



## **A Case Report on Ibuprofen Induced Toxic Epidermal Necrolysis**

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**Abstract:** Ibuprofen is a non steroidal anti-inflammatory drug that exhibits analgesic and antipyretic activities by inhibiting prostaglandin synthesis. Though available as an OTC drug, ibuprofen is potent enough to cause serious dermatologic adverse reactions like erythema multiforme, erythroderma, SJS (Stevens - Johnson syndrome), TEN (toxic epidermal necrolysis). TEN is a potentially life threatening dermatologic disorder and a severe cutaneous ADR that involves skin and mucous membrane, characterized by widespread erythema, necrosis and bullous detachment, resulting in exfoliation & possible sepsis and/or death, which is most commonly drug induced. Toxic epidermal necrolysis is characterized by inappropriate immune activation in response to certain medications or their metabolites. The exact pathogenic mechanism of TEN is still uncertain. The exposure to drugs has increased with demographic shifts associated with a higher morbidity of the population. Along with this phenomenon, a rise in the incidence of adverse drug reactions (ADRs) has been observed. Hypersensitivity-syndrome associated with ibuprofen is a host-dependent idiosyncratic drug-reaction. Though ibuprofen is most widely used over the counter (OTC) medication, which is considered to be relatively safe, it is essential to understand its potential adverse effects. This rare case report addresses the fact that severe hypersensitivity reactions can occur with ibuprofen, which can be potentially dangerous and life threatening. This case report also adds a note on the diagnosis and management of Toxic Epidermal Necrolysis.

**Keywords:** Ibuprofen, erythema, SJS (Stevens - Johnson syndrome), TEN (toxic epidermal necrolysis), exfoliation.

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## I. INTRODUCTION

The exposure to drugs has increased with demographic shifts associated with a higher morbidity of the population. Along with this phenomenon, a rise in the incidence of adverse drug reactions (ADRs) has been observed<sup>1</sup>. According to WHO an ADR could be defined as 'A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function'<sup>2</sup>. Ibuprofen is a non steroidal anti-inflammatory drug that exhibits analgesic and antipyretic activities whose principal effect is inhibition of cyclooxygenase (prostaglandin-synthase), thus impairing the final transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. Despite the fact that any drug can be an impending cause of hypersensitivity reactions, Ibuprofen, an over-the-counter drug used extensively as an analgesic and antipyretic in Asia, is considered to be relatively safe<sup>3</sup>. It is available as an OTC (over the counter) drug with the doses 200 to 400 mg oral dosage forms for various FDA labeled indications such as fever, headache, migraine, osteoarthritis, pain, primary dysmenorrhea, rheumatoid arthritis. But, ibuprofen intake could result in serious dermatologic adverse reactions which include, Erythema multiforme (oral, less than 1%), erythroderma, SJS (Stevens – Johnson syndrome), TEN (toxic epidermal necrolysis)<sup>4</sup>. The latter two are life-threatening, bullous cutaneous diseases considered as immune-mediated reactions to drugs characterized by epidermal necrosis, extensive detachment of the epidermis, erosions of mucous membranes and severe constitutional symptoms<sup>5</sup>. Toxic epidermal necrolysis is a severe cutaneous ADR, involving skin and mucous membrane which is characterized by inappropriate immune activation in response to certain medications or their metabolites. The separation between the epidermis and the dermis causes blistering and epidermal desquamation resulting in >30% skin loss. The condition is also known as Lyell's syndrome as it was elucidated by Lyell in 1956<sup>6</sup>.



**Fig 1: Dusky, reddish colored plaques on upper body, legs respectively**

## Laboratory investigations (Table 1)

**Table 1. Abnormalities in complete blood picture.**

S. No.	Blood parameters	Day 1	Day 5
1.	Hemoglobin	12.9	4.9
2.	RBC	3.25	1.26
3.	WBC	3.08	2.15
4.	PLT	182	130
5.	Peripheral smear	RBC- Macrocytic, normochromic, anisocytosis WBC- Leukopenia PLT- Thrombocytopenia	

## I.I PATHOGENESIS

In general, acute TEN is considered a T-cell mediated type IV Hypersensitivity disorder. It mostly results from a cumulative effect of risks from the drug structure, drug metabolism, HLA alleles and T cell clonotypes<sup>7</sup>. However, the precise mechanism of TEN is still unknown. Apoptosis or necroptosis causes keratinocytes to lose their shape, adhesion, and necrosis predominates within a few days. Total epidermal necrosis separates the epidermis from the dermis. TEN is regarded as an immune reaction with predominantly CD8+ T lymphocytes, monocytes/ macrophages, and natural killer cells. Impaired regulatory T-cells, T-helper 17 cells, cytotoxic granules such as perforin-granzyme and granulysin, tumor necrosis factor  $\alpha$ , annexin, microRNA-18a-5p, and drug metabolites are all thought to be involved<sup>8-10</sup>. This rare case report addresses the fact that severe hypersensitivity reactions can occur with ibuprofen, which can be potentially dangerous and life threatening. It is thus important for the clinicians to be alert to such severe hypersensitivity reactions even with drugs which are deemed to be probably safe<sup>11</sup>.

## I.2 CASE PRESENTATION

A 30 year old female patient with past medical and medication history of tuberculosis was admitted in the dermatology department of a tertiary care hospital with the chief complaints of fluid filled lesions, bleeding from mouth since 3 days, hemoptysis since 2 days. The fluid filled lesions initially started in the feet that later progressed to the entire body. She presented a history of intake of Ibuprofen 400mg tablet for body pains, 1 week ago. On examination, the patient was found to be conscious and coherent, thin built and poorly nourished. BP-120/90 mmHg, PR-84bpm, RR-18/min, P/A-soft, pallor, icterus. As shown in Fig 1, cutaneous examination revealed dusky, reddish colored maculae and plaques, fluid filled bullae of varying sizes all over the body, oral lesions/erosions along with eyes, hair and nails involvement.

Clinical serology of urine revealed polymicrobial growth. CUE report revealed the presence of albumin, sugar<sup>+</sup> and was loaded with pus cells. The condition was treated by using the following drugs (Table 2)

**Table 2. Treatment given to the patient during her course of stay in hospital**

S.No.	Drug name	Generic name	Dose	Roa	Frequency
1.	Inj.Decadron	Dexamethasone	2cc-1cc	IV	BD
2.	Inj.Taxim	Cefotaxime	1gm	IV	BD
3.	Inj.Pantop	Pantoprazole	40mg	IV	OD
4.	Inj.Avil	Pheniramine	1cc	IV	OD
5.	Mucopain gel	Benzocaine	20% w/w	E/A	30 min before food
6.	TESS gel	Triamcinolone	0.1%	E/A	BD
7.	Chlorhexidine mouthwash	Chlorhexidine Gluconate	10 ml	Buccal	OD
8.	Lacrigelocular lubricant	Hypromellose	2% w/v	Ophthalmic	BD
9.	Tears naturale eye drops	Dextran-70 Disodium hydrogen citrate	2 drops	Ophthalmic	BD
10.	Syp.citralka		5ml	P/O	TID
11.	Tab.Norflox	Norfloxacin	400mg	P/O	OD
12.	Tab.Augmentin	Amoxicillin&Potassium clavulanate	500mg+125mg	P/O	BD

**Drugs on discharge: (Table 3)**

**Table 3. Drugs prescribed to the patient upon discharge**

S. No.	Drug name	Generic name	Dose	Roa	Frequency
1.	Tab.Wysolone	Prednisolone	30mg-10mg 30mg	P/O	BD
2.	Tab. Pantop	Pantoprazole	40mg	P/O	OD
3.	Multivitamin tablet	Vitamins+essential elements	1 tablet	P/O	OD
4.	Tab. Vit C	Ascorbic acid	500mg	P/O	OD
5.	Cap. A&D	Vitamin A-Ergocalciferol (D2)	1 tablet	P/O	OD
6.	Tab.IFA	Elemental iron and folic acid	100mg+500mcg	P/O	OD
7.	Mucopain gel	Benzocaine	20%	E/A	SOS

## 2. DISCUSSION

Toxic epidermal necrolysis (TEN), also referred to as Lyell's syndrome is a rare, life-threatening drug-induced skin disease with an annual incidence of approximately 0.4-1.2 cases per million individuals and mortality rate of approximately 30%<sup>12,13</sup>. The clinical hallmark of TEN is a marked skin detachment caused by extensive keratinocyte cell death associated with mucosal involvement. The exact pathogenic mechanism of TEN is still uncertain. This extensive keratinocyte cell death results in the separation of significant areas of skin at the dermal-epidermal junction with the production of bullae followed by skin sloughing. This extensive cell death also leads to mucous membrane detachment and contributes to the characteristic symptoms of TEN, which include high fever, mucositis, and moderate to severe skin pain, anxiety, and asthenia. In this case, the patient had a past medical history of tuberculosis, for which she was rationally treated with ATT (Anti tubercular therapy) and was recovered. Patient reported to have consumed ibuprofen as an OTC medication for body pains on 01/07/2019, noticed an immediate cutaneous reaction and was brought to hospital on 02/07/19. Patient was under intensive observation for 4 days and the conformational diagnosis was Ibuprofen induced TEN. Hypersensitivity-syndrome associated with ibuprofen is a host-dependent idiosyncratic drug-reaction. The adverse reaction was managed by prompt withdrawal of the offending drug, and its removal from the body fluids through severe IV resuscitation, oral and IV corticosteroids along with supportive care that included analgesics and emollients. Corticosteroids have been reported to be effective in curbing the progression of condition and reducing mortality<sup>10</sup>. Conservative treatment of the wounds with topical emollients, restoring the body's

homeostasis by fluid resuscitation were found useful in achieving early control. Patient was under observation and found to be improved in both systemic and topical symptoms after one month of treatment.

## 3. CONCLUSION

TEN is a serious disease that must be treated with utmost care by isolating the patient. Prompt removal of the causative agent followed by management of the complications of extensive skin loss must be ensured. Sensitivity to drugs differs in individuals and may lead to potential ADRs. Though ibuprofen is the most widely used OTC medication, it is also essential to understand its potential adverse effects. As a clinical pharmacist, it is important to caution the patient regarding the use of the drug and avoid the ADR in future as the patient has been found sensitive to the drug.

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## 5. AUTHORS CONTRIBUTION STATEMENT

Harshitha Chanduri collected the case and drafted the manuscript. Neelam Injeti guided throughout the study and evaluated the manuscript.

## 6. CONFLICTS OF INTEREST

Conflict of interest declared none.

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