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STEVEN JOHNSONS SYNDROME FOLLOWING TREATMENT WITH CARBAMAZEPINE: A CASE REPORT

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ABSTRACT

A case of Steven Johnsons Syndrome (SJS) induced by Carbamazepine in a patient who was treated for seizures with Tab.Tegretol, after a bike accident is reported. A 21yr old male patient developed symptoms of soreness of mouth and Lips, redness and burning of eye and purpuric rash over the trunk region after two weeks of treatment with Tab. Tegretol (CBZ) for his seizure control.The patient's symptoms relieved after two week of treatment with topical Steroids, Immunosuppresive agent and Antihistamine for his allergic skin reactions. Cutaneous adverse reaction is most common manifestation of Anti epileptic drug allergy, particularly causing Steven Johnson's syndrome and Toxic epidermal necrosis. A large data suggest a strong association between AED (Carbamazepine) induced SJS/TEN where the triggering factor is HLA-B 1502* allele, revealing an ethinic specificity. Keeping in view, the vast use of carbamazepine for seizure control and adverse consequences of SJS/TEN, the author suggest carrying out a risk management approach prior to initiation of carbamazepine therapy in order to reduce the prevalence and morbidity of the syndrome.

KEYWORDS: Carbamazepine, Steven Johnson Syndrome, Toxic epidermal Necrosis, Adverse drug Reaction.

INTRODUCTION

SJS is a rare, life-threatening mucocutaneous reaction characterized by confluent epidermal necrosis with minimal associated inflammation and is commonly associated with fever, myalgia, arthralgia with more extensive mucosal (conjunctival, oral, nasal cavity, genital,

urethral) and facial lesions. An epidermal detachment of < 10% of the total body surface area (BSA) is considered as SJS. On the other hand, an epidermal detachment of > 30% of the total BSA is termed as TEN. TEN is a life-threatening illness characterized by high fever and confluent erythema which may lead to necrolysis.

Stevens Johnson syndrome and toxic epidermal necrolysis, that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. It is estimated that 1 in 20 patients with HLA-B*1502 will have TEN, SJS when taking carbamazepine. Prevalence of HLA-B*1502 has not been studied in many regions of Asia. However, , a rough FDA guide suggest as South Asians, including Indians to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but higher in some groups. HLA-A*3101 is expected to be carried by more than 15% of patients of Japanese, Native American, Southern Indian (e.g., Tamil Nadu) and some Arabic ancestry. According to the immunological Hypothesis, there is striking evidence of strong association between HLA-B*1502 allele and Carbamazepine induced SJS/TEN. The cytotoxic response mediated by CD8+ T-cell is considered to be the major event in SJS.

Hung et al. (2006) in a case control study in Taiwan found that of 59 out of 60 patients with SJS/TEN associated with carbamazepine were positive for HLA-B*1502 and suggest an initial estimate of 5% absolute risk of SJS/TEN in HLA-B*1502 positive patients exposed to Carbamazepine.

Case Report

A 21 year old man was admitted to the hospital for his complaints of fever associated with chills and rigors since a week and 3-4 episodes of bloody vomiting. On Examination, his skin was found to be scaly with Hyperpigmented lesion and blood stained over the face. His eyes were reddened and eyelids had crust formation. The patients BP was recorded as 110/70 mmHg, PR-90 b/min.

History of Illness suggest that Twelve days prior to admission, the patient had a bike accident where he was diagnosed for Epidural Hematoma during which he received Carbamazepine (Tegretol) for his early traumatic seizure control. On day one of the hospitalization, the Physician advised for the following Lab parameters.

Complete blood picture, Serum Electrolytes, Complete Urine analysis and Liver function Test.

Investigations revealed an ESR 30mm in 1hour and 55mm in 2nd hour, SGOT levels- 84 IU/L (16-40 IU/L) and SGPT – 108 IU/L (10-41 IU/L), Alkaline phosphate- 228 IU/L (40-129 IU/L).

Day 1 medications include Pantoprazole 40mg IV BD, Pheniramine maleate 1amp IV OD, Methyl prednisolone 60mg IV BD, Lacto calamine lotion locally OD, Piroxicam 1amp IM BD and IV fluids 80ml hourly.

On 2nd day, the patient moved for dermatologist concern where he was found to have sore mouth and lips, reddening and burning sensation in eyes and purpuric rash over the trunk region. On further examination, the patient was observed to be Febrile with Blanchable palmar erythema, purpuric macules and vesicles over the chests which were slowly progressing towards the face. Conjuctival oedema and oral mucosal erosions were also observed. The patient reported a similar rash in 2000 after using Carbamazepine for his Epilepsy and was recently received the same drug for his seizure control after a TBI (traumatic brain injury). The dermatologist gave the provisional diagnosis as Steven Johnson Syndrome progressing to TEN due to Carbamazepine drug allergy and prescribed the following medications to be continued along with the earlier medicines.

Tab. Cyclosporine 100mg BD

Inj. Methyl prednisolone 40mg IV BD

Tear plus eye drops.

The same day, Patient was send for an Ophthalmologist concern and was reported to have crusty eye beds, erythema of eyelids with mucoid margins and congestion of tarsula, although cornea was normal. The ophthalmologist suggested Tab. Moxifloxacin 10mg QID and refresh tear gel.

During the 3rd of treatment, the patient complaint of oral ulceration with difficulty to open the mouth and Genital ulceration with rash. The rash over the face and chest was found to be reduced but buccal mucosa and lips were swollen and erythematous. Injection Gentamycin 50mg IV twice daily and Tab. Zincovit was then added to the above treatment.

On Day 4, the patient was coherent, taking oral fluids and PR increased to 92/min BP-110/90mmHg. The patient complained of pain and tenderness of abdomen and constipation. On examination, erythema over chest and face were mild Blanchable erythema on palms and few vesicles on the arm with persistent burning sensation, Genital ulcers, crusted lips and congested eyes. Methylprednisolone (systemic Steroids) was removed and Heparin sodium gel to be applied locally twice daily and syrup Ofloxacin 2tbsp BD were included to the treatment plan.

On 5th day, patient was clinically improving with Diminishing Oral ulcers but developed lesions over the scrotum for which powder Nebasulf was given.

For next two days, the patient had no fresh complaints and the oral and genital ulcers were on healing stage and Rash over chest and arms were persistent.

On day 8 of treatment, patient had acute protruded tongue and constipation. The same treatment plan was continued with liquid paraffin added for his smooth bowel movement.
The patient had no new complaints and was found to be clinically improving with subsiding rashes and buccal ulcers although Genital ulcers were mild, in process of healing. The patient requested for discharge at the end of 2nd week and discharge summary was made. Tab. Cyclosporine 100mg, and syrup Mucaine gel 2 tbsp, and syrup Ofloxacin 2 tbsp were advised.

DISCUSSION

Steven Johnson syndrome is a life threatening, T cell mediated delayed type drug hypersensitivity with diverse clinical manifestations of serious blistering of skin and mucous membrane with systemic complications and multiple organ involvement.

HLA-B 1502* allele is frequently found in patients from southeast Asian countries and genetic predisposition of this specific HLA complex to Carbamazepine drug metabolite is considered as a strongest association reported so far. Pathogenesis of Cutaneous adverse drug reactions like Steven Johnson syndrome and toxic epidermal necrosis involves activation of cytotoxic T lymphocytes (CTL) through Major Histocomatibility complex restricted presentation of drug metabolite. Several hypotheses have been proposed which explains the classic peptide antigen pathway (direct pharmacologic interaction of drug with immune cell receptor) responsible for initiation of SJS/TEN in patients taking Carbamazepine drug.

A recently hypothesized model of association between HLA-B1502* and Carbamazepine induced SJS/TEN reflects a pharmacoimmunologic mechanism in which HLA-B 1502* proteins directly and covalently binds to CBZ or its metabolite and then activates CTLs in patients with SJS/TEN. This indicates that specific endogenous peptide residues of HLA-B102* protein are required for Carbamazepine presentation and T cell activation. Therefore, it could be considered that HLA-B 1502*, peptides, CBZ and TCR of CTLs form an immune synapse to initiate the robust immune reactions in patients with CBZ induced SJS/TEN. The lesions observed in patients with SJS/TEN are predominantly known to be induced by activation; proliferation and release of circulating skin homing.

The patient developed symptoms of cutaneous reactions 2 weeks after the treatment with Carbamazepine (Tab. Tegretol) and was effectively treated using immunosuppressive agent Cyclosporine, Topical steroids including methyl Prednisolone and Beclomatasone, Antibiotics as eye drops and gels. His condition was critical at the time of admission and was fairly stabilized following 2 weeks treatment. His condition can be described as Steven Johnson syndrome progressing towards TEN as his lesions and macules were slowly reaching from upper body (face and arms) to lower body parts (scrotum).

Pharmacist assessment for detection of adverse drug reaction was carried out using Naranjo's causality Assessment scale, where with a score of 8, the drug Carbamazepine was concluded to be a probable cause of SJS/TEN. To potentially reduce the incidence of such adverse drug reaction, genetic screening for HLA-B1502*before administration of Carbamazepine should be adopted as a necessary step. Also, the US Food and Drug Administration has advised the healthcare providers to screen the patients for the HLA-B*1502 allele before starting treatment with Carbamazepine and suggested that other Anti epileptic drugs should not be prescribed unless the expected benefit clearly outweighs the increased risk of serious skin reactions.

The Naranjo's adverse drug reaction probability scale

Sl.no	Questionnaire	Yes	No	Do not know	Score
1.	Are there previous conclusive reports on this reaction?	+1			0
2.	Did the adverse event occur after the suspected drug	+2			+2
3.	Did the adverse reaction improve when the drug was	+1			+1
4.	Did the adverse reaction reappear when the drug was readministered?			0	0
5.	Are there alternative causes (other than the drug) that could solely have caused the reaction?		2		+2

6.	Did the reaction reappear when a placebo was given?			0	0
7.	Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?			0	0
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1			+1
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1			+1
10.	Was the adverse event confirmed by any objective evidence?	+1			+1
Total Score					= 8

*Naranjos Causality assessment scale was utilized to determine the cause of Steven Johnson syndrome in the patient and results were documented as above.

CONCLUSION

The overall estimated risk of SJS/TEN associated with carbamazepine is based on countries with mainly Caucasian populations, and is fairly low, 1- to 6 per 10,000 new users. A clear understanding and knowledge of the association between HLA-B 1520* and Carbamazepine might be helpful in preventing life-threatening skin reactions. By screening patient for HLA-B*1502 before prescribing high-risk AED (CBZ)**,** Adverse drug reactions like Steven Johnson syndrome and toxic epidermal necrosis can be omitted**.** This will allow the clinician to ensure safe and effective therapy and therefore prevent Adverse drug Reactions.

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AUTHOR STATEMENT

There is no conflict of interest of any of the author in this work.

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