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A Retrospective Study of Drugs Suspected for SJS/TEN Reactions in a Tertiary Care Center of North India

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Abstract
Steven Johnson syndrome and Toxic epidermal necrolysis are types of severe adverse cutaneous reactions. Though they are rare, they are potentially fatal reactions endangering a patient's life. This retrospective study was done to detect the probable drugs implicated in SJS-TEN is our hospital and their clinical outcome. SJS-TEN is seen to occur among most commonly prescribed drugs. All patients of either sex, with the clinical diagnosis of SJS, SJS-TEN overlap or TEN (according to Bastuji et al criteria), who were admitted in the Dermatology department from April 2010 till August 2017 were included in the study. All relevant data including demographics of patient, symptoms, drug intake, duration of rash, reaction time (time taken for the reaction to appear since the last exposure to the drug), previous history or family history regarding drug allergy, history of complications arising, details of clinical examination at the time of presentation, along with significant systemic findings and clinical outcome were noted in a proforma. Baseline investigations, if done at the time of presentation, were noted down in the proforma. Drug(s) that had been taken within four weeks preceding the onset of symptoms were considered as ''culprit drugs''. If the patient had taken more than one drug, all of them were considered culprit drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) (33.9%) was the most common causative drug group followed by antimicrobials (32.03%), xanthine oxidase inhibitors (13.6%) and antiepileptic drugs (5.83%) in this study. Early identification of the causative drug will help in prompt withdrawal of the drug thus reducing the morbidity and mortality among patients with SJS-TEN. This study aims to create awareness among the treating physicians about the drugs implicated in life threatening reactions to facilitate the judicious use of these drugs in future.
Key words: SJS, TEN, SJS-TEN overlap, drugs.

Introduction

Adverse drug reactions (ADR) account for 6 % if the total hospital admission[1]of which cutaneous adverse drug reactions (CADRs) are the most common type[2]. CADRs have a prevalence of 8.259% and account for 2 – 3% of total hospital admissions[2,3].

CADRs have varied presentations. They may present as mild and self limited reactions like maculopapular or exanthematous eruptions, urticaria, fixed drug eruptions, lichenoid eruptions, drug induced mucositis and sometimes as severe drug eruptions like Steven-Johnson syndrome, toxic epidermal necrolysis (TEN). SJS-

TEN overlap, drug induced exfoliative dermatitis, drug reaction with eosinophilia with systemic symptoms (DRESS) syndrome, Acute generalized exanthematous pustolosis (AGEP) and drug induced urticaria with angioedema which are associated with high mortality and morbidty[4]. The percentage of potentially serious reactions varies and is estimated to be above 2%[2].

SJS and TEN are rare but potentially fatal reactions endangering a patient's life. The incidence of SJS ranges from 1.2 to 6 patients per million per year while for TEN it's between 0.4 to 1.2 patient's per million per year[5].The risk increases when there is co-infection with either mycoplasma pneumonia, herpes simplex virus 1 (HSV-1) or HIV virus, which are independent etiologies of SJS/TEN[6,7]. The mortality for SJS varies from 3 to 10% and for TEN from 20 to 40%[8].

Historically, SJS was first described in 1922 by two American physicians named, Stevens and Johnson. They described and acute mucocutaneous syndrome in two young boys characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis[9]. TEN, also known as Lyell's syndrome was first described by the Scottish dermatologist Alan Lyell in 1956. He reported 4 patients with an eruption resembling scalding of the skin objectively and subjectively, which he referred to as toxic epidermal necrolysis or TEN[10].

SJS/TEN are characterized by high grade fever, wide spread erythematous and/or purpuricmacules with more or less severe epidermal detachment presenting as blisters and areas of denuded skin, and atypical target like lesions, accompanied by mucosal involvement in the form of mucocutaneous tenderness and typically hemorrhagic erosions[9]. The clinical diagnosis of SJS, SJS-TEN overlap and TEN is based on the degree of epidermal detachment. SJS is characterized by epidermal detachment <10% of the body surface area (BSA) plus widespread erythematous or purpuric macules or flat atypical targets with mucosal involvement where 2 or more sites are usually affected; SJS-TEN overlap is characterized by epidermal detachment between 10% and 30%nof BSA plus widespread purpuric macules or flat atypical targets; TEN with spots is characterized by detachment > 10% of the BSA with large epidermal sheets and without any purpuric macule or target.[9] In addition to the severe skin symptoms, they are often accompanied by complications in numerous organs, such as the liver, kidney, and lung.[7]

Although the exact pathogenesis of SJS and TEN remains unclear, apoptotic mechanism, including involvement of cytotoxic T cells, tumor necrosis factor (TNF)-α, and Fas (CD95), Fas ligand (FasL) interaction are considered to be relevant to these diseases.[11]

As reported, the rate of occurrence of SJS & TEN to medications is low.[3, 12] However, drugs are most commonly implicated for SJS, TEN and SJS-TEN overlap and other possible causes include infections, immunizations, environment chemicals and radiation therapy. [3, 12] The major causative drugs are antimicrobials like sulfa drugs, aminopenicillins, quinolones and cephalosporins[7], anti-epileptics like carbamezapine, phenytoin and phenobarbitone and NSAIDs like paracetamol and nimuselide.[13] In Euro SCAR study, the antiretroviral drug, nevirapin, is the leading culprit in HIV- positive patients.[14]

This retrospective study was done to detect the probable drugs implicated in SJS-TEN in our hospital and their clinical outcome. SJS-TEN is seen to occur among most commonly prescribed drugs. Early identification of the drug will help in prompt withdrawal of the drug thus reducing mortality and morbidity among the patients with SJS TEN. This study aims to create awareness among the treating physicians about the drugs implicated in life threatening reactions to facilitate judicious use of these drugs in future.

Aims and Objectives

This retrospective study was done to detect the probable drugs implicated in SJS-TEN in our hospital and the clinical outcome.

Materials and Methods

This retrospective study of data acquired from April 2010 till August 2017, pertaining to patients admitted in Department of Dermatology Christian Medical College and Hospital, with the clinical diagnosis of SJS, SJS-TEN and overlap or TEN, was done at Department of Dermatology, Christian Medical College and Hospital, Ludhiana. Institutional ethics committee permission was taken to carry out this

Inclusion Criteria

All patients of either sex, with the clinical diagnosis of SJS, SJS-TEN overlap or TEN (according to Bastuji *et al* criteria), who were admitted in Dermatology Department of Christian Medical College and Hospital, Ludhiana, from April 2010 till date, were included in the study.

Exclusion Criteria

1) Any patient who had taken loose medications or was not able to recall the name of the medications taken during the last 4 weeks prior to the onset of lesions.
2) Any patient who had taken ayurvedic or homeopathic medications during this period.

CADRs with epidermal detachment were assessed using rule of 9 and were classified (according to Bastuji *et al* criteria) as:

1. SJS- If the epidermal detachment is < 10%.
2. SJS-TEN overlap- If the epidermal detachment is in between 10-30%.
3. TEN- If epidermal detachment is >30%.

All relevant data including demographics of the patient, symptoms, drug intake, duration of rash, reaction time(time taken for the reaction to appear since the last exposure to the suspected drug), previous history or family history regarding drug allergy, any associated comorbidities, history of complications arising, details of clinical examination at time of presentation including morphology of the lesions and mucosal involvement, along with significant systemic findings and clinical outcome were noted in a proforma (ANNEXURE 1). Baseline investigations like complete blood count, serum blood urea levels, serum creatinine levels, serum electrolytes, liver function tests, random blood sugars, microscopic examination of urine and chest X-ray findings, if done at time of present-ation, were also noted down in the proforma.

Drug(s) that had been taken within four weeks preceding the onset of symptoms were considered as ‘’culprit drugs’’. If the patient had taken more than one drug, all of them were considered culprit drugs.

All patients were treated with barrier nursing with regular monitoring of vitals, fluid and electrolyte balance, strict asepsis and nutrition. Prophylactic antibiotics were given. All patients were given short course of systemic steroids which were gradually tapered.

Statistical Analysis

Descriptive Analysis was performed to express the continuous variables in terms of Mean ± Standard deviation and Median (IQR) and the categorical variables were expressed in count (percentage). Kruskal wallis was used to obtained the association of diagnosis with reaction time. The significance level was set at $p<0.05$ All statistical analysis was performed using SPSS, version 21.0. Armonk, NY: IBM corp.

Results

Out of a total of 43 cases, we found 26 cases of SJS, 10 cases of TEN, and 7 cases of SJS-TEN overlap. 25 patients (58.1%) were male and 18 patients (14.9%) were female, with a sex ratio of 1.39:1. The maximum number of patients with a skin rash were seen in the age group of 35-44 years among which 7 patients (58.3%) were males and 5 patients (41.7%) were females. The demographic profile is given is given in Table 1.

As shown in Table 2, a total of 35 drugs were implicated for causing skin lesions in our study population.

As shown in Table 3, majority of patients consumed more than one drug (35 cases), whereas in 8 cases, a single drug was implicated. Maximum number of drugs consumed was 5.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (33.9%) and antimicrobials (32.03%) were the

most prevalent drug groups causing skin lesions followed by xanthine oxidase inhibitors (13.6%), and antiepileptic drugs (5.83%). (Table 4)

Paracetamol (24 of 43 cases), allopurinol (12 of 43 cases), ofloxacin (6 of 43 cases), norfloxacin (5 of 43 cases) and diclofenac (5 of 43 cases) were found to be the most commonly associated drugs. Phenytoin and allopurinol (3 each out of 8 cases) were the most common drug among the single drug culprit cases. Xanthine oxidase inhibitors and antiepileptics were associated with serious form of adverse reaction (TEN: 40% each; 4 patients out of 10) than other drugs.

Systemic comorbidities were present in 26 patients, some of them had more than one comorbidity, as shown in Table 5.

Time duration between drug intake and onset of symptoms ($p = 0.006$) was 2 days (1-36 days) in SJS, 28 days (1-64 days) in TEN, and 2 days (1-85 days) in SJS-TEN overlap.

Various complications noted in cases of SJS, TEN, and SJS-TEN overlap were altered liver function tests, electrolyte imbalance, leucocytosis, leucopoenia, thrombocytopenia, hyperglycemia, secondary infection, mucocutaneous adhesions, corneal ulceration, urinary retention, renal failure, intestinal perforation, septicemia. Renal involvement was the most common complication (16.2%) noted.

Mortality rate was 13.95% among all cases; 3.85% in SJS, 28.57% in SJS-TEN overlap and 30% in TEN.

Table 1: Demographic profile

Age (years) Mean±S.D	47±14.61
Gender n (%)	
Male	25 (58.1)
Female	18 (14.9)
Skin rash	
Yes	43 (100.0)
No	0 (0)
Pruritus	
Yes	41 (95.3)
No	2 (4.7)
Duration of rash	5±3.28
Duration of pruritus	5±3.71
Reaction time (days) Median (IQR)	2(2-15)

Table 2: Drugs implicated for causing skin lesions

ANTIMICROBIALS	
CEPHALOSPORINS	Cephalexin Cefuroxime Cefixime Ceftazidime
FLUOROQUINOLONES	Ofloxacin Norfloxacin Ciprofloxacin Levofloxacin
PENICILLINS	Amoxicillin
TETRACYCLINES	Azithromycin
MACROLIDES	
COTRIMOXAZOLE	Tinidazole
ANTIPARASITIC	Ornidazole
NONSTEROIDAL ANTIINFLAMMATORY DRUGS	
Paracetamol Diclofenac Aceclofenac Nimesulide	Ibuprofen Chlorzoxazone Tramadol
ANTIEPILEPTICS	
Phenytoin Cabamazepine Clobazam	Levaricetam Oxycarbamazepine
ANTIDIABETICS	
Glimepride Metformin	Glynase
ANTITUBERCULAR DRUGS	
Rifampicin Ethambutol	Pyrazinamide
XANTHINE OXIDASE INHIBITORS	
Allopurinol	

Table 3: Number of drugs given to the patients

No. of Drugs	Frequency	Percentage
1	8	18.6
2	17	39.5
3	12	27.9
4	5	11.6
5	1	2.3

Table 4: Prevalence of various drugs causing rash

Drugs	Frequency	Percentage
Anti-microbials	33	32.03%
Non-steroidal anti-inflammatory	35	33.9%
Anti-epileptics	6	5.83%
Anti-diabetics	3	2.91%
Anti-tubercular	5	4.85%
Xanthine oxidase inhibitors	14	13.6%
Miscellaneous	7	6.79%

Table 5: Prevalence of systemic comorbidities

Comorbidity	Frequency	Prevalence
Diabetes	17	39.5%
Hypertension	9	20.9%
Thyroid disease	2	4.7%
Tuberculosis	1	2.3%
Malignancy	1	2.3%
Others	18	41.86%

Discussion

Cutaneous drug eruptions are one of the most frequent manifestations of adverse drug reactions.[2] Adverse cutaneous drug reactions are found to affect 2-3% of hospitalized patients.[3]

The rate of occurrence of SJS and TEN to medications is low. However, drugs are most commonly implicated for SJS, TEN and SJS-TEN overlap and other possible causes include infections, immunization, environment chemicals and radiation therapy. The major causative drugs are antimicrobials like sulfa drugs, aminopenicillins, quinolones and cephalosporins[7], antiepileptics like carbamazepine, phenytoin and phenobarbitone and NSAIDs like paracetamol and nimesulide[13].

A total of 43 patients with drug rash within the SJS-TEN spectrum were included in this study. Our study had a male preponderance (58.1% male and 14.9% female), unlike female preponderance in earlier studies.[2,15,16] Maximum number of patients were in the age group of 35-54 years similar to a study by Roujeau *et* al[17]where most of the patients were in the 5th decade.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (33.9%) was the most common causative drug group followed by antimicrobials (32.03%), xanthine oxidase inhibitors (13.6%) and antiepileptic drugs (5.83%). This is in contrast with previous reports where antimicrobials were the most common causative agents.[2, 15]Although, in a French survey, NSAIDS were found to be the culprit drugs.[17]Among NSAIDs, paracetamol (24 out of 43 cases, 55.81%) was found to be the most common culprit. Among antimicrobials group, the most common implicated drug group was of fluoroquinoles (12 cases out of 20, 60%) which was in concordance to a study conducted in Karnataka.[18] However, in a study by Yamane *et al*[19] in Japan, the most common antibiotic was cephalosporin. Beta lactams were the most common antibiotics causing SJS-TEN in a study by Wong *et al*.[20] Nevirapine and cotrimoxazole were the most common antimicrobials associated in another study.[2] Sulphonamides (50.6%) and nevirapine (23.6%) were the most commonly implicated drugs from Togo.[21]In our study population, no patient had history of taking nevirapine.

Paracetaomol (24 of 43 cases) and allopurinol (12 of 43 cases) were the most commonly associated individual drugs in our study, as compared to phenytoin and carbamazepine which were reported to be more common in previous studies.[2, 16] Higher reporting of paracetamol may be because it is widely prescribed and available over-the-counter. Many other less prescribed drugs have more ADR than paracetamol. Paracetamol is confounded by its use to treat nonspecific symptoms such as fever or pain, the early signs of the adverse reaction or infection both.[22]However, pararacetamol is found to be a potential risk factor in children when data from pediatric patients from the SCAR and Euro SCAR studies are pooled.[23] Various studies had mentioned paracetamol as a suspected causative agent.[2,16,24] Among NSAIDs, paracetamol was the most common to cause the reaction in our study and as described in other Indian study.[2] This may be due to different genomic factors or drug utility pattern influencing both the populations. We did not find any oxicam derivative as culprit which is mentioned as the most commonly responsible among NSAIDs in an American study.[25]

Xanthine oxidase inhibitors and antiepileptic drugs were the most common drug groups causing TEN in our study. They had the higher chance (40%) of causing this severe drug eruption than other drugs. This is lower as compared with the previous report (70%).[2]

In our study, all were treated with systemic steroids, and mortality rate was found similar to previous study in which patients were treated with

steroids.[2] Though the role of steroids is controversial in treatment of SJS and TEN, beneficial effect may be there if steroids are started early in treatment with proper dose.[26]

Complications were seen more frequently in TEN group (63.4%), the most common being secondary infection (28.1%). One patient died in SJS group, whereas in SJS-TEN overlap the mortality rate was 28.57%. Mortality rate in TEN group was 30%, which is similar to an earlier study (26%).[2]

In conclusion, SJS, TEN, and SJS-TEN overlap are serious cutaneous adverse reactions most commonly caused by antimicrobials, xanthine oxidase inhibitors, NSAIDs, and antiepileptic drugs. It is highly important thatphysicians are able to recognize these drugs as causative agents for SJS-TEN type of reactions and on doing so withdraw the culprit drugpromptly for a better outcome.

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