

Diclofenac Associated Urticaria Angio-oedema, A case report

Akwue Tochukwu Anthony^a MD, Aneke Chukwuebuka Somto^b MD

^a. Emergency Physician, Department of Emergency Medicine, Abha clinic and Emergency Hospital, Directorate of Health Affairs in Aseer region, kingdom of Saudi Arabia.

^b. General Physician, Department of Paediatrics, Mosogar General Hospital, Ethiopie West LGA, Delta State, Nigeria.

Correspondence Address; Department of Emergency Medicine, Abha clinic and Emergency Hospital, Directorate of Health Affairs in Aseer region, kingdom of Saudi Arabia.

Abstract:

Diclofenac can cause anaphylaxis manifesting as urticaria or angio-oedema or both and which can be life threatening if not properly identified. Care should be taken when prescribing this therapy in patients who are susceptible to drug induced hypersensitivity reactions.

Keywords: *Diclofenac, anaphylaxis, urticaria, angioedema, life threatening*

Introduction

The drug Diclofenac can be described as an aryl-acetic derivatives with an analgesic, anti-pyretic and anti-inflammatory properties which inhibit prostaglandin synthesis, short-lived anti-platelet action and invariably, the most extensively used non-steroidal anti-inflammatory drugs, commonly employed in rheumatoid arthritis, osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, post traumatic and post operative inflammatory conditions vis-a-vis quick relief of pain and wound oedema.¹ It can be given orally, rectally, parentally or topically and it is well tolerated, however, uncommon adverse effects can occur¹.

However, hypersensitivity to nonsteroidal anti-inflammatory drugs especially diclofenac, can result in urticaria and angioedema, with a prevalence rates range from 0.1-0.3% which could partly due to the large size of the exposed or at risk population.² Some predisposing factors for these cutaneous manifestations have been identified and which include atopic dermatitis, female sex, young adulthood, previous history of chronic urticaria, and chronic use of nonsteroidal anti-inflammatory drugs for relief of pain,²

Pedro et al 2016, and Tejas PK et al 2014 opined that angioedema as one of the adverse effect of this drug therapy can present as a manifestation of anaphylaxis, or can be a separate entity or can coexist with urticaria, or threatening hypersensitivity reactions.^{3,4,5,6}

Moreover, the concept of angio-oedema can be as a result of deep dermal subcutaneous and submucosal swelling with high morbidity and when they affect the larynx, can predispose to death by asphyxiation if not properly identified on time.^{3,4,5,6}

Below is a case of 12year old male child with angioedema following diclofenac ingestion for relief of acute abdominal pain.

Case Presentation:

A 12 year old male adolescent, known asthmatic, but not on inhaler, presented to the emergency room with a 24hours complaint of abdominal pain, which was gradual in onset, located at umbilical area, initially dull. As the day progress, the pain becomes generalized with increasing intensity with associated nausea but no vomiting. There was no history of watery or bloody diarrhea and no change in urinary frequency. Vital signs at presentation were within normal limit. Examination findings revealed a young boy in moderate abdominal painful distress with diffuse tenderness and no guarding on deep palpation. A diagnosis of acute gastritis was made and he was given a start dose of 75mg of intramuscular diclofenac. Few minutes of initiating the regime, he was noted to be in moderate respiratory distress as evidenced by flaring of alae nasi, subcostal retractions with moderate facial swelling as well as urticarial rashes on the trunk. Immediately, Intravenous epinephrine 5mg was commenced with empirical 10mg of intravenous chlorpheniramine and 6mg of intramuscular dexamethasone were given. Urgent Laboratory results showed mild eosinophilia (white blood count-10,600; differentials: neutrophils-50% (normal 30-70%), eosinophils- 07% (normal 1-6%), ESR- 60/mm per 1st hr. He was subsequently admitted to the ward and was discharged after 3days when the symptoms completely resolved.

Discussion;

Angio-edema may sometimes result in respiratory tract obstruction⁷, which can prove fatal. Less severe reactions subside with medical treatment but severe ones may require tracheostomy or intubation⁸.

Consequently, the description of two different arachidonic acid cylo-oxygenase (COX) about a decade ago, designated as COX-1 and COX-2 and the incorporation into the therapeutic armamentarium of more selective enzyme inhibitors for the control of inflammation and pain have significantly led to an improved understanding of the pathogenesis of these adverse reactions². The prevalent theory about the pathogenesis of urticaria and angioedema in relation to nonsteroidal anti-inflammatory drugs in cross-reactive patients assumes that the inhibition of COX-1 leads to a shunting of arachidonic acid metabolism towards the 5-lipoxygenase pathway which results in an increased synthesis and release of more potent leukotrienes². NSAIDs themselves can cause angioedema by either immunological (IgE-mediated) or non-immunological (pseudoallergic) reactions, which in the latter are likely a result of increased leukotriene production due to cyclooxygenase blockage⁽⁹⁻¹⁵⁾. Therefore, concurrent use of NSAIDs may precipitate or worsen angioedema in patients with ACEI therapy.¹⁴

Although COX-2 inhibitors are well tolerated by the majority of classic nonsteroidal anti-inflammatory sensitive patients, cutaneous reactions to highly selective COX-2 inhibitors have been described in some of these individuals, casting some doubts about the relevance of such hypotheses². Also, It has been suggested that the common adverse drug reactions of diclofenac when used for acute pain in children are similar to those in adults. Serious adverse reactions occur in <0.8% of children and the incidence of diclofenac-induced bronchospasm in asthmatic children is <2.7%¹⁶.

On the other hand, in patients who react to a single nonsteroidal anti-inflammatory drug and chemically similar products (single rector), specific immunoglobulin E antibodies to haptenated non-steriodal anti-inflammatory metabolites have been suspected, although not demonstrated by any methods².

Facial (periorbital) angio-oedema constitutes the most common form of clinical presentation and one-third of the patients show a mixed clinical pattern of cutaneous (urticaria and or angio-oedema) and respiratory symptoms which include upper respiratory tract oedema, rhinorrhea, cough, breathlessness and tearing¹²⁻¹⁶. Severe symptoms of other forms of angioedema may be treated with epinephrine injection and less severe symptoms are often controlled by antihistamine. The use of corticosteroids may reduce the possibility of relapse,¹³. A case report by Tiwari AK et al in 2013, a patient who was injected with diclofenac sodium 50mg intramuscular, developed chest pain, and itching over the lip with redness and wheal over the site of injection¹⁶⁻²³ while Hedar A 2010, reported that a 39 year old women, developed angio-oedema and profound hemodynamic shock after receiving a diclofenac suppository for analgesia 6hours after cesaren section²⁴. Deepalatha et al 2013, reported a 13year old male adolescent with complaint of itching and swelling over both eyelids after receiving 50mg of oral diclofenac.²² Mary et al 2017 reported a case of a 56 years old lady who underwent Percutaneous Nephrolithotomy and DJ stent placement for renal alculi presented with complaints of diffuse abdominal pain to

the casualty for which injection diclofenac 2c.c intramuscular was administered and developed angio-oedema 20minutes following administration of injection diclofenac²⁵.

Conclusion;

Diclofenac and other NSAIDs especially Ibuprofen and aspirin are widely prescribed drugs either to be used as over the counter medications or as intravenous or intramuscular agents or both. It has been seen as one of the causes of urticarial angio-oedema²⁶ which can be self-limiting or very fatal if not noted on time. Therefore, early recognition and prompt treatment with corticosteroid and antihistamines is essentially lifesaving.

Care should be taken when prescribing or administering the drug especially in patients with comorbid conditions such as chronic asthma, diabetics, atopic dermatitis or in patients with hereditary angio-oedema.

Sponsorship or Monetary Inducement: None

Conflict of Interest: No conflict of interest in this report.

References

1. Tripathi KD; Essential of Pharmacology; NSAIDs and Antipyretic-Analgesics, Chapter 14: Jaypee Brothers Med Pub, 2008: 193-194
2. Mario S.B, Arnaldo CH, Fernan CF: NSAID induced Urticaria and Angio-oedema; A Reappraisal of its Clinical management; American J Clin Dermatology;2002;3; 599-607
3. Pedro GB, Marcelo VA, Edgardo JJ, Jarge K: Angio-oedema Associated with NSAIDs; Curr op in Allergy Clin Immunol; Aug 2016; 16(4): 323-332
4. Tejas KP, Parvati BP, Manish JB, Tripathi CB; Drug Induced Anaphylactic reactions in Indian Population Review: Indian J Critical Care Med; 2014: 18(12); 796-806
5. Sai Keerthana PC, Anila KN, Rashma Reji: Naproxen-Induced Erythema Multiforme- A rare case report; Int J Pharm and Pharm Sci 2017: 9(3): 294-295
6. Bertazzani G, Spine MT, Scarpellini MG, Buccelletti F, De Simeone M, Gregori M, Valeriano V, Drugliese FR, Ruggieri MP, Magnanti M, Susi B, Minetola L, Zulli L, D'Ambroglio F: Drug Induced Angio-oedema; experience of Italian Emergency Departments; Internal and Emergency Med J; 2014: 9: 455-462.
7. Wun-YH, Tsu MC, Su-Feng K, Wen HC, Yi-Giien T; A case report of a 3year old child with Anaphylactic shock after a diclofenac suppository confirmed by serial tryptase and a basophil activation test; Frontier in Paediatrics J; 2022; Vol 9:802715; 1-2. Doi:10.3389/fped.2021.802715
8. Rudrajit P, Gautam L, Tanmay JS, kunal H, Rajesh P, Asim S; Extensive Fixed drug eruption due to Diclofenac; Sultan Qabos Univ Med J; 2017, 17 (1), 121-122
9. Obrien WM; Adverse reactions to NSAIDs; Diclofenac compared with other NSAIDs; Am J Med 1986;80:70-80
10. Munni R, Sudeshna M, Veena P; Diclofenac Induced fatal Anaphylactic Reaction: Indian Paediatrics J, 1999: 36; 1067-1069

11. Alkhawajah AM, Eifawal M, Meh SF; Fatal Anaphylactic Reaction to Diclofenac; *Forensic Sci Internal* 1993;60:107-110
12. Milman U, Hermoni D: Anaphylactic Reaction to Oral Diclofenac Sodium Sustained release tablet; *Isr J Med Sci* 1994: 30; 909-910
13. Nettis E, Marcandrea M, Di Maggio G, Ferrannini A, Tursi A; Retrospective Analysis of Drug Induced Urticaria and Angio-oedema; a survey of 228 patients, *immunopharmacology and Immunotoxicology J*, 2001: 23(4);585-595. (doi.org/10.1081/IPH-100108604)
14. Thatchai K; Recurrent Severe Angio-oedema Associated with Imidapril and Diclofenac; *Allergology Inter J* 2008: 57; 441-443
15. Kaplan AP, Greaves MW; Angio-oedema. *J Am Acad Dermatol* 2005;53;373-388
16. Kanokvalani k, Suklum J, Kanarut B, Koingt J; Angio-oedema: Clinical and Etiological Aspects, clinical and developmental Immunology, Vol 2007; ID: 26438; DOI. 10.1155/2017/26438
17. Joseph FS, Kuan O, Simon K, Richard FH, Imogen S, Ian CKW; Prospective Observational Study of Adverse drug reactions to diclofenac in Children; *British Journal of Clinical Pharmacology*; 2009: 68:2;243-251. Doi: 10.1111/j.1365-2125.2009.03447.x
18. Roujeau JC, Stern RS. Medical progress: severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;331:1272-85.
19. Carder RK. Hypersensitivity reactions in neonates and infants. *Dermatol Ther* 2005;18:160-75.
20. Pise HN, Padwal SL. Diclofenac-induced angioedema: a case report. *Asian J Pharm Clin Res* 2015;8(2);4-5
21. Patel TK, Patel PB, Barvaliya MJ, Tripathi CB. Drug-induced anaphylactic reactions in Indian population: A systematic review. *Indian J Crit Care Med* 2014;18:796-806.
22. Deepalatha C, Prasad RV, Chandra S, Mohan PM, Lakshmi V. Diclofenac-induced urticaria in paediatric patient. *Asian J Pharm Clin Res* 2013, Vol 6: Suppl 3; 1–2.
23. Tiwari AK, Tomar GS, Kapoor MC, Kouis syndrome resulting from anaphylaxis to Diclofenac, *Indian J Anaesth*, 2013; 57(3): 282-84
24. Heda A, Holeberg G, Mazor M; Anaphylactic shock after diclofenac sodium (voltaren), *Harefuah*, 2000; 138(3): 211-12
25. Mary RP, Shashidhar R, Prasanna V, Sangeeth KK, Jagadish L; Diclofenac Induced Urticarial Angio-oedema; a case report; *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*; e-ISSN: 2279-0853; p-ISSN: 2279-0861; Vol 16, Issue 5 version V (May 2017); pp 23-24; www.iosrjournals.org. DOI: 10.9790/0853-1605062324
26. Settippone GA; Aspirin and allergic disease: *Am J Med* 1983; 74: 1022-10