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Case Study

Carbamazepine Induced Allergic Reaction; Stevens-Johnsons Syndrome

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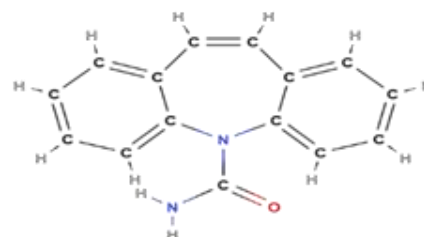
ABSTRACT

A common antiepileptic and mood stabilizer, carbamazepine is used to treat bipolar affective disorder, trigeminal neuralgia, and seizure disorders. Despite its effectiveness, carbamazepine has been linked to toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), two uncommon but serious cutaneous adverse drug reactions. Skin detachment, mucosal involvement, and extensive epidermal necrosis are the hallmarks of SJS, a potentially fatal mucocutaneous disease. It is thought that the pathogenesis entails a delayed-type hypersensitivity reaction that is mediated by cytotoxic T lymphocytes and is frequently linked to specific HLA genotypes, specifically HLA-B and HLA-A

INTRODUCTION

Carbamazepine belongs to the class of anti-seizure drugs. Brand name of carbamazepine is Tigretol, used in treating epilepsy, neuropathic pain resulting from trigeminal neuralgia. Carbamazepine is a GABA (gamma amino butyric acid) agonist. Brain contains a large electrical network. These neurons communicate with each other through electrical signals. In an abnormal condition, the neurons produce electrical signals in a very fast and rapid way. Sodium channels are present in neurons which control the flow of electrical signals. During seizures and other conditions sodium voltage gated channels open

and close too often causing overload to neurons. Carbamazepine blocks the activity of Na^+ at sodium voltage gated channels in the neurons which then helps in controlling seizures. [1,2]



Carbamazepine

PHARMACOKINETICS

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ABSORPTION

Carbamazepine has a bioavailability of 75–85% of the dose that is consumed.³ In a pharmacokinetic study, the C_{max} carbamazepine was found to be 1.9 ± 0.3 mcg/mL following a single 200 mg oral extended-release dose. A T_{max} of 19 ± 7 hours was recorded. Peak levels of carbamazepine were found to be 11.0 ± 2.5 mcg/mL following multiple doses of 800 mg every 12 hours. They lowered the T_{max} to 5.9 ± 1.8 hours. Over a 200–800 mg range, extended-release carbamazepine showed linear pharmacokinetics.^[3-8]

DISTRIBUTION

One pharmacokinetic study determined that the volume of distribution of carbamazepine was 1.0 L/kg. According to a different study, carbamazepine's volume of distribution falls between 0.7 and 1.4 L/kg. Unlike lung and brain tissue, carbamazepine is found in higher concentrations in the liver and kidney after crossing the placenta. The way carbamazepine passes through the blood-brain barrier varies.^[3-8]

METABOLISM

The liver is where carbamazepine is mostly metabolized. The primary liver enzyme responsible for breaking down carbamazepine into its active metabolite, carbamazepine-10,11-epoxide¹², is CYP3A4. Epoxide hydrolase then breaks it down into its trans-diol form. ¹⁶ CYP2C8, CYP3A5, and CYP2B6 are additional hepatic cytochrome enzymes that aid in the metabolism of carbamazepine. ¹⁷ Additionally, the UGT2B7 enzyme hepatically glucuronidases carbamazepine, and a number of other metabolic processes take place, leading to the production of quinone and minor hydroxy metabolites. ¹⁷ It's interesting to note that carbamazepine triggers its metabolism.^[3-8]

ELIMINATION

Following an oral dose of radio-labelled carbamazepine, the urine contained 72% of the administered radioactive dose while the faeces contained the remaining portion. The majority of carbamazepine's excretion consists of conjugated and hydroxylated metabolites, with trace amounts of the original medication.^[3-8]

PHARMACODYNAMICS

The main characteristic of carbamazepine's pharmacodynamics is that it functions as a voltage-gated sodium channel blocker, stabilizing neuronal membranes by stopping action potentials from firing repeatedly. By attaching itself to sodium channels that are not in use, it lowers neuronal excitability and, consequently, synaptic transmission. Additional effects include effects on neurotransmitter systems (serotonin and noradrenaline), possible modulation of other ion channels (such as calcium), and effects on the release of antidiuretic hormones.^[9]

DOSE

- Epilepsy in adults – 200mg BD, children – 10-20mg/kg/day divided into 2-4 doses.
- Trigeminal neuralgia in adults – 100g BD increases gradually by 200mg/day as needed for pain control.
- Bipolar disorder (mania) in adults 200mg OD or BD daily.
- Neuropathic pain in adults 100-200mg OD or BD daily.^[10]

ADVERSE DRUG REACTION

Fatigue, drowsiness, dizziness, vomiting and feeling queasy, loss of coordination, unsteadiness (ataxia), mouth dryness, headache, gaining weight, Painful, red or purple rash that spreads and blisters,



Skin that peels off, Sores in your mouth, nose, genitals, Flu-like symptoms, including fever, Swelling of the face, eyes, tongue. Damage to the liver; serious liver damage manifests as jaundice, yellowing of the skin or eyes, either light coloured stools or dark urine, our stomach's right-side hurts.

Severe Skin Reactions - These can be life-threatening and include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).^[11]

ALTERNATIVES TO CARBAMAZEPINE

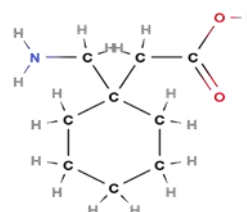
Other medications are used to treat severe pain, neuralgia, epilepsy with less adverse drug reactions and safer than carbamazepine. Few of those drugs are gabapentin, oxcarbazepine, lamotrigine, zonisamide, valproate, topiramate etc.

Gabapentin: It belongs to the class anticonvulsants, which has structure similar to GABA (gamma aminobutyric acid). Gabapentin appears to block release of excitatory neurotransmitters in the presynaptic region by showing a strong affinity for binding sites throughout the brain that correspond to the presence of voltage-gated calcium channels.^[12]

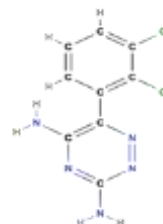
Lamotrigine: It belongs to anticonvulsants class of drug. Used as a second-line drug in treating seizures and also acts as mood stabiliser. It inhibits sodium voltage gated channels there by decreases neuronal excitability and seizures. It reduces the release of glutamate, a chemical that can overstimulate the brain if there's too much of it. By keeping glutamate in check, lamotrigine may also help stabilize mood, especially in bipolar disorder particularly by preventing the low, depressive episodes.^[13]

Oxcarbazepine: oxcarbazepine and gabapentin both belongs to the same class anticonvulsant. Oxcarbazepine shares similar mechanism of gabapentin, blocks voltage gated sodium channels.^[14]

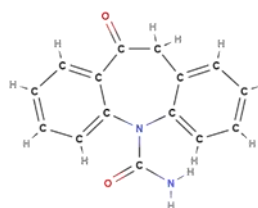
Valproate: Valproate acts in different mechanism like inhibiting GABA receptors, blocking voltage gated sodium channels, altering other genes and etc., which will eventually regulate neuronal excitability.^[15]



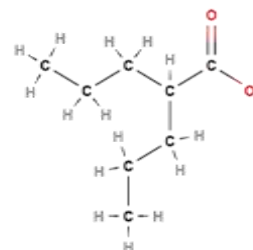
Gabapentin



Lamotrigine



Oxcarbazepine



Valproate

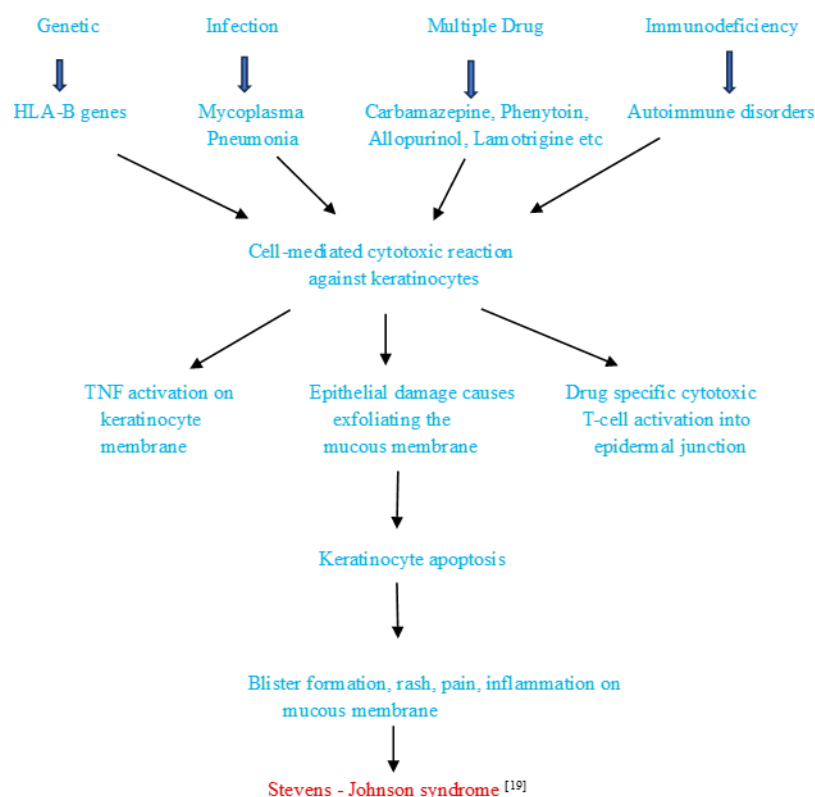
STEVENS – JOHNSON SYNDROME

A flu infection and a few medications are the main causes of Stevens-Johnson syndrome, an allergic reaction. The skin is affected by this potentially fatal condition. Stevens-Johnson Syndrome (SJS) as an extreme, runaway allergic reaction that severely damages your skin and the moist linings (mucous membranes) of your body. A fast emergency treatment is required as it spreads rapidly and damages mucous and skin membranes. The syndrome Stevens-Johnson is also known by terms like Lyell's syndrome, toxic epidermal necrolysis, drug – induced SJS, mycoplasma – induced SJS, erythema multiforme exudative. toxic epidermal necrolysis spectrum. [16,17]

ETIOLOGY

- The major cause of SJS is due to different drugs like carbamazepine, phenytoin, non-steroidal anti-inflammatory drugs like ibuprofen, sulfa- containing antibiotics, anticonvulsant drugs.
- The other major cause of toxic epidermal necrolysis is infection, which is caused by a bacteria Mycoplasma pneumonia which can trigger infection more especially in children.
- Genetic predisposition – presence of HLA (human leukocyte antigen) genes can precipitate the risk of infection.
- Immune response – autoimmune cells destroy their own T-mediated cells and worsen the reaction.
- Keratinocyte apoptosis, and other unknown factors which leads to Stevenson-Johnson syndrome. [18]

PATHOPHYSIOLOGY



SYMPTOMS

Blisters that hurt, facial, lip, and throat swelling, vision issues, genital sores, and hypersensitivity



reactions, sores in the mucous membranes, drooling, painful urination. [20]

DIAGNOSIS

- Physical examination

Appearance of blisters on mucous membrane, pinkish- red colored sores.

Skin removal or peeling of skin, rashes, exfoliation of skin cells.

Medication history, other comorbidities

- Genetic history

Presence of HLA-B genes

- Skin biopsy

A small sample of skin is taken and examined under a microscope. The definitive histopathological finding in SJS is full-thickness epidermal necrosis (death of skin cells) with minimal inflammatory infiltrate.

- Immunofluorescence test

A second skin biopsy may be taken for direct immunofluorescence testing. The results are typically negative, which helps differentiate SJS from other autoimmune blistering diseases like pemphigus.

- Complete blood examination

Blood tests can find out abnormalities in any parameters of blood.

- Culture sensitivity test

This test can determine the spread and strains of bacteria in the body as well as the presence of *Mycoplasma pneumonia* bacteria. [21]

MANAGEMENT

NON-PHARMACOLOGICAL THERAPY

- Stop taking the medication that resulted in the serious side effect.
- Avoid taking multiple medications.
- Steer clear of caffeine compounds and foods that trigger them.
- Maintain your stress levels and get enough sleep. Get emergency medical attention.
- Wear appropriate clothing and sun protection.
- At every stage, get routine examinations and disease monitoring. [22]

PHARMACOLOGICAL THERAPY

1. Corticosteroids:

Especially in the early stages of the disease, corticosteroids are used to suppress the overactive immune response that causes SJS. Their use is debatable, though, as some studies indicate early high-dose therapy may improve outcomes while others report no mortality benefit and an elevated risk of infection.

2. Intravenous Immunoglobulin (IVIG):

This treatment blocks the mechanisms that lead to widespread skin cell death by using antibodies from healthy donors. Studies on its effect on mortality have produced conflicting findings, and its efficacy is debatable.

3. TNF-Alpha Inhibitors:

TNF inhibitors such as infliximab and etanercept: Tumor necrosis factor-alpha (TNF-(alpha)), a protein implicated in skin cell inflammation and apoptosis (cell death), is the target of these biological medications. Larger-scale trials are required, but research in this area is just getting



started, and some studies indicate they might be helpful.

4. Cyclosporin:

Cyclosporin is an immunosuppressant which inhibits T-cells activation on skin cell.

5. Plasmapheresis:

This technique purges the blood of inflammatory substances and medication metabolites that might be contributing to the reaction. Plasmapheresis is a technique which purifies chemicals from the blood, also known as therapeutic plasma exchange technique. [23,24]

SUPPORTIVE THERAPY

1. Pain Killers:

NSAIDS and other painkillers are used to decrease pain at the effected regions on skin upon their peeling.

Eg: Acetaminophen

2. Topical and Systemic Corticosteroids:

Corticosteroids used to reduce inflammation and redness of blisters on skin or mucous membrane.

Eg: Methylprednisolone, Prednisone.

3. Eye Drops:

Lubricant eyedrops containing corticosteroids, heparin eyedrops, cyclosporin eyedrops are used to protect from further reaction and protect the ocular surface and infections caused in the eyes.

4. Other Medications:

Other medications include antacids, anticoagulant's etc., [25]

CASE DISCUSSION

A patient of 55 yrs female has admitted in medical department with the chief complaints of seizure activity at home – 3 episodes at 11;30 am lasting for 1 min and tongue bite, post-ictal status. Patient has a known history of seizure disorder since 2 yrs, not on medications. History of present illness is nausea sensation in the last 4 days, giddiness and sudden fall, there might be denova hypertension and denova diabetes mellitus type-2.

Past medical history (R_x) was on anti-epileptic drugs but discontinued due to skin allergic reaction to carbamazepine 2 yrs ago. From then the patient was not on any medications.

Now the patient has admitted for further treatment, on examination the patient is conscious and coherent and Temperature – 98°F, Pulse rate -79 bpm, Blood pressure – 170/100mmHg, SPO2 - 90% @RA, GRBS - 309mg/dl.

On 01/06/2025 the patients

Vitals of the patients were abnormal with blood pressure – 170/100mmHg, GRBS – 309mg/dl. Laboratory investigations were normal and advised for CT brain, MRI brain, 2DECHO. The drugs prescribed and given to the patient are INJ. PAN – 40mg, INJ. ZOFRER – 4mg, INJ. PCM – 1gm, INJ. MANNITOL – 100ml, INJ. LEVIPIL – 500mg, TAB. NICARDIA – 10mg, INJ. MONOCEF – 1gm, INJ. OPTINEURON – 1 amp, TAB- QUIETIAPINE – 25mg.

On 02/06/2025 the patients

Vitals of the patient on second day with blood pressure – 150/70mmHg, GRBS – 145 mg/dl, Patient is highly irritable, post-ictal confusion. Glassgow coma scale (GCS) shows E₃, V₅, M₆. Laboratory findings were normal. Reports of CT BRAIN gives right frontal bleed indicating



intracranial frontal bleed, MRI BRAIN reports for the patient with hemorrhage location on right frontal region, 2DECHO reports are concentric LVH, NO LVRWMA, grade-2 DD, NO clot/VGH, ICV – normal. Same medications are followed and Betadine mouth wash.

On 03/06/2025 the patients

Vitals of patient on third day with blood pressure – 130/80 mmHg, GRBS -152 mg/dl. Continued same treatment. No abnormalities detected.

On 04/06/2025 the patients

Vitals of the patient on fourth day with blood pressure – 110/70 mmHg, GRBS – 141 mg/dl. Continued same treatment with addition of ZYLE GEL for oral application, removal of INJ.MANNITOL – 100ml.

On 05/06/2025 the patients

Vitals are blood pressure – 130/80 mmHg. Continued same treatment with the addition of TAB. V TOTAL women and the patient was not willing for further MRI + ANGINA SCAN + MRV examination.

CONCLUSION

The patient of 55 yrs female has diagnosed with seizure disorder, Intracranial bleed on right frontal region, Denova Hypertension, Denova diabetes mellitus type-2, Drug allergic to carbamazepine-Stevens-Johnson syndrome. Seizure disorder and abnormal eye movement are controlled by the drug LEVIPIL and QUITIAPINE. Patient had previously experienced allergic reaction, which is stevens-Johnson syndrome to carbamazepine but no allergic reaction found after discontinuation of drug.

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