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A Retrospective Analytical Study on Drug Induced Stevens Johnson Syndrome and Toxic Epidermal Necrolysis in a Tertiary Care Hospital in Telangana.

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Abstract:
Objective: *To assess the relationship between age, sex of the patient, and seasons of the year with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and to find out common causative drugs and clinical outcome of SJS and TEN cases reported from Osmania Medical College.*
Materials and methods*: A retrospective analytical study done on drug induced SJS and TEN using the data collected from the individual case safety reports (ICSRs) reported from Adverse drug reaction Monitoring Center (AMC), Osmania Medical College (OMC) to National Co-ordination Center, Pharmacovigilance Program of India (NCC, PvPI) from January 2015 to March 2017. UMC-WHO causality assessment scale was uses to assess the causality.*
Results: *Total 24 cases of drug induced SJS and TEN were reported over a period of 26 months. 62% were male and 38% were female. Patient's age ranges from 3years to 71 years. Antiepileptics and antibiotics were suspected to be common causative drugs for SJS and TEN. More cases of antibiotic induced SJS were reported during winter. Causality assessment was certain in 2 cases and probable in 22 cases. SJS and TEN is a serious ADR associated with 8% mortality in this study.*
Discussion: *In this study we observed male predominance and more cases were reported during winter. Antiepileptics and antibiotics were the common suspected drugs for SJS and TEN. It is a serious ADR associated with fatal out come in elderly patients.*

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I. Introduction

Stevens-Johnson syndrome and toxic epidermal necrolysis, two forms of same acute life threatening mucocutaneous adverse drug reactions, are caused by a wide variety of drugs including antibiotics, analgesics and antiepileptics. TEN is a serious form of SJS. It is a rare adverse drug reaction (ADR) affects 1or2 in 1million users[1].

Strong association observed between Human Leukocyte Antigen (HLA) and drug specific SJS. Studies done on Han Chinese revealed a strong association between the human leukocyte antigen HLA-B*1502 and SJS induced by carbamazepine[2]. Studies done in Japanese population revealed association between HLA-A* 3101 and SJS induced by carbamazepine [3]. Allopurinol induced SJS were found to be significantly associated with HLA-B 5801[4]. Some studies revealed that low N-acetylation capacity is a risk factor for sulfonamide induced SJS.[5][6]

SJS is an idiosyncratic delayed type IV hypersensitivity reaction typically involving the skin and mucous membranes. Certain drugs or its metabolites acts as antigens induce epidermal necrolysis through activation of CD8+ T cells. Granzyme B is a protease and granulysin a substance create holes in the target cells, secreted by Cytotoxic T cells responsible for keratinolysis and epidermal necrolysis[7][8].

SJS is characterized by mucosal erosions, small blisters or purpuric macules on the skin followed by detachment of 10% or less of body surface area. Fever and lesions of the respiratory and gastrointestinal tract are seen in 10%–30% of patients.

TEN is characterized by skin and mucosal lesions with confluent erythema, large sheets of necrotic epidermis and total detachment of the skin over more than 30% of the body surface area. Fever, eosinophilia, atypical lymphocytes and multi-organ involvement are present in 30%–50% of patients.

Drugs that are most commonly responsible for SJS are Allopurinol, Trimethoprim-sulfamethoxazole and other sulfonamide-antibiotics, aminopenicillins, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital and NSAID's of the oxicam-type [1].

This study was done to study the demography, seasonal influence, causative drugs and outcome of SJS and TEN cases reported from AMC-OMC over a period of 26 months.

II. Materials and methods

A retrospective study done on drug induced Stevens Johnson syndrome(SJS) and Toxic epidermal necrolysis(TEN) from the records of Adverse drug reaction monitoring center(AMC), Osmania Medical College using data collected from the ICSRs reported from AMC to National Co-ordination Center, Pharmacovigilance Program of India (NCC, PvPI) from January 2015 to March 2017.

In this study we analyzed the association of SJS and TEN with age, sex of the patient and with seasons. Offending agents (drugs), causality assessment, and outcome of SJS and TEN. UMC-WHO causality assessment scale was uses to assess the causality of reported SJS and TEN cases.

III. Results

Age and Gender distribution: Total number of drug induced SJS and TEN cases reported from Jan 2015 to March 2017 are 24. Youngest patient was 3 yrs old and oldest patient was 71yrs. 25% (6/24) of SJS case were reported from less than 20years age group, 58% (14/24) of SJS cases were from21 to 55 years age group and 17% (4/24) of SJS cases were from elderly age group of more than 56 years. Out of 24 cases 15 (62%) are male and 9 (38%) are female, this shows higher incidence in male. One interesting feature is female patients are more in 20 – 55 years age group where as male patients are more in pediatric and elderly age group.

Age and Gender distribution:

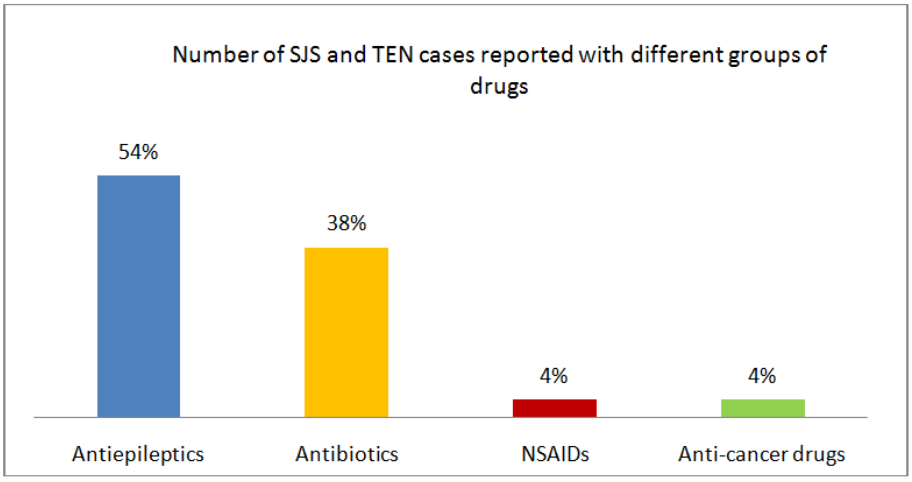
Age (3 to 71 yrs)	Male (15)	Female (9)
3-20 yrs	5	1
21-55yrs	6	8
56 to 71	4	0

Seasonal distribution of SJS & TEN: During the study period from January 2015 to March 2017, 54% (13/24) of SJS cases reported during winter (November to February) , 29% (7/24) of SJS cases reported during summer (March to June) and 17% (4/24) of SJS cases were reported during rainy (July to October) season.

Seasonal distribution of SJS/TEN:

Season	No. of cases reported
Winter (November to February)	13
Summer (March to June)	7
Rainy (July to October)	4

Drugs responsible for SJS and TEN cases reported from AMC, OMC to PvPI: The groups of drugs causing SJS and TEN were antiepileptics (13/24, 54%), antimicrobials (9/24, 38%), NSAIDs (1/24, 4%) and anticancer drugs (1/24, 4%).



Among antiepileptic drugs, Phenytoin was responsible for 6 cases (6/24,25%), Sodium Valproate, Carbamazepine and Oxcarbazine for 2 cases (2/24, 8%)each, Lamotrigine and Leveteracetam combination responsible for 1 case(1/24, 4%), where as in antibiotics Beta-lactum antibiotics responsible for 4 cases (4/24, 16%), Fluoroquinolones for 3 cases (3/24, 12%), cotrimoxazole for 1 (1/24, 4%)and INH for 1(1/24, 4%), Nimesulide (NSAID) and Capicitabine are responsible for 1 case (1/24, 4%)each, of total 24 drug induced SJS cases. More cases were reported with anticonvulsants.

Drugs responsible for SJS and TEN cases:

Name of Drug group	Name of the suspected drug	No of SJS/TEN cases caused by suspected drug/drugs	Total No of SJS/TEN cases caused by drug group
Antiepileptic drugs	Phenytoin	6	13
	Carbamazepine	2	
	Oxcarbazine	2	
	Sodium Valproate	2	
	Lamotrigine and Leveteracetam combination	1	
Antibiotics	Beta-lactum antibiotics (Amoxycillin ,Cloxacillin)-1 Cefixime-1 (nj.Piperacillin; Tazobactam & Levofloxacin & lomefloxacin) -1 (Ampicillin;Cloxacillin)-1	4	9
	Fluroquinolones : Ciprofloxacin-1 Ofloxacin-1 Moxifloxacin-1	3	
	cotrimoxazole	1	
	INH	1	
NSAIDs	Nimesulide	1	1
Anticancer drugs	Capicitabine	1	1

Morbidity and mortality: 22 patients (22/24, 92%) recovered with medical intervention but 2 patients 2/24, 8%) died. Patients who have not recovered are male, aged more than 50yrs and alcoholics associated with cardiovascular diseases.

Causality assessment: All cases were well documented. Causality assessment was done with UMC-WHO causality assessment scale. Causality assessment was certain in 2 cases and probable in 22 cases.

IV. Discussion

In this study we observed male predominance, 15 males (15/24, 62%) and 9 females (9/24, 38%) were reported with SJS. One interesting feature is gender distribution is not uniform in all age groups; female patients are more in 20 – 55 years age group where as male patients are more in pediatric and elderly age group. Similar gender distribution was described in the study done by Ratan J. Lihite et.al, in northeast India.[9]

Maximum cases, 58% (14/24) reported from young and middle age group (20 to 55yrs), 25% (6/24) of cases are from less than 20years age group where as 17% (4/24) of cases reported from elderly age group of more than 56years. Maximum mortality was observed in elderly people; 2 out of 4 cases reported with fatal outcome in this age group. Reason may be age, severity of the reaction and already existing medical conditions. Similar results were published in the study done by Sanmarken AD et,al.[10]

In winter season maximum number of cases (54%) were reported. 29% cases were reported in summer and 17% cases were reported in rainy season. Interestingly suspected drugs were antibiotics in 6 cases out of 13 SJS cases reported during winter. In our study antibiotics are the suspected drugs for 9 SJS cases. Among these 9 cases 6 cases were reported during winter. With this in mind, please note the following observation, number of SJS cases during winter is comparatively higher than other seasons which happen to coincide with higher usage of antibiotics during winter season and antibiotics being a suspect for ADRs confirms that higher antibiotic usage caused higher number of SJS cases. Many studies stated that usage of betalactam antibiotics and macrolids were more during winter months. [11]

In our study all patients gave history of drug intake prior to SJS. Antiepileptic drugs are responsible for 54% of SJS cases, antibiotics are responsible for 38% of SJS cases, NSAIDs and anticancer drugs, each are responsible for 4% of SJS cases. Similar results were found in the study done by Kim HI et.al. [12]

Causality assessment was certain in 2 cases and in remaining 22 it was probable. Fixed dose combinations, polypharmacy and improper medication history are some of the obstacles in causality assessment.

V. Conclusion

SJS and TEN are serious adverse drug reactions and high mortality associated with TEN. Antiepileptics and antibiotics are some of the commonly offending drugs for SJS and TEN. Personalized treatment in epileptics may reduce SJS in these patients. Avoiding antibiotic misuse and improving general health of the people by other nonpharmacological approach may reduce the SJS incidence.

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