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Carbamazepine (Cbz) Induced Toxic Epidermal Necrolysis(Ten) – Lyell's Syndrome: A Case Study And The Critical Role Of Clinical Pharmacists In Preventing Adverse Drug Reactions

Dr. Preet T. Desai

1. *Pharm D Intern student, Department of Pharmacy Practice, Maliba Pharmacy college, Bardoli-Mahuva Road, District: Surat, Gujarat, India,394350*

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ABSTRACT:
Objective: This case study aims to assess the significance of detecting, evaluating, and reporting adverse drug reactions, with the goal of enhancing medication adherence. **Methods:** This case report is based on observations made during daily ward rounds at Metas Adventist Hospital in Athwalines, Surat. **Results:**A case report describes a 45-year-old male patient who developed toxic epidermal necrolysis (TEN) following the administration of carbamazepine (CBZ). The patient had a medical history including ischemic stroke, Type-2 diabetes mellitus, accelerated hypertension, and Wegener's granulomatosis with polyangiitis. Causality assessment indicated the adverse event was "probable" according to both the WHO scale and the Naranjo causality assessment scale. The Karch and Lasagna scale categorized the reaction as "severe". Additionally, the SCORTEN scale, which assesses the severity of TEN to predict in-hospital mortality, was utilized.**Conclusion:**Carbamazepine (CBZ) is increasingly prescribed daily to manage pain in patients with ischemic stroke who experience territory infarction with hemiparesis. It is crucial for physicians to be aware of the drugs associated with life-threatening reactions to prevent such occurrences through careful prescribing practices. Additionally, thorough patient counselling regarding medication use is essential, especially in situations where treatment guidelines are not well-defined, to ensure patient safety and adherence.

KEYWORDS: Carbamazepine, Toxic Epidermal Necrolysis, pruritic, erythematous, papular lesions, Wegner granulomatosis, Adverse drug reaction, Probable.

I. INTRODUCTION

The skin, as the body's outer covering, enables interaction with our environment. However, it is susceptible to various conditions caused either by external substances it encounters or by the substances we ingest. Toxic epidermal necrolysis (TEN), including Stevens-Johnson syndrome (SJS), are rare but severe drug reactions that affect the skin and can potentially be fatal [1,2]. Toxic epidermal necrolysis

(TEN) is a rare but life-threatening mucocutaneous condition that causes the top layer of the skin to detach from the lower layers. It is triggered by a severe reaction to medications or infections, and often lead to extensive skin and mucous membrane damage, as well as other systemic symptoms. Symptoms of TEN usually begin with flu-like symptoms, such as fever and fatigue, followed by painful red or purplish skin lesions that quickly spread and merge. As the disease progresses, the skin may start to peel or blister, leaving large areas of raw, exposed tissue that can easily become infected. Additionally, TEN can cause damage to the eyes, mouth, throat, and other mucous membranes, leading to vision problems, difficulty swallowing and other complications [3].Several theories have gained widespread acceptance. Recent research has demonstrated a significant association between HLA-B*1502 and CBZ-induced TEN/SJS.

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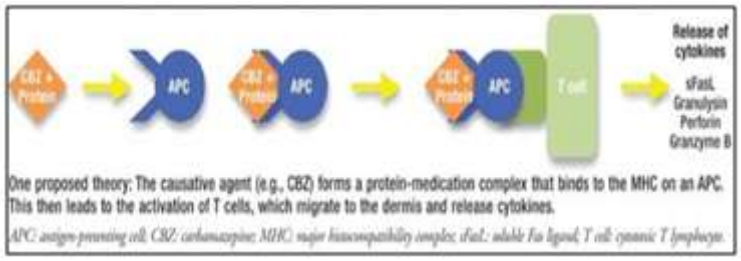

FIGURE 1.1 MECHANISM OF CBZ INDUCED TEN: [3]

The image presents a proposed theory for the pathogenesis of carbamazepine (CBZ)-induced toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS). It illustrates the following sequence of events:

1. Formation of Protein-Medication Complex: The causative agent, in this case, CBZ, forms a complex with a protein.
2. Binding to Antigen-Presenting Cell (APC): This complex binds to the major histocompatibility complex (MHC) on an APC.
3. Activation of T Cells: The protein-medication complex presented by the APC activates T cells.
4. Migration and Cytokine Release: The activated T cells migrate to the dermis and release cytokines such as sFasL, granulysin, perforin, and granzyme B.

These cytokines contribute to the severe cutaneous reactions observed in TEN/SJS.

Characteristic	EM	SJS	SJS-TEN Overlap	TEN
% BSA involved in detachment	<10%	<10%	10%-30%	>30%
≥ 1 mucous membrane affected	Up to 70%	>90%	>90%	>90%
Typical targets	Yes	No	No	No
Spots	No	Yes	Yes	Yes
Atypical targets	Raised	Flat	Flat	Flat
Mortality	Rare	10%	30%	50%
Common cause	Infection	Medication	Medication	Medication
Recurrent[a]	Yes (30%)	No	No	No

FIGURE 1.2 DIFFERENCES IN THEIR CLINICAL CHARACTERISTICS: ERYTHEMA MULTIFORME, SJS AND TEN [3]

This table provides a comparative overview of the characteristics, causes, recurrence, and long-term complications of Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS), SJS-TEN Overlap, and Toxic Epidermal Necrolysis (TEN) which further helps for proper diagnosis of disease.

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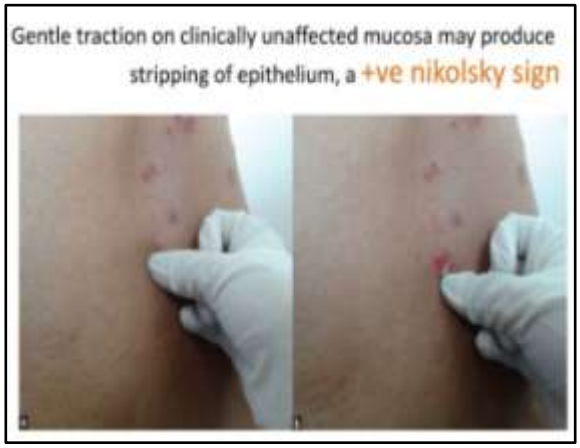

FIGURE 1.3 NIKOLSKY's SIGN: A PATHOGNOMIC BOON

Nikolsky's sign is pathognomic for toxic epidermal necrolysis, and staphylococcal scalded skin syndrome (SSSS).

* This sign basically differentiates intraepidermal blisters from sub epidermal blisters.

* It is elicited by applying lateral pressure by a thumb or a finger in the perilesional skin, affected skin, normal skin which results in a force that dislodges upper layers of epidermis from lower layers.

Risk Level	Drugs
High risk	*Antigout:* allopurinol *Antibiotics:* sulfamethoxazole, sulfadiazine, sulfadoxine *GI conditions:* sulfasalazine *Anticonvulsants:* carbamazepine, lamotrigine, phenobarbital, phenytoin, fosphenytoin *Antiretroviral:* nevirapine *NSAIDs (oxicam):* meloxicam, piroxicam
Lower risk	*Antibiotics:* aminopenicillins, cephalosporins, quinolones, tetracyclines, macrolides *NSAIDs (acetic acid):* diclofenac *Anticonvulsants:* valproic acid, oxcarbazepine *Antidepressant:* sertraline
Reported cases	Acetaminophen, corticosteroids, other NSAIDs (except aspirin), zonisamide, lenalidomide, acetazolamide, ethambutol, mirtazapine, oseltamivir
No evidence of risk	Aspirin, sulfonylurea, thiazide diuretics, furosemide

FIGURE 1.4 LIST OF CAUSATIVE MEDICATIONS AND LEVEL OF SUSPICION [3]

The primary supportive measures for patients include the use of protective dressings, pain control, nutritional support, and maintaining electrolyte and fluid balance. Isolation is also crucial. Early transfer to an intensive care unit or burn care unit can significantly reduce hospitalization duration, mortality rates, and infection rates. It is essential to immediately discontinue the causative agent. Careful administration of fluids, guided by urine output and central venous pressure, is necessary, with an average requirement of 3–4 litres for patients with 50% of their body surface area affected. The goal of pharmacotherapy in TEN is to prevent complications and reduce morbidity. Supportive care typically involves antiseptics,

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analgesics,anticoagulants,antihistamines, antibiotics, and crystalloids, though no specific treatment modality is universally accepted. The use of corticosteroids in managing TEN remains a topic of debate.

Carbamazepine (CBZ) is frequently used to treat left residual body weakness in ischemic stroke patients, as well as for simple and complex partial seizures, neuralgia, and alcohol withdrawal syndrome. This medication possesses anticonvulsive and anticholinergic properties, which help to reduce excessive nerve signals in the brain and restore normal nerve activity balance. Side effects of CBZ can include ataxia, vertigo, drowsiness, confusion, headache, maculopapular rash, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), xerostomia (dry mouth), and aplastic anemia. Here, we present an intriguing case of CBZ-induced TEN treated at a tertiary care hospital in the western Indian state of Gujarat. The details and analysis of this case are discussed below.

II. CASE DESCRIPTION

A male patient, aged 45 years, was admitted to the hospital with c/o- Pruritic, erythematous, papular lesions, blackish scaly skin all over the body, fever, headache, peeling of the skin, intense inflammation of eyes, lips, nose, genitalia, and oral cavity on 3rd Jan 2024. He had a past medical h/o Ischemic Stroke since Jan 2022, Type-2 Diabetes Mellitus, Accelerated hypertension since May 2022 and Wegner granulomatosis with polyangiitis since Oct 2022. He was taking Tab. Ecosprin AV-75(clopidogrel 300 mg & aspirin 75 mg) one tab once daily after dinner, Tab. Gluformin G1, Cap. Homocheck and Tab. Telmiride 40 mg. After 10 months, he visited a neurologist with the residual weakness of the left side of the body. He was prescribed with Tab. Carbamazepine (CARBETOL) 200 mg and was taking from past 16 days. On physical examination, the patient presented with a temperature of 40°C and a blood pressure of 180/100 mmHg. On clinical examination, there was generalised peeling of skin with crusting almost half of the body including scalp and genitalia, Nikolsky's sign was positive, erythematous rash all over body with as epidermal detachment of 70% BSA, congestion of conjunctiva with mucopurulent discharge and keratitis were also present. Liver and spleen were not palpable. ulcerated lesions on the oral mucosa. Extensive erythematous plaques were present over the rest of the body (more than 30% of the body surface). The patient was subsequently admitted in the Metas Adventist Hospital with a diagnosis of TEN probably due to CBZ (Lyell's Syndrome). He had no personal or family history of skin diseases, neither was he an allergic to any known allergens, food or drugs. He had social history of chewing tobacco since 1-2 years.

During the physical examination, the patient exhibited hypertension with a blood pressure reading of 180/100 mm Hg, tachycardia with a pulse rate of 120 beats per minute, and tachypnoea with a respiratory rate of 55 breaths per minute. The patient also had a fever but showed no signs of lymphadenopathy. Liver function tests revealed elevated levels of aspartate aminotransferase (AST) at 180 U/L (normal range: 10-45 U/L) and alanine aminotransferase (ALT) at 100 U/L (normal range: 6-48 U/L). The total white blood cell count was 5000 (normal range: 4-10×10^9/L), with no atypical lymphocytosis or eosinophilia. Platelet count was within normal limits, while haemoglobin was low at 9.5 g/dl. Serum creatinine levels were normal at 1.2 mg/dl. The patient had hyponatremia (sodium at 110 mmol/L) and hyperkalemia (potassium at 7.5 mmol/L), both of which were corrected accordingly.

The causality of the event was evaluated using the Naranjo causality assessment scale, resulting in a total score of 5, indicating a "Probable" causal relationship between the drug and the reaction. According to the WHO causality scale, the score also suggested a "Probable" relationship. The assessment using the Karch and Lasagna scale determined the severity of the reaction to be severe.

Based on subjective and objective evidence, we can conclude that the patient was diagnosed with CBZ induced TEN (Lyell's Syndrome) with k/c/o Ischemic Stroke since Jan 2022, Type-2 DM and Accelerated HTN since May 2022, Hyperhomocysteinemia and Wegner Granulomatosis with polyangiitis due to arachnoiditis since Oct 2022. The suspected drug was stopped immediately. He was treated conservatively with Inj. Dexamethasone (DEXONA) 8 mg IM twice daily, Inj. Pheniramine Maleate (PHENVIL) 45.5 mg IM once daily to reduce cutaneous problems. Inj. Pantoprazole (PANFIZ-IV) 40mg sos, Inj.Ondansetron(ERISET) 4 mg 8 hrly as an anti-emetic. To maintain fluid and electrolyte balance DNS-RL 5% in 100 ml BID was given. Inj. Human Actrapid 40 IU/ml was given according to RBS. Cap. HOMOCHECK 1/10/400 mg once daily in afternoon, Cap. ECOSPRIN-AV 75/300 mg at night and Tab. TELMIRIDE 40 mg twice daily for hypertension was continued.

The treatment regimen included the topical application of Clonate (clobetasone propionate)

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lotion, 25 ml three times daily; Kezicort (triamcinolone) 0.1% w/v oromucosal paste, twice daily; and Betadine (povidone-iodine) mouthwash, 2% w/v once daily. To prevent the patient's skin from adhering to the bed, they were placed on a sterile banana leaf. Eye lesions were managed with topical antibiotics (ciprofloxacin, gentamicin, chloramphenicol, and a combination of moxifloxacin and dexamethasone) and ocular lubricant solution (Lacrigel), with the eyes covered using saline-soaked sterile pads.

Supportive care measures included the administration of parenteral opioids (fentanyl patches) for pain relief, intravenous fluids, and intravenous albumin. Nutritional needs were met by providing a protein powder preparation via a Ryle's tube. Once the lesions began to heal, the patient was transitioned to oral betamethasone, 2 mg daily, which was gradually tapered off and discontinued after five weeks. The lesions healed with post-inflammatory hyperpigmentation by approximately the 15th day. After one month, the progression of the skin lesions ceased, the patient's overall condition significantly improved, and they were discharged in a hemodynamically stable state, tolerating oral feeds well, and encouraged to maintain a normal diet. A follow-up appointment was scheduled 10 days later in Dr. Amit Shah's outpatient department.

SR NO.	QUESTIONS	YES	NO	DON'T KNOW
1.	Are there previous conclusive reports on this reaction?	+1	0	0
2.	Did the adverse event appear after the suspected drug was administered?	+2		0
3.	Did the adverse reaction improve when the drug was discontinued or a specific ant agonist was administered?	+1	0	0
4.	Did the adverse drug reaction reappear when the drug was readministered?	+2	-1	0
5.	Are there iterative causes (other than the drug) that could solely have caused the reaction?	-1	2	0
6.	Did the reaction re-appear when a placebo was given?	-1	+1	0
7.	Was the drug detected in blood (or other fluids) in a conc. known to be toxic?	+1	0	0
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9.	Did the patient have a similar reaction to the same or similar Drugs in any previous exposure?	+1	0	0
10.	Was the adverse event confirmed by objective evidence?	+1	0	0
TOTALSCORE:5				

III. DISCUSSION

Our patient is a 45-year-old male with a history of Ischemic Stroke, Type-2 DM, Accelerated HTN, Hyperhomocysteinemiaand Wegner Granulomatosis with polyangiitis. He was started on carbamazepine for the managementof left sided residual weakness of the body. Moreover, this might have contributed to the occurrence of TEN. Naranjo adverse drug reaction probability scale, WHO scale and Karch and Lasagna scale was used to score and assess the causality of TEN in this context, and it was found to be 5 (probable). The patient recovered after stopping the drug. De-challenge was performed and it showed definite improvement. Re-challenge was not performed. WHO-causality assessment scale showed PROBABLE as the event had a reasonable relationship with drug intake but unlikely attributed to disease other drugs. Predisposing factors include underlying autoimmune disease(wegner granulomatosis) and other possible cause include Cyclophosphamide drug.Karch and Lasagna Causality scaled showed severe as causality is highly probable.Figure 3.1 below shows Naranjo Causality scale.

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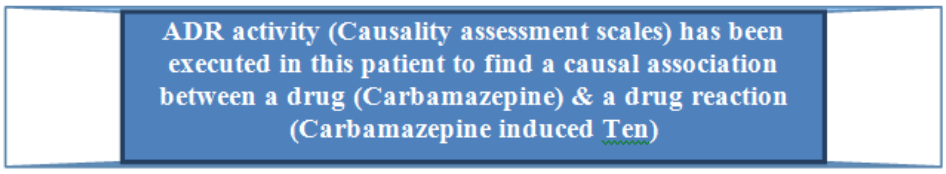

FIGURE 3.1 NARANJO CAUSALITY SCALE

PREDISPOSINGFACTORS	Under lying autoimmune disease (Wegner granulomatosis)
OTHER POSSIBLE CAUSE	Cyclophosphamide drug
DE CHALLENGE	Yes(Definite Improvement)
RE CHALLENGE	No
CAUSALITY	WHO: PROBABLE, Naranjo: PROBABLE, Karch & Lasagna: SEVERE
SEVERITY	Level5(required intensive care unit)
PREDICTABILITY	Predictable
PREVENTABILITY	Definitely Preventable
FATE OF SUSPECTED DRUG	Drug Withdrawn
TREATMENT GIVEN	Symptomatic
OUTCOME	Recorded
PATIENT INTER VIEWED	No
ALERT CARD PROVIDED	No
ADR DISCUSSED WITH CONSULT ANT?	Yes
ANY SUGGESTION GIVEN?	No

IV. PHARMACIST-INTERVENTIONS MADE DURING THE CASE:

- The patient was taking Tab. Cyclophosphamide for Wegner's Granulomatosis but patient didn't inform in the hospital & was not justified in the past medication history. So when talked with their relatives regarding usage of medications relatives showed me all his past medications and got to know that patient was also taking Tab. Cyclophosphamide since Oct 2022 along with Tab. Carbamazepine.
- So, this can be an alternative cause (other than carbamazepine) that could solely might have caused the reaction.
- Furthermore, articles showing the reports of "Cyclophosphamide induced TEN" have also been published.[5]
- Advice for ANA & Anti-dsDNA test to rule out the adverse reaction.
- Reports showing effective use of corticosteroids have contributed to reduced mortality in TEN without increasing secondary infection.
- Thus, by stopping Tab. Cyclophosphamide and shifting patient on Tab. Prednisone as induction therapy for 3-6 months and then on Tab. Mycophenolate mofetil as maintenance therapy later on for Wegner's granulomatosis with polyangiitis can be effective. [6]
- By the different route of administration-the interaction of drugs is been neglected. The proper absortion of drugs was found.
- The systemic administration of dexamethasone is very important dosage move & it's been increased the efficacy of drugs than the adverse effects. Higher efficacy than side effects is proved. [7]
- In discharge medication, Tab. Nexpro RD (Esomeprazole Mg^{2+}& Domperidone) – after food has been prescribed.
- It should be prescribed before food; its efficacy rate is higher & long lasting when taken at least 1 hour before food.
- Advice to check HOMOCYSTEINE LEVEL as patient is k/c/o HYPERHOMOCYSTEINEMIA as it can increase your risk of forming blood clots.
- SCORTEN SCALE (Score of TEN) i.e. specific severity-of-illness score has been performed to predict in-hospital mortality.
- Human Leukocyte Antigen (HLA) genotype testing should be performed in this pt. to predict the likelihood of ADR associated with a

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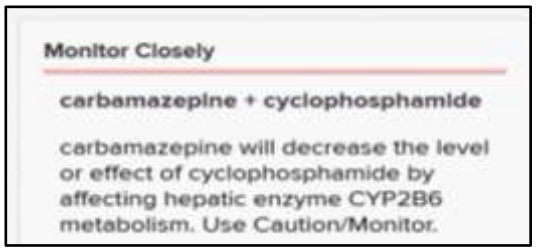
specific HLA type. This can be the realistic potential approach to improve patient outcomes. [8]



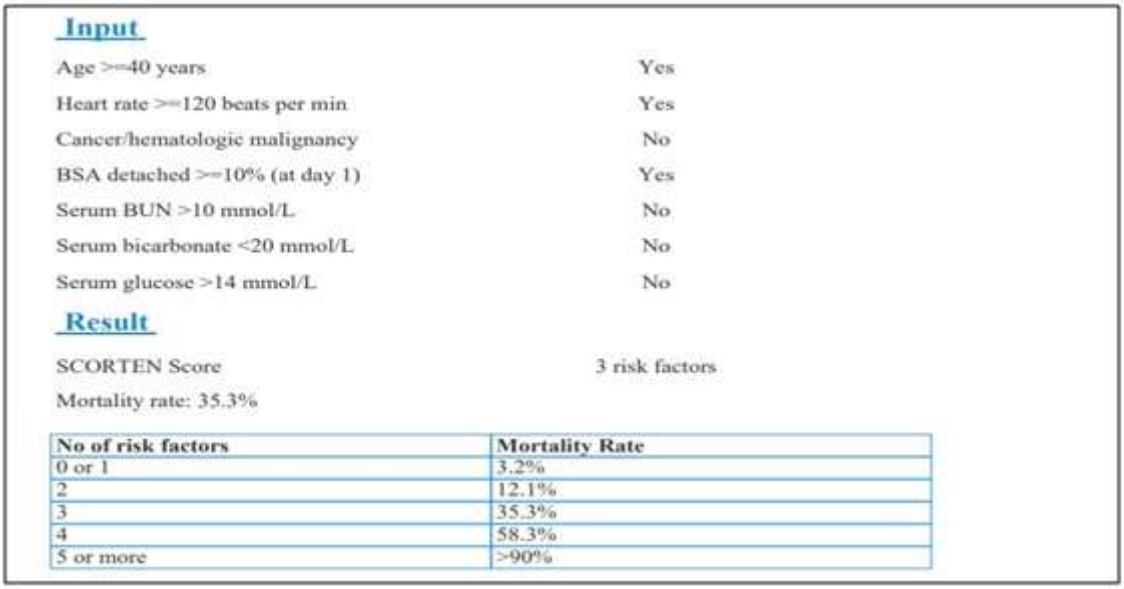


FIGURE 4.1 SCORTEN SCALE

V. CONCLUSION

Toxic Epidermal Necrolysis (TEN) is a severe, life-threatening condition and constitutes a medical emergency. There appears to be a familial predisposition to developing TEN with the use of carbamazepine (CBZ). Consequently, thorough counselling about medication use is crucial, especially in scenarios where treatment protocols are not well-defined. It is essential to educate patients who have previously experienced serious adverse drug reactions (ADRs) about potential risks and to ensure these reactions are reported to the appropriate authorities.

Carbamazepine is increasingly prescribed not only as an anti-seizure medication but also for managing pain and left residual weakness of the body in ischemic stroke. Raising awareness about medications that can cause severe drug reactions will assist healthcare professionals in the early identification and prevention of ADRs through careful administration of such drugs.

Clinical pharmacists play a critical role in preventing ADRs by providing expert advice on drug selection, dosing, and monitoring. They can conduct thorough medication reviews, identify potential drug interactions, and educate patients on the proper use of their medications. By staying informed about the latest drug safety information and guidelines, clinical pharmacists help ensure that medications are used safely and effectively, thus reducing the risk of adverse drug reactions.

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