite frequent and NSAIDs induced nonallergic angioedema are quite rare. The detailed information of these reactions is necessary to decrease morbidity and mortality associated with the reactions. The early recognition and discontinuation of suspected drug should be done in order to avoid further complications. Here, we report a case of a patient with non allergic angioedema in association with use of Ketorolac.

*Corresponding Author

Name: Shilpa Palaksha
Phone:
Email: shilpapaksha@jssuni.edu.in

ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v11i3.2650>

Production and Hosted by

IJRPS | www.ijrps.com

© 2020 | All rights reserved.

INTRODUCTION

Non- Steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed category of drugs . NSAIDs are the main cause of allergic reactions both in adults and children ([Ensina et al., 2019](#)). Hypersensitivity reactions due to NSAIDs involve 0.3% to 0.5% of the overall population ([Andri and Falagiani, 2007](#)). Among the different types of NSAIDs induced hypersensitivity reactions, urticaria and angioedema are the most common ([Ensina et al., 2019](#)) . Angioedema is a swelling of the skin and mucous membranes of the face, lips, mouth, throat, larynx, extremities and

genitalia (Leeyaphan *et al.*, 2009). Angioedema can be of two types, allergic (IgE) & Nonallergic (Non IgE) mediated (Bas *et al.*, 2007). Allergic angioedema is immune mediated but non allergic angioedema mimic immune mediated allergic reaction without underlying evidence of immunological mechanism which can cause diagnostic difficulties for the clinician (Lewis, 2013; Warrington *et al.*, 2018). Distinguishing immune-mediated and non-immune-mediated reactions can be difficult, so careful evaluation is needed (Saff, 2018).

Case Presentation

A 42 year-old female came with complaints of having back pain for 4 years without any comorbidities. The patient was on ayurvedic medications and was on massage therapy for relief of back pain. The patient stopped ayurvedic medications a month before opting allopathy. She was prescribed with diclofenac. She complained of only angioedema without urticaria, which was unusual. She developed angioedema without itching, which was unusual, therefore, she was prescribed with other NSAIDs like nimesulide, Ibuprofen for which she developed the same reaction. She developed 3 episodes of drug-induced reaction in one month, which was always at least 10 hours after the ingestion of the drug, which was unusual. The patient was suspected to have a drug allergy to NSAIDs. To confirm whether she does indeed have a drug allergy, as a cause of angioedema, initially skin prick test was advised for Diclofenac and to check the cross-reactivity with other NSAIDs, it was also advised to do for paracetamol. The patient was given an informed consent form and explained orally about the skin prick test procedure, its use and side effects in the patient's local language. The procedure was carried out after obtaining a written, informed consent form. SPT was done for diclofenac and paracetamol, they are without preservatives, pure form and the concentration used were 0.5 mg/ml & 0.2mg/ml for paracetamol & diclofenac respectively. The patient was observed for 45 min and no weal reaction was found for paracetamol and diclofenac followed by intradermal test. SPT, when negative was followed by the Intradermal test, which was done for diclofenac using a test dose of 22.5 mg/ml, which was negative. A key option to confirm drug allergy is a controlled drug challenge. Oral drug challenge test was done using ketorolac 10 mg sublingually because the patient had never used it so far, she had a history of definite reaction to other drugs, previous clinical experience showed that some patients who did not tolerate diclofenac tolerated ketorolac and patient was monitored. The patient couldn't tolerate 50% of 10 mg ketoro-

lac. After 9 hours, the patient complained about throat irritation without skin rashes. Inj. Pheniramine and Inj. Betamethasone was prescribed as a stat dose to subside the reaction. The patient had shown minimal response to anti-allergic medications. This was an indication that angioedema developed due to NSAIDs is probably non-allergic reaction, as non-allergic angioedema takes several hours to days to develop and it is mediated either bradykinin or cysteinyl leukotrienes without skin rash, minimal response to anti-allergic medications, abdominal manifestations are more common, respiratory tract involvement is uncommon, symptoms can last for five days and minimal response to anti-allergic medications. Whereas drug-induced allergic angioedema is mediated by histamine, with the rapid onset of swelling of mucosa and submucosa tissues with an urticarial rash. Symptoms respond rapidly to antihistamine, epinephrine and corticosteroid therapy. Based on these observations and clinical response the reaction was confirmed to be NSAIDs induced non-allergic angioedema. The only management of this reaction is complete avoidance of the drug (Kalambay *et al.*, 2017).

Case Discussion

Pathomechanism of nonallergic angioedema is based on two pathways,

cysteinyl leukotrienes synthesis

This pathway is followed by NSAIDs that inhibit the function of cyclooxygenase, which directs the metabolism of arachidonic acid towards the 5-Lipoxygenase pathway which produce intermediate 5-HPETE which generates LTA₄ through LTA synthase. LTA₄ gives rise to (LTB₄ (by LTA₄ hydrolase) and LTC₄ (by LTC₄ synthase) (Figure 1). LTC₄ is extracellularly converted into LTD₄ and then to cysLTs, a stable metabolite, which acts on G-protein coupled LTE₄ receptors to induce bronchoconstriction, vascular leakage & eosinophilia (Zhang *et al.*, 2018; Thompson *et al.*, 2019).

Bradykinin Mechanism

The Kallikrein Kinin System (KKS) is a proteolytic enzymes in which plasma kallikrein breaks human high molecular weight kininogen and generates bradykinin which activates beta 2-adrenergic receptors and results in the release of nitric oxides and eicosanoids (prostaglandins, thromboxanes, leukotrienes) which result in local vasodilatation and increased vascular permeability which leads to the development of angioedema. NSAIDs inhibit the synthesis prostaglandins, thromboxanes and release leukotrienes which result in angioedema (Figure 2). Other medications such as ACE inhibitors

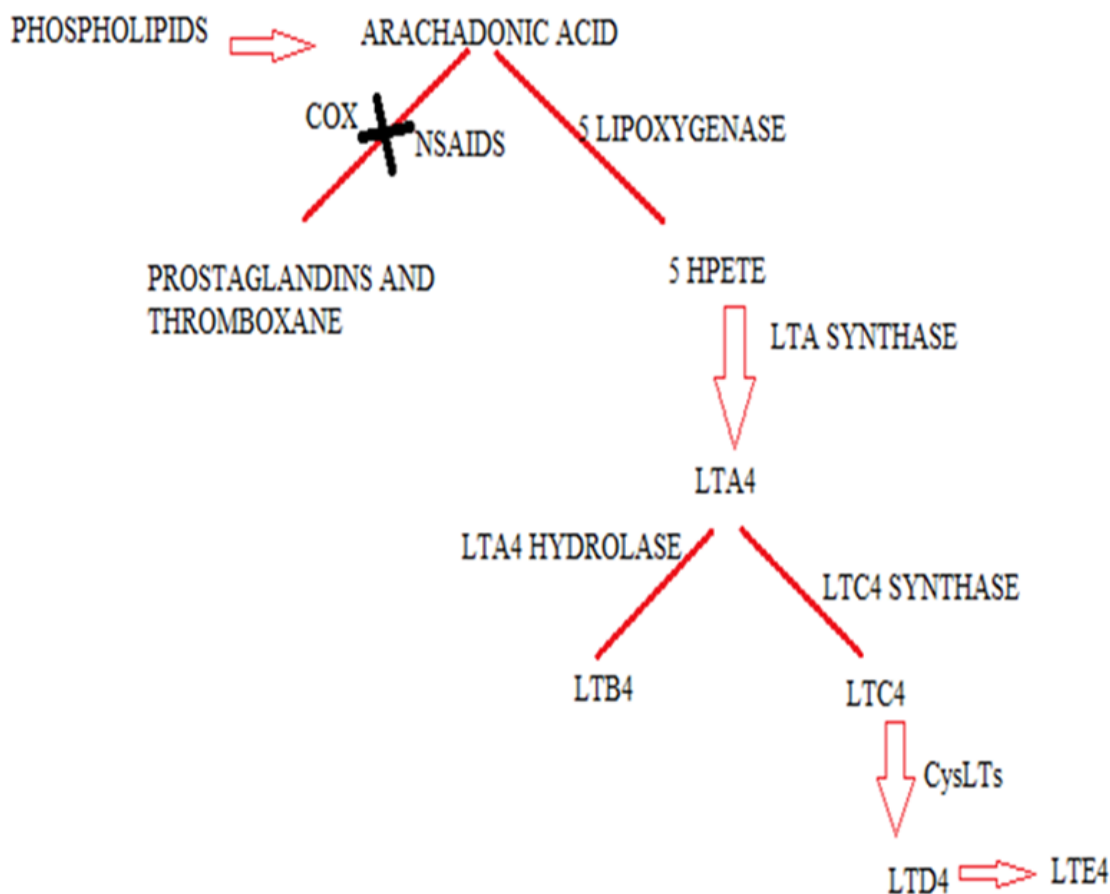


Figure 1: The role of Cysteinyl leukotriene in the development of non-allergic angioedema.

Table 1: Differences between allergic & Nonallergic angioedema

Characteristics	Allergic angioedema	Nonallergic angioedema
Itching	Frequent	No
Urticaria	Frequent	No
Time of onset	Less than an hour	Several hours to days
Response to treatment	Effective	Not effective
Duration to subside	Within 24 hour	Last up 3 to 5 days
Abdominal pain	Possible	Frequent
Bronchospasm	Frequent	Rare
IgE antibodies	with Elevated specific serum IgE antibodies.	without Elevated specific serum IgE antibodies.
Tryptase	With Elevated tryptase level	Without elevation of tryptase level
Chymase	With Elevated chymase level	Without elevated chymase level
C1 INH	Present	Absent

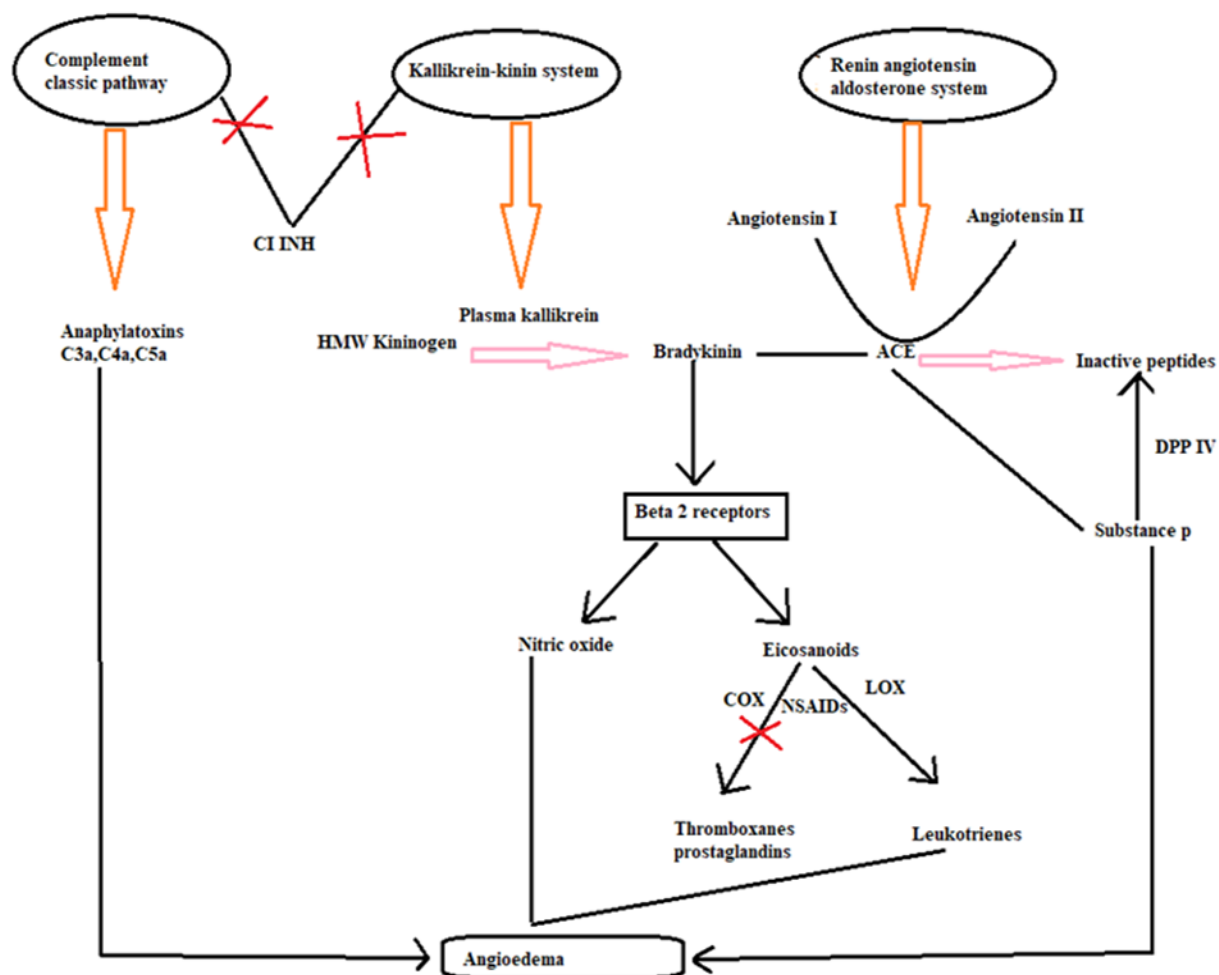


Figure 2: The Kallikrein and the bradykinin pathways and the mechanisms for nonallergic angioedema due to NSAIDs and ACE inhibitors

also are known to cause non-allergic angioedema via the same pathway (pathway (Figure 2).

The KKS antagonizes the renin-angiotensin-aldosterone system (RAAS) in its vascular effect. The KKS & RAAS are paired by the ACE. The function of ACE is to metabolize Bradykinin in the KKS and generate angiotensin II from angiotensin I in the RAAS. This antagonism results in the accumulation of Bradykinin which leads to angioedema.

Another function of proteolytic enzymes is through the activation of complement system which result in the release of anaphylatoxins (C3a, C4a, and C5a). Anaphylatoxins leads to the development of angioedema.

The KKS is paired with complement system by the C1 inhibitor. The C1 INH is a serine protease that inhibits both KKS and complement system which induces angioedema. Dipeptidyl peptidase IV inactivates substance P, a vasoactive peptide that causes swelling whereas dipeptidyl peptidase IV inhibitor like sitagliptin may cause angioedema.

Both bradykinin and substance P are metabolized by ACE. During ACEI accumulation of bradykinin and substance, P results in Angioedema (Rhaleb *et al.*, 2011; Kalambay *et al.*, 2017).

Differences between allergic & Nonallergic angioedema based on clinical manifestations and laboratory parameters is presented in Table 1, (Ogawa and Grant, 2007; Stone *et al.*, 2010; Kalambay *et al.*, 2017; Tarbox *et al.*, 2018).

CONCLUSION

A high degree of suspicion is needed to identify non-allergic angioedema. It is extremely important to note that, desensitization cannot be performed in these patients. The main cause of concern in non-allergic angioedema is that these, patients do not respond to any anti-allergic medication, treatment is only supportive and sometimes angioedema can be fatal, especially when there is laryngeal edema. Stopping the culprit drug is the most important and only treatment.

Funding Support

None.

Conflict of Interest

None.

REFERENCES

Andri, L., Falagiani, P. 2007. Safety of Celecoxib in patients with cutaneous reactions due to ASA-NSAIDs intolerance. *Allergologia et Immunopathologia*, 35(4):126–129.

Bas, M., Adams, V., Suvorava, T., Niehues, T., Hoffmann, T. K., Kojda, G. 2007. Nonallergic angioedema: role of bradykinin. *Allergy*, 62(8):842–856.

Ensina, L. F., Martin, R. P., Filippelli-Silva, R., Veronez, C. L., Sole, D., Pesquero, J. B. 2019. Angioedema-Induced by Nonsteroidal Anti-inflammatory Drugs: A Genotype-Phenotype Correlation in A Brazilian Population. *Journal of Investigational Allergology and Clinical Immunology*, 29(4):305–307.

Kalambay, J., Ghazanfar, H., Pena, K. A. M., Munshi, R. A., Zhang, G., Patel, J. Y. 2017. Pathogenesis of Drug Induced Non-Allergic Angioedema: A Review of Unusual Etiologies. *Cureus*, 9(8):8–15.

Leeyaphan, C., Kulthanan, K., Jongjarearnprasert, K., Dhana, N. 2009. Drug-induced angioedema without urticaria: prevalence and clinical features. *Journal of the European Academy of Dermatology and Venereology*, 24(6):685–691.

Lewis, L. M. 2013. Angioedema: Etiology, Pathophysiology, Current and Emerging Therapies. *The Journal of Emergency Medicine*, 45(5):789–796.

Ogawa, Y., Grant, J. A. 2007. Mediators of Anaphylaxis. *Immunology and Allergy Clinics of North America*, 27(2):249–260.

Rhaleb, N. E., Yang, X. P., Carretero, O. A. 2011. The Kallikrein-Kinin system as a regulator of cardiovascular and renal function. *Comprarison of Physiology*, 1(2):971–93.

Saff, R. 2018. Epidemiology of Drug Allergy.

Stone, K. D., Prussin, C., Metcalfe, D. D. 2010. IgE, mast cells, basophils, and eosinophils. *Journal of Allergy and Clinical Immunology*, 125(2):S73–S80.

Tarbox, J. A., Bansal, A., Peiris, A. N. 2018. Angioedema is swelling caused by fluid leakage from blood vessels into the surrounding skin and tissue. *JAMA*, (19):319–319.

Thompson, G., Bundell, C., Lucas, M. 2019. Paracetamol allergy in clinical practice. *Australian Journal of General Practice*, 48(4):216–219.

Warrington, R., Silviu-Dan, F., Wong, T. 2018. Drug allergy. *Allergy, Asthma & Clinical Immunology*, 14(S2):1–11.

Zhang, B., Li, Q., Shi, C., Zhang, X. 2018. Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms. *Pharmacology*, 101(1-2):104–110.