Original Article

Drug-induced Stevens–Johnson Syndrome in Indian Population: A Multicentric Retrospective Analysis

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Abstract

Background: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening hypersensitivity reactions mainly caused by drugs. Data on incubation period, hospital stay, and outcome for HIV-positive patients are sparse. Role of corticosteroids in their management is still controversial. **Methods:** Indoor cases of SJS, SJS–TEN overlap, and TEN were analyzed for causative drugs, incubation period, a severity-of-illness score for toxic epidermal necrolysis (SCORTEN) score, HIV status, treatment, and outcome. Comparison of parameters between HIV and non-HIV cases was done. Utilization pattern of corticosteroids and their role in outcome were evaluated. **Results:** Four SJS, 15 SJS-TEN overlap, and 21 TEN cases were evaluated. Antimicrobials (27.1%), antiviral (23%), antiseizure drugs (8.4%), and analgesics (8.4%) were commonly associated drugs. Among 12 (30%) HIV-reactive cases, nevirapine (97.6%) and cotrimoxazole (41.6%) were common causative drugs. Males (75%) were affected more than females (25%) among HIV-positive individuals. Incubation period was significantly higher in HIV-reactive patients. Total 30 (75%) patients were treated with corticosteroids. Dexamethasone (90%) and prednisolone (26.6%) were most commonly used. No significant difference was found among cases treated with or without corticosteroids. **Conclusions:** Antimicrobial drugs are common to cause SJS/TEN. Among HIV-reactive patients, male have more risk, incubation period is more and severity of reaction is less. Effectiveness of corticosteroids for treatment of SJS/TEN is inconclusive.

Keywords: *Causative drugs, corticosteroids, HIV, Stevens–Johnson syndrome, toxic epidermal necrolysis*

Date of Acceptance:
09-Mar-2017

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening mucocutaneous immune complex-mediated hypersensitivity reactions. The incidence of SJS and TEN is estimated 1–6 and 0.4–1.2 cases per million person-years, respectively.[1] Clinically, the disease is characterized by polymorphic lesions such as erythematous macules, papules, plaque, vesicles, and bullae affecting distal extremities with positive Nikolsky's sign. Mucosal surface is involved in the form of erosion or ulceration.[2] According to the involvement of body surface area (BSA), the disease can be classified into SJS (<10% BSA), SJS–TEN overlap (10%–30% BSA) and TEN (>30% BSA).[3]

Drugs are found to be one of the important causes. More than 100 drugs have been implicated in causing SJS and TEN.[1] Other causes of SJS and TEN are infection, malignancy, and radiation therapy.[4] In India, human immunodeficiency virus (HIV) infection is the most common co-morbid condition associated with SJS/TEN.[5] The incidence of SJS and/or TEN in HIV-reactive patients is estimated approximately 1–2 per 1000 individuals.[6] Nevirapine is found to be the most common causative agent among HIV-reactive patients.[4,7]

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Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_122_16

How to cite this article: Hirapara HN, Patel TK, Barvaliya MJ, Tripathi C. Drug-induced Stevens–Johnson syndrome in Indian population: A multicentric retrospective analysis. Niger J Clin Pract 2017;20:978-83.

However, data on incubation period, hospital stay, outcome, and cost of management for HIV-reactive patients are sparse.

Immediate cessation of an offending drug and adequate supportive care in intensive care unit remain the mainstay of management of SJS/TEN. There is no specific treatment strategy available for this condition. Systemic corticosteroids, intravenous immunoglobulin therapy (IVIG), and other immunosuppressive therapy are used for its management.[8] According to the previous report, combination of IVIG and corticosteroids shows tendency to decreases mortality rate as compared to corticosteroids alone.[9] Another study suggests that early stage short-term dexamethasone pulse therapy (DPT) contributes to decrease in mortality rate without increasing healing time.[8] The role of corticosteroid therapy in SJS/TEN is controversial.[10,11] The present retrospective study was designed to analyze causative drugs, impact of HIV infection, and effectiveness of steroid treatment in drug-induced SJS, SJS–TEN overlap and TEN.

Materials and Methods

The present multicentric retrospective study was conducted after approval from institutional review board (IRB), Government Medical College, Bhavnagar (Gujarat). IRB approval no. 287/2012, pharmacology 31/2012 (research work) dated: December 11, 2012. Permissions from institution's heads and/or human ethics committees (HEC) for data collection were also taken from the respective institutes. Consent waiver was granted by institutional review board, Government Medical College, Bhavnagar. We scrutinized the indoor case records of admitted patients between July 2009 and December 2012 in six tertiary care teaching hospitals from Gujarat, India–Sir Takhatsinhji General Hospital, Bhavnagar; Pandit Deendayal Upadhyay Civil Hospital, Rajkot; Sir Sayaji General Hospital, Vadodara; GMERS Medical College and Hospital, Gotri, Vadodara; New Civil Hospital, Surat and Guru Gobindsingh General Hospital, Jamnagar. SJS/TEN cases were included based on the confirm diagnosis as written on the clinical case papers. We included cases of drug-induced SJS, SJS–TEN overlap, and TEN from all age groups and excluded the cases of doubtful diagnosis and insufficient information.

Data were collected in a case record form for demographics, causative drugs, time period between drug intake and onset of skin lesion (incubation period), mucosal involvement, daily % of BSA involvement, laboratory investigations, HIV status, duration of hospital stay, treatment given, healing days, complications, and clinical outcome. In cases treated with corticosteroid, data were collected for their name, dose, route and frequency of administration, total duration of treatment, and starting day in relation to lesion. SCORTEN score data were calculated for day 1 of admission.[12] The causality assessment for drug–adverse drug reaction (ADR) pair was performed as per Naranjo's algorithm.[13] The economic burden of drugs and laboratory investigations were calculated as per Indian Drug Review 2015 and Pathologist Association of Bhavnagar, Gujarat, India.

Data were analyzed for demographic variables, average incubation period, average hospital stay, proportion of causative drugs, average cost of management, proportion of complications, and mortality rate. Data were expressed as proportion and mean [95% confidence interval (CI)]. To assess the impact of HIV infection on SJS/TEN, different variables between HIV and non-HIV cases were compared by chi-square test and unpaired *t* test/Mann–Whitney test for categorical, and continuous variables, respectively. Comparison of variables between cases treated with and without corticosteroids was done by chi-square test and Mann–Whitney test for categorical and continuous variables, respectively. $P < 0.05$ was considered statistically significant. All statistical analysis was done on GraphPad Instat 3.0 demo version.

Results

Out of 52 scrutinized cases, 40 cases were included in analysis. The reasons for excluded cases were doubt about diagnosis or insufficient information. Twenty-five (62.5%) patients were male and 15 (37.5%) patients were female, with the age range of 6–78 years. The mean age of the patients was 38.4 years (95% CI 32.2–44.4). Among 40 included cases, 4 (10%), 15 (37.5%), and 21 (52.5%) cases were of SJS, SJS–TEN overlap, and TEN, respectively. Average incubation period was 6.5 days (95% CI 4.4–8.6) and hospital stay was 12.7 days (95% CI 9.7-15.6) [Table 1].

Total 48 drugs were found as suspected causative agents. Antimicrobials (27.1%) were the most commonly associated group of drugs followed by antiviral (23%), antiseizure drugs (8.4%), and analgesics (8.4%). Nevirapine (23%), cotrimoxazole (10.4%), paracetamol (8.3%), carbamazepine (4.2%), amoxicillin (4.2%), amoxicillin+clavulinic acid (4.2%), and chloroquine (4.2%) were found commonly associated drugs [Table 2]. Single drug was suspected in 31 (77.5 %) cases and common causative drugs in these subgroups were unknown antipyretic 16 (40%), nevirapine seven (17.5%), chloroquine two (5%), and carbamazepine two (5%). As per Naranjo's algorithm for the causality assessment, in 26 cases drugs were "probable" cause of eruption, whereas "possible" cause of eruptions in 14 cases. Mortality was seen in two (5%) cases of TEN. Average cost of managing these ADRs was Rs. 3316.6 (95% CI 2711.1-3922.2).

Table 1: Comparison of demographic data, incubation period, SCORTEN score, hospital stay, and cost of management among cases of SJS, SJS–TEN overlap, and TEN

Variables	SJS	SJS–TEN Overlap	TEN	All cases	P
Age (years), mean (95% CI)	38 (16.8–59.1)	41.1 (31.6–50.4)	36.4 (26.6–46.3)	38.35 (32.2–44.4)	0.60
Male, n (%)	4	9	12	25 (62.5)	0.26
Female, n (%)	0	6	9	15 (37.5)	
Incubation period (days), mean (95% CI)	4.2 (-1.9–10.4)	8.3 (3.6–12.8)	5.7 (3.3–8.1)	6.5 (4.4–8.6)	0.74
Average SCOREN score on day 1, mean (95% CI)	0.75 (-0.04–1.5)	1.8 (1.4–2.8)*	1.9 (1.6–2.3)*	1.8 (1.5–2.0)	0.01
Hospital stay (days), mean (95% CI)	6 (1.7–10.3)	11.1 (7.3–14.8)	14.9 (10.3–19.5)*	12.7 (9.7–15.6)	0.02
Cost of management (INR), mean (95% CI)	2234.9 (-244.9–4714.8)	3254.4 (2109.7–4399.1)	3567.1 (2736.5–4397.8)	3316.6 (2711.1–3922.2)	0.19
Cost of management (US Dollar), mean (95% CI)	34.86 (-3.82–73.54)	50.76 (32.91–68.62)	55.64 (42.68–68.60)	51.73 (42.29–61.68)	
Mortality, n (%)	(0) 0%	(0) 0%	(2) 9.5%	(2) 5%	0.38

* $P < 0.05$ as compared to SJS by Dunn's multiple comparison test. 1 US Dollar = 64.11 INR

Number of patients in SJS, SJS–TEN overlap, and TEN groups are 4, 15, and 21, respectively. SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis, 95% CI = 95% confidence interval.

Table 2: Causative individual drugs and drug groups for SJS, TEN, and SJS–TEN overlap

Drugs	SJS	SJS–TEN overlap	TEN	All cases
Antimicrobials, n (%)	01 (2.1)	02 (4.2)	10 (20.8)	13 (27.1)
Co-trimoxazole	00	01	04	05
Amoxicillin + clavulinic acid	00	01	01	02
Amoxicillin	00	00	02	02
Chloroquine	01	00	01	02
Cefpodoxime	00	00	01	01
Linezolid	00	00	01	01
Antiviral, n (%)	00 (00)	08 (16.7)	03 (6.3)	11 (23)
Nevirapine	00	08	03	11
Anti epileptics, n (%)	00 (00)	02 (4.2)	02 (4.2)	04 (8.4)
Carbamazepine	00	01	01	02
Lamotrigine	00	00	01	01
Phenytoin	00	01	00	01
Analgesics, n (%)	00 (00)	01 (2.1)	03 (6.3)	04 (8.4)
Paracetamol	00	01	03	04
Unknown antipyretics, n (%)	03 (6.2)	04 (8.3)	09 (18.7)	16 (33.2)
Total drugs	04 (8.3)	17 (35.4)	27 (56.3)	48 (100)

Number of patients in SJS, SJS–TEN overlap, and TEN groups are 4, 15, and 21, respectively. SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis.

We evaluated and compared the variables between HIV and non-HIV cases. Out of 40, 12 (30%) patients were HIV reactive. Nevirapine (97.6%) and cotrimoxazole (41.6%) were found to be common causative drugs. Comparison of variables between HIV and non-HIV-reactive patients is shown in Table 3. As compared to non-HIV-reactive patients, occurrence of SJS (0 vs. 14.3%) and TEN (33.7% vs. 60.7%) were significantly less among HIV-reactive patients. Incubation period was significantly higher among HIV-reactive patients as compared to non-HIV-reactive patients [11.8 days (95% CI 6.6–16.9) vs. 4.3 days (95% CI 2.6-5.8); $P < 0.05$, Table 3].

Total 30 (75%) patients were treated with corticosteroids. The mean delay between occurrence of first blister and first dose of corticosteroid was 5.63 days (95% CI 3.4-7.8). As shown in Table 4, there was significant difference in mean age of patients treated with and without corticosteroids [34.8 years (95% CI 27.4–42.1) vs. 49 years (95% CI 40.3–57.6); $P < 0.05$]. The most commonly

Table 3: Comparison of variables between HIV reactive and HIV nonreactive cases

	HIV reactive	HIV non-reactive	P
Age (years), mean (95% CI)	38.2 (29.3–46.9)	38.4 (30.2–46.6)	0.95
Incubation period (days), mean (95% CI)	11.8 (6.7–16.9)	4.3 (2.6–5.8)	0.001
Severity of cases, mean (95% CI)			
TEN	4 (33.3 %)	17 (60.7 %)	0.03
SJS–TEN overlap	8 (66.7 %)	7 (25 %)	
SJS	0 (0 %)	4 (14.3 %)	
Hospital stay (days), mean (95% CI)	9.5 (7.3–11.6)	14.2 (9.9–18.4)	0.29
Cost of management (INR), mean (95% CI)	2999.7 (2091.8–3907.5)	3452.5 (2650.2–4254.8)	0.49
Cost of management (US Dollar), mean (95% CI)	46.79 (32.63–60.95)	53.85 (41.34–66.37)	
Expired cases, n (%)	0 (0 %)	2 (7.14 %)	0.8

Numbers of patients in HIV reactive and nonreactive groups are 12 and 28, respectively. P value for chi-square or unpaired ``t''/Mann–Whitney U test. SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis, HIV = human immunodeficiency virus. 1 US Dollar = 64.11 INR; 95% CI: 95% confidence interval.

Table 4: Comparison of variables between corticosteroids given and not given cases

	Corticosteroids given (n = 30)	Corticosteroids not Given (n = 10)	P
Age (years), mean (95% CI)	34.8 (27.4–42.2)	49 (40.4–57.6)	0.039
Male, n (%)	17 (56.7 %)	8 (80 %)	
Female, n (%)	13 (43.3 %)	2 (20 %)	0.34
Incubation period (days), mean (95% CI)	6.4 (3.8–8.9)	6.9 (2.5–11.3)	0.78
TEN, n (%)	18 (60 %)	3 (30 %)	
SJS–TEN overlap, n (%)	10 (33.3 %)	5 (50 %)	0.20
SJS, n (%)	2 (6.7 %)	2 (20 %)	
Hospital stay (days), mean (95% CI)	13.4 (9.7–16.9)	10.9 (4.8–16.9)	0.29
Cost of management (INR), mean (95% CI)	3395.1 (2695.3–4094.8)	3081.9 (1628.2–4534.6)	0.49
Cost of management (US Dollar), mean (95% CI)	52.96 (42.04–63.87)	48.07 (25.4–70.73)	
SCORTEN score average, mean (95% CI)	1.8 (1.5–2.1)	1.8 (1.3–2.3)	0.98
Mortality, n (%)	2 (6.67%)	0	0.40

Numbers of patients in corticosteroids given and not given patients are 10 and 30, respectively. P value for chi-square or Mann–Whitney U test. SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis. 1 US Dollar = 64.11 INR

used corticosteroid was parenteral dexamethasone (90%) followed by prednisolone (26.6%), hydrocortisone (10%), and betamethasone (10%). Corticosteroids were started with delay of 4 days (95% CI -8.7–16.7) in SJS cases, 4.4 days (95% CI 3.3–5.4) in SJS–TEN overlap cases and 7.1 days (95% CI 3.3–10.8) in TEN cases. Corticosteroids were given for 5 days (95% CI 5–5) in SJS, 4.7 days (95% CI 3.2–6.2) SJS–TEN overlap, and 6.9 days (95% CI 4.6–9.3) in TEN cases. Average first day dose of dexamethasone was 5.6 mg (95% CI 4.9–6.3; n = 25), hydrocortisone 200 mg (95% CI 200–200; n = 3), and prednisolone 17.5 mg (95% CI -141.3–176.3; n = 2). Comparison of variables between cases treated with and without corticosteroids is shown in Table 4.

Discussion

The present study evaluated cases of drug-induced SJS/TEN from six tertiary care teaching hospitals of State of Gujarat, India. Mean age of our study population was in fourth decade, which is in accordance with the previous studies.[14-18] We observed male preponderance for development of SJS/TEN. Both male[4,14,19] and female[16,20] preponderance had been reported in the literature. In line with the previous report,[21] mean incubation period was 6.5 days in our study. In accordance with previous studies,[4,22] hospital stay was higher in TEN than SJS patients in this study. As in previous Indian study,[4] the average cost of management of TEN was higher than SJS. The cost of management

included the cost of drugs and laboratory investigations; direct costs for the hospital stay, additional procedures, professional and nursing charges, and indirect costs were not considered. With these excluded factors, actual economic impact seems greater than what is estimated by this study. In our cases, overall mortality was 5%, whereas mortality in TEN cases was 9.5%. This is in accordance with previous studies.[15,23] A recent systematic review on SJS/TEN reported fatality rate of 12.95% overall and 28.20% for TEN cases in India.[5] Both expired cases had SCORTEN score of 3. No mortality was observed for SCORTEN 0-1 and 2. This suggests its importance for predicting mortality.

In the present study, most commonly incriminated drug groups were antimicrobials, antiseizure drugs, and analgesics which is in line with other Indian studies.[4,5,21] Similarly, other Asian studies[15,16] also reported antimicrobials as most common incriminated drug group. Antiseizure drugs are also commonly reported in various Asian studies.[14,19,20,24,25] Studies from France[17] and Serbia[26] showed NSAIDs as most common causative group. Nevirapine (23%) and cotrimoxazole (10.4%) are most commonly associated drugs as seen in previous study.[4] Carbamazepine[14,22,24,25] and phenytoin[20,21] were most common causative drugs in other studies. Although cephalosporins and allopurinol were reported as most common agents by Yamane *et al.*[15]and Sharma *et al.*[16], respectively. Among 16 (33.2%) cases, unknown antipyretic drugs were responsible for causing the eruption. Nine out of these 16 cases were having severe eruption (TEN). This highlights the risk of over the counter medicines for such rare and serious ADR. In 77.5 % cases in our study, single drug was found responsible as higher to 60% seen in previous study.[20]

Total 30% cases in our study were HIV reactive. The proportion of HIV-reactive patients is in accordance with previous report from India.[4] Whereas it is 7.3% in European study[27] and 76% in South African study.[18] Thus, chances of developing SJS/TEN are higher among HIV-reactive patients. Male preponderance was noted among HIV-reactive patients. Total 75% HIV reactive patients who developed the reaction were male in our study. Drugs and/or their metabolites act as haptens and bind with keratinocytes. Keratinocytes–drug complex induces immune reaction. This leads to cytotoxic T cell-mediated apoptosis of keratinocytes in susceptible individuals.[28] In HIV infection, immune status of individual gets compromised. This could be the reason for long incubation period and less severe cases among HIV-reactive as compared to non-HIV cases. Nevirapine was culprit in 11 cases, whereas cotrimoxazole was responsible in five out of 12 HIV cases. Out of four HIV-reactive patients who developed TEN, three patients were taking simultaneous cotrimoxazole along with nevirapine. Chances of severe reaction are increased when cotrimoxazole is given along with nevirapine.[27]

This study shows inconclusive results for corticosteroid treatment as compared to supportive therapy. Previous studies[26,29] showed corticosteroids have no significant effect on mortality as compared to supportive therapy. One systemic review suggested no trend toward benefit from corticosteroid therapy and supportive therapy should be priority in management.[30] Corticosteroids were administered with an average delay of 5.63 days that may also be responsible for inconclusive effect. Previous studies [24,31-33] suggests that corticosteroids started early in the disease reduces morbidity and improves outcome. There was a trend for the longer hospital stay in corticosteroid group. Singh *et al.*[33] found that corticosteroids prolongs hospital stay and increases mortality in SJS/TEN. Two patients were expired of corticosteroid group were having TEN and had SCORTEN score 3. This mortality could be due to the severity of reaction. We are not able to make any conclusion on the effectiveness of corticosteroids for reduction in mortality due to the small sample size.

There are several limitations of this study. Because of retrospective nature, we could not analyze incidence of SJS/TEN and risk ratio for the incriminated drugs. We were unable to correlate between CD4 cell count and severity of SJS/TEN among HIV-reactive patients. The data on duration of healing of lesions after starting corticosteroid therapy were not available after the discharge of the patients.

In conclusion, antimicrobial drugs are common to cause SJS/TEN. Among HIV reactive, males have more risk for developing reaction. Incubation period is longer and severity of cases is less in HIV reactive patient as compared to non-HIV reactive patient. Effectiveness of corticosteroid for treatment of SJS/TEN is inconclusive. Proper monitoring and record keeping is required to monitor the effectiveness of steroid therapy.

Acknowledgement

We are thankful to Head of the institutions and/or Institutional Review Boards (IRBs) of Sir Takhatsinhji General Hospital, Bhavnagar; Pandit Deendayal Upadhyay Civil Hospital, Rajkot; Sir Sayaji General Hospital, Vadodara; GMERS Medical College and Hospital, Gotri, Vadodara; New Civil Hospital, Surat and Guru Gobind Singh General Hospital, Jamnagar for allowing us to collect data from Medical Record Sections of the respective hospitals.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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