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Case Report

Pharmacology Section

Use of Cyclosporine for the Treatment of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis Induced by Carbamazepine- A Case Report

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ABSTRACT

Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, potentially life threatening, severe mucocutaneous adverse reactions characterised by extensive epidermal detachment, erosion of mucosa and severe constitutional symptoms. However, the use of Carbamazapine may be associated with a plethora of adverse effects, the most serious being SJS/TEN, wherein the patient typically presents with fever, skin eruption and mucosal involvement. It occurs between 1/1,000 and 1/10,000 new exposures to the drug. Here, the authors report a case of severe life threatening SJS/TEN induced by Carbamazepine in a three-year-old boy who presented with high grade fever, skin rash and all mucosal involvement. This condition is best approached with immediate discontinuation of offending drug and prompt administration of oral cyclosporine. The case is being reported to emphasise the need for timely diagnosis and prompt treatment with cyclosporin for successful outcome as it can cause irreversible organ damage or death if untreated early.

Keywords: Antiepileptic, Immunomodulator, Pseudo-Nikolsky signs, World health organisation

CASE REPORT

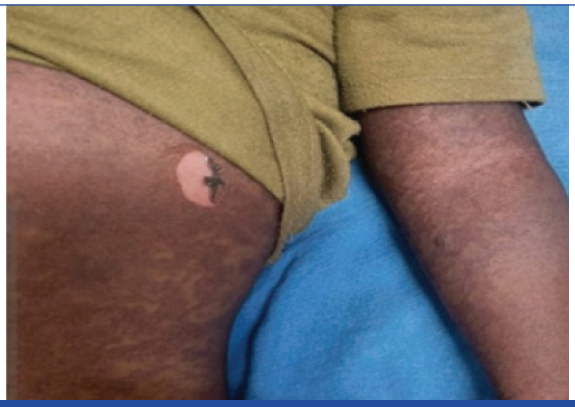
A three-year-old male child, developmentally normal with 12 kg body weight admitted in the intensive care unit in the Paediatrics Department, presented with wide spread erythema, necrosis and bulla with involvement of conjunctiva, oral and rectal mucosa. The child was known case of partial epilepsy since one month and history of intake of anti-epileptic drug Carbamazepine in a dose of 10 mg/kg three times a day one week back. Detailed personal and family history of allergy to any medications was taken and immunisation was appropriate with the age. There was no history of allergy to carbamazepine or any other medications. The baby was normal seven days back, before the intake of carbamazapine and developed fever, acute in onset and continuous in nature associated with chills and rigour. On second day, boy developed rashes over chest that progressed to the entire body, followed by swelling of the lower limbs, upper limb, abdomen and entire body including face. Following investigations were done as shown below [Table/Fig-1].

Laboratory Investigations	Values
Haemoglobin %	7.7g%
Total white blood count	15,100 cells/cu mm
Neutrophils	48%
Lymphocytes	45%
Eosinophils	03%
Monocytes	4%
Basophils	0%
Erythocyte Sedimentation Rate (ESR)	12 mm/1Hour
Blood urea	16 mg/dL
Serum creatinine	0.2 mg/dL
Uric acid	2.2 mg/dL
Total bilirubin	0.7 mg/dL
Direct	0.2 mg/dL
Indirect	0.5 mg/dL
Serum Glutamic-Oxaloacetic Transaminase (SGOT)	133 IU/L
Serum Glutamic Pyruvic Transaminase (SGPT)	231 IU/L
Alkaline phosphatase	1047 IU/L
Total Protein	4.5 g/dL
Albumin	2.4 g/dL
Globulin	2.1 g/dL
Albumin/Globulin ratio	1.2 g/dL
Serum sodium	133 mmol/L
Serum potassium	56 mmol/L
Serum chloride	101 mmol/L
Chest radiography	Normal
Abdominal sonography	Normal
Random Bloos Sugar (RBS)	110 mg/dL
Peripheral smear for malaria parasite	Normal
Latex Slide Agglutination and Tube Agglutination (WIDAL) tests	Normal
Human Immunodeficiency Virus (HIV) test	Negative

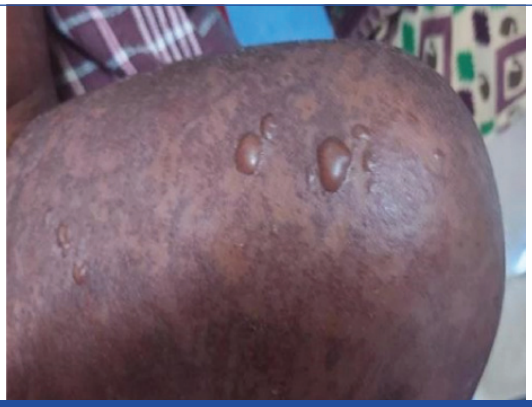
[Table/Fig-1]: Laboratory investigations.
WIDAL: Widely investigated diagnosed assay laboratory

The case was referred to dermatologist for the above signs and symptoms. On dermatological examinations, multiple ill-defined reddish to violaceous macules with few blisters and erosion present all over the body sparing palms and soles. Oral mucosa, genital mucosa and eye mucosa were involved as shown in the [Table/Fig-2-5]. Pseudo-Nikolsky signs were negative for SJS. False Nikolsky's sign has been seen in a variety of diseases including the most important of them are Bullous pemphigoid and Epidermolysis bullosa are ruled out [1]. Thus, it was concluded that this was the case of SJS/TEN induced by Carbamazepine and the patient recovered after stopping Carbamazepine on the third day. Further re-challenging with oral Carbamazepine was not done in the interest of the patient and due to ethical constraints and patient was followed from first day of admission to ninth day i.e., day of discharge from hospital and followed for about two months. No test was done for

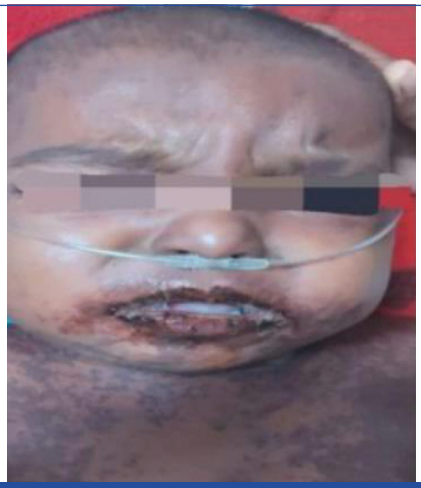
Human Leukocyte Antigens (HLA)-B1502 which is more common in Asian groups due to unavailability of the test in the area where this case was reported and as there was just one patient. The causality assessment was done by using, the Naranjo's Scale/Algorithm and score was 6 and the causality assessment using the World Health Organisation-Uppsala Monitoring Center (WHO-UMC) scale was also done and this case was put in the probable/likely category of Adverse Drug Reaction (ADR) [2]. The medical college where this case was reported had an ADR monitoring center and the case details were reported to Pharmacovigillance Programme of India (PvPI) (VIGIFLOW) located in Ghaziabad with worldwide unique ID: IN-IPC-300653013 dated 24/07/2022.



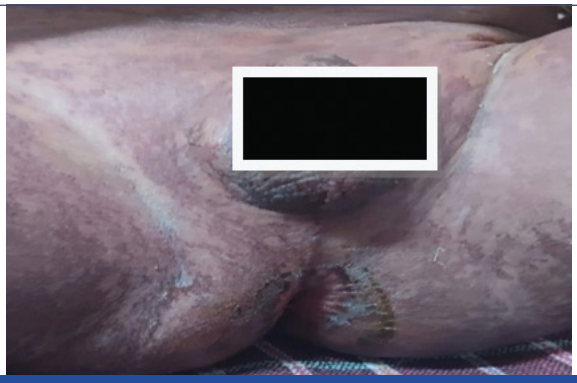
[Table/Fig-2]: Erosion on the upper chest.



[Table/Fig-3]: Blisters on the lower limb.



[Table/Fig-4]: Ulcerative stomatitis.



[Table/Fig-5]: Blisters on the genitalia.

The patient was treated symptomatically with injection Amoxicillin's+ Clavulanate (200 mg+28.5 mg) i.v. 8 hourly daily; injection Pantoprazole 10 mg i.v. 6 hourly; injection Ondensetron 2 mg i.v. 12 hourly, i.v. DNS 750 mL/day, i.v. Ringer lactate 700 mL/day, syrup. Hydroxyzine two times a day (through Naso gastric tube), Fusidic acid cream for topical application two times a day, Dermadew baby lotion, normal saline compress for local application over lip. The above treatment was given for five days. With the specific treatment of tablet cyclosporin 12 mg oral three times a day for eight days and dose reduced to 6 mg three times a day for next six days, the child responded remarkably without any sepsis or complications and was discharged after nine days of hospitalisation when above laboratory studies revealed normal findings.

DISCUSSION

SJS and TEN are both rare skin reactions that are often triggered by particular medications such as antiepileptic drugs, non steroidal anti-inflammatory drugs and certain antibiotics and can be life-threatening [3]. It affects all age groups, affecting more of those individuals that have Human Immunodeficiency Virus (HIV), autoimmune diseases, immuno-compromised patients and those who have an underlying malignancy. Also, it is thought to be an immune mediated drug reaction with higher rates in certain population linked to Han Chinese and other Asian groups due to HLA-B1502 [4]. The annual incidence of SJS and TEN in the general population is known to be 1-6 and 0.4-1.2 per million people, respectively [5]. Here, a case of Carbamazepine induced SJS/TEN being successfully treated using cyclosporine has been presented.

The exact mechanism of SJS/TEN remains unclear. Keratinocyte death is thought to be caused by cytotoxic T cells and natural killer cells and triggered by soluble Fas ligand, perforin/granzyme B and granulysin produced by such activated cells [5,6]. Tumour Necrosis Factor-alpha (TNF-α), a major pro-inflammatory cytokine is highly expressed in the skin of SJS/TEN and suggested to be responsible for extensive skin necrosis [7]. It was also demonstrated that the necroptosis pathway contributes to keratinocyte death in SJS/TEN through the interaction between monocyte-derived annexin A1 and formyl peptide receptor 1 expressed on keratinocytes [8]. Carbamazepine, which is widely used to treat seizure disorder, bipolar disorder, trigeminal neuralgia and chronic pain, is one of most common causes of drug hypersensitivity reactions. The reported frequency of serious carbamazepine hypersensitivity reaction is between 1/1,000 and 1/10,000 new exposures to the drug [9]. Immediate withdrawal of all the suspected drugs is the key to the management of SJS and TEN.

From Indian perspective of the disease, similar cases were reported in the past, systemic steroids have been used for decades in the management of SJS and TEN. Early treatment with steroids was associated with improved outcome. Oral steroids, instituted within 24-48 hour of onset of disease and tapering over the next 7-10 days gives best results [10]. Methylprednisolone pulse therapy has been found to reduce the levels of pro-inflammatory cytokines such as Interferon-gamma (INF-γ), TNF-α and Interleukin-6 (IL-6) [10]. One of the studies done by Dhar S; on use of steroids for long term associated with an increase in the duration of hospital stay and infective complications associated with SJS and TEN [11].

The similar study done by Viard I et al., Intravenous Immunoglobins (IVIg) was the most common immune modulator used worldwide

in the treatment of SJS-TEN which interferes with death ligand-induced apoptosis [12] and it also pointed out that the progression of skin lesions was not arrested after IVIG administration [13,14]. It specifically targets granulysin, an important mediator of apoptosis of keratinocytes and thus, leads to arrest of disease progression. A previous study has shown that cyclosporine can be used to treat SJS and TEN as an off-label use [15]. A similar case study on use of cyclosporine has shown promising therapeutic effectiveness in curing similar diseases, although its therapeutic role has not yet been fully understood [16]. In a recent study, patients from India, where cyclosporine was given at a dose of 3 mg/kg in three divided doses for 7 days and then tapered over the next seven days, the mean duration of hospital stay was significantly lower with no mortality [17]. Cyclosporine inhibits the activation of CD4+ and CD8+ Cytotoxic T-cells in the epidermis by suppressing IL-2 production. Cyclosporine has also been shown to inhibit TNF-α production [18].

Most common side-effects associated with cyclosporine treatment are hypertension and renal toxicity but they are not seen in treatment with short duration as used in SJS/TEN [19]. This patient did not experience these side-effects and the treatment was well tolerated despite being administered to acutely ill patients. Cyclosporine is an immunosuppressant and increased risk for developing lymphomas and other malignancies. But due to shorter duration of treatment in SJS/TEN, the risk of malignancy or infection incurred from cyclosporine treatment is likely to be negligible. Hence, it is recommended that cyclosporine 12 mg three times a day through oral route can be used as the first line-specific immunomodulator in SJS/TEN on account of its safety, efficacy, reduced morbidity and mortality. The duration of treatment was for maximum of about 14 days by the time re-epithelisation occur.

CONCLUSION(S)

As there is less available literature on use of cyclosporine in the treatment of SJS/TEN in children, an experience and evidence-based approach is needed in the management of SJS/TEN. Cyclosporine is a good choice of drug as it is cost-effective both as a direct cost of the drug and indirect cost by shortening hospital stay which in this case was a mere eight days for SJS/TEN.

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