Case Report

Carbamazepine induced Toxic Epidermal Necrolysis in pediatrics patients

Geetanjali Purohit, Bhavana Srivastava*, Reena Bhardwaj, Sanjay Gaur

Department of Pharmacology, Govt. Medical College Haldwani.

Uttarakhand, India.

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Abstract

Objective: Toxic epidermal Necrolysis (TEN) and Steven Johnson syndrome (SJS) are two forms of a life threatening skin condition in which death of keratinocytes leads to separation of dermis from epidermis. **Material and methods**: The patient presents with fever, blister formation and denudation of skin involving whole body including the mucous membrane leading to severe dehydration and in extreme cases multiorgan failure with superadded infection leading to death. The most common cause are certain medications like antibiotics (sulphonamides, cephalosporin) anticonvulsants (carbamazepine, phenytoin), NSAIDs, antiviral, allopurinol etc. Presenting a case of an eight year old female patient who was suffering from Neurocysticercosis and was prescribed Tablet Carbamazepine 200mg twice daily, patient landed into emergency department with denudation of skin that involved more than 30% of body surface area, with fever and conjunctivitis. On examination blood pressure was low, with tachycardia and low urine output. Patient was managed in pediatric intensive care unit. WHO Causality assessment: probable: dechallenge done. **Results and conclusion:** Carbamazepine is a widely prescribed drug for Seizure and Trigeminal Neuralgias, physician should be aware with its adverse and life threatening side effects and drug should be prescribed judicially. The patient and care takers should also be encouraged to immediately report any abnormal manifestation following use of Carbamazepine to prevent potential life threatening condition.

***Key words*:** Toxic Epidermal Necrolysis (TEN), Carbamazepine, WHO causality assessment

Introduction

Toxic Epidermal Necrolysis (TEN)/Lyell Syndrome is a serious and life threatening idiosyncratic mucocutaneous reaction characterized by acute hypersensitivity due to viral infections, malignancies and drug . The underlying exact pathology of toxic epidermal necrolysis is not known but it has been observed that in TEN due to drugs there is impaired capacity to detoxify the reactive intermediate metabolite which further acts as an antigen and evokes immune response, mainly CD8T Helper cells mediated$_{I}$. These immune complexes are deposited at various sites including skin, leading to separation of dermis from epidermis and manifest as fever, conjunctivitis, bullae formation on mucosa, trunk and extremities, further progressing to denudation of skin involving more than 30% of total body surface area and severe dehydration (Villada et al., 1992).

The Etiological factors of Toxic epidermal necrolysis are Viral infections (herpes, AIDS, influenza), Malignancies, Drugs which includes antibiotics (penicillin, vancomycin, levofloxacin, sulfonamides, azithomycin), antiepileptics (valproate, barbiturates, carbamazepine, phenytoin, ethosuxiamide), diclofenac, ibuprofen, allopurinol, Antiretroviral drugs (nevirapine), antiviral (oseltamavir), isotretinoin, fluconazole (Bolognia et al., 2008).

Carbamazepine: It is a derivative of iminostilbene with a carbamyl group at the 5th position, which is responsible for its antiseizure activity. Its active metabolite is 10, 11-epoxide, which inhibits or slowdowns the rate of recovery of voltage activated sodium channel hence limits the repetitive firing of action potential. Its Peak plasma concentration seen after 4-6 hours of oral ingestion, therapeutic level is 6-12 microgram/ ml. Metabolised in liver by CYP3A4 enzyme induction, excreted mainly in urine principally as

**Address for Corresponding Author:*
Dr. Geetanjali Purohit
Department of Pharamacology,
Govt. Medical College Haldwani, Uttarakhand- 263139 India.
Email:geetanjalipurohit@hotmail.com
Mobile No: +919760927824

glucouronides. Toxicity or side effects are seen mainly above 9 microgram/ml of plasma concentration as hyperirritability, convulsions and respiratory depression. Long term therapy may cause drowsiness, vertigo, ataxia and blurred vision. Serious adverse effects may include hematological toxicity (aplastic anemia) and hypersensitivity reaction (dangerous skin reaction: Steven Johnson Syndrome, Toxic Epidermal Necrolysis). Drug interactions with valproate, lamotrigine, haloperidol and phenytoin have been seen due to CYP3A4 enzyme induction. Inspite of all its adverse effects and drug interaction, Carbamazepine is still widely used in treatment of Generalized tonic clonic seizure, Trigeminal neuralgias, Bipolar disorder, Diabetic neuropathy and as adjuvant with antipsychotic drugs. Presently its indication is also seen in pregnant females with epilepsy as it is devoid of any fetopathic or sedative effects (Goodman and Gillman, 2011).

Case report

An 8 year old female patient diagnosed with Neurocysticercosis and was under treatment, had TEN on 5th day and landed in emergency department in life threatening condition. Patient admitted in Pediatric Intensive unit.Five days prior to admission patient had history of three seizure episodes, was diagnosed as neurocysticercosis in some other hospital and prescribed Tab. Carbamazepine 200mg, Clobazam5mg, Albendazole 100mg. On second day of oral medication she complained of fever , conjunctivitis, dry mouth, difficulty in swallowing and maculopapular lesions , for which she consulted a local physician who misdiagnosed her as a case of chicken pox and advised her to continue same medication.But on 5th day patient condition got worse, and patient came in emergency department, Parents noticed and reported that her problem got aggravated whenever she took tablet Carbamezepine.

The patient diagnosed as case of drug induced Toxic Epidermal Necrolysis. Patient admitted to pediatric intensive care unit, offending drug stopped. Patient managed with fluid replacement, injection Pheniraminemaleate (0.5mg/kg), injection Dexamethasone (0.15mg/kg), intravenous antibiotics, and antipyretics. The proper dressing of denudaded epidermis area, along with nutritional support and care were given. Patient showed improvement in three weeks and discharged on tablet levetiracetam and clobazam.

Discussion

The clinical presentation of this patient with blisters and denuded skin involving more than 30% of body surface area following Tab. Carbamazepine, favours clinical diagnosis of drug induced Toxic Epidermal Necrolysis. Precluding diagnosis of Steven Johnson Syndrome, Staphylococcal Skin Scalded Syndrome, Erythema Mutiforme and generalized Fixed Drug Eruption. The other medication Tab. Librium and Tab. Albendazole are not related or reported with this type of drug effects, moreover she started developing TEN symptoms with in 4to 6 hours of intake of carbamezepine.

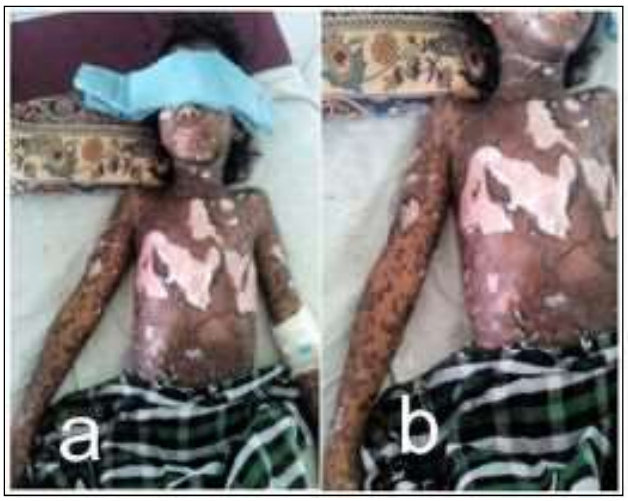

Figure 1. (a) Toxic Epidermal Necrolysis due to Carbamazepine (b) Toxic Epidermal Necrolysis pretreatment

On withdrawal of drug and supportive care patient improved remarkably but had hyper pigmentation on skin as post TEN sequele. Rechallenge was not done on ethical ground and considering age of patient.

As par WHO Uppsala Monitoring center (WHO UMC) standardized case casuality assessment criteria and Naranjo Algorithm this event considered as a probable reaction due to Carbamazepine. TEN due to carbamazepine has also been reported previously. The drugs most commonly involved are antibiotics (Sulfonamides, beta lactam, tetracycline) Anticonvulsants such as Phenytoin, Phenobarbitone and Carbamezipine.AntiRetroviral like Nevirapiene. NSAIDs and Allopurinol.

In a retro prospective study (2008) conducted in 30 TEN/SJS patients, anticonvulsants (35.08%) were the most commonly implicated drugs followed by antibiotics (33.3%) and NSAIDs (24.56%) (Mazumdar and Shome, 2014). The present study shows that carbamazepine induced TEN is a life threatening condition and requires immediate Supportive care and Treatment as well immediate diagnosis.

Conclusion

Carbamazepine is a widely prescribed drug for Seizure and Trigeminal Neuralgias, physician should be aware with its adverse and life threatening side effects and drug should be prescribed judicially. The patient and care takers should also be encouraged to immediately report any abnormal manifestation following use of Carbamazepine to prevent potential life threatening condition.

References

Bolognia JL, Jorizzo JL, Rapini RP. 2008. Stevens-Johnson syndrome and toxic epidermal necrosis. Dermatology. 2nd ed. Amsterdam: Elsevier Limited; p.291-300.

Goodman and Gillman`s. 2011. The Pharmacologist Basis of Therapeutics. 12th ed.New York: Mc Graw Hill; p.1428-30.

Mazumdar G, Shome K. 2014. Steven-Johnson syndrome following use of metronidazole in a dental patient. Indian Journal of Pharmacology, 46:121-2.

Villada G, Roujeau JC, Clerici T, Bourgault I, Revuz J. 1992. Immunopathology of toxic epidermal necrolysis. Keratinocytes, HLA-DR expression, Langerhans cells, and mononuclear cells: An Immunopathologic study of five cases. Achieves of Dermatology, 128:50-53.

WHO-UMC Causality Categories. In WHO-UMC Causality assessment-Uppsala Monitoring center. Accessed from: http://www.who-umc.org/Graphics/24734.