Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS-TEN overlap: A retrospective study of causative drugs and clinical outcome

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ABSTRACT

Background and aims: Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS-TEN overlap are serious adverse cutaneous drug reactions. Drugs are often implicated in these reactions. Methods: A retrospective analysis of inpatients' data with these dermatological diagnoses were carried out for three years, to study the causative drugs, clinical outcome, and mortality in these conditions. Results: Thirty patients (15 TEN, nine SJS-TEN overlap, and six SJS) were admitted. In 21 cases, multiple drugs were implicated whereas single drugs were responsible in nine. Anticonvulsants (35.08%) were the most commonly implicated drugs followed by antibiotics (33.33%) and NSAIDS (24.56%). Twenty-five patients recovered whereas five died (four TEN, one SJS-TEN overlap). Conclusion: Anticonvulsants, antibiotics and NSAIDs were the most frequently implicated drugs. TEN causes higher mortality than both SJS and SJS-TEN overlap.

Key Words: Anticonvulsants; SJS-TEN overlap; Stevens Johnson syndrome; toxic epidermal necrolysis.

INTRODUCTION

Cutaneous drug eruptions are one of the most frequent manifestations of adverse drug reactions.[1] Adverse cutaneous drug reactions are found to affect 2–3% of hospitalized patients.[2] The reported percentage of "potentially serious" adverse drug reactions varies greatly and is estimated to be above 2%.[2] Some of the serious reactions include Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and the overlap category of SJS and TEN. SJS is a serious mucocutaneous illness with systemic symptoms characterized by the presence of flat, atypical target lesions and the epidermal detachment is < 10% of the total body surface area (BSA). Two or more mucosal sites are usually affected.[3] TEN is a life-threatening serious illness characterized by high fever and confluent erythema followed by necrolysis.[3] The epidermal detachment is > 30% of the total BSA. Flat, atypical target lesions may also be seen (TEN with spots) and sometimes, extensive necrolysis can occur without target lesions (TEN without spots).[3] In the SJS-TEN overlap category, the epidermal detachment is 10–30% of the total BSA.[3] Drugs are implicated in most of these serious adverse drug reactions.[2] These reactions are often associated with significant mortality.[3]

In this retrospective study, we present data on the causative drugs, clinical outcome and mortality of our patients with SJS, TEN or the SJS-TEN overlap category.

METHODS

Analysis was performed of the inpatient records of all patients hospitalized between July 2003 and September 2006 with the diagnosis of SJS, TEN or the SJS-TEN overlap category. The following details were recorded: the duration of the rash, drug intake, the time period between the drug

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intake and the appearance of the rash, systemic symptoms, the types of target lesions, extent of epidermal necrosis or detachment, mucosal involvement, and systemic evaluations. The diagnosis of SJS, TEN and the SJS-TEN overlap were made as per the criteria laid down by Bastuji *et al*.[3] Drug(s) that have 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 as culprit drugs.

All the patients were given barrier nursing care including regular monitoring of vitals, fluid and electrolyte balance, strict asepsis, and nutrition. Prophylactic antibiotics were administered to address infections due to gram negative and/or gram positive organisms. All except one patient were given short (2-14 days) courses of tapering doses of systemic steroids—inj. dexamethasone dose ranging from 4-8 mg or an equivalent corticosteroid.

RESULTS

A total of 30 patients were admitted during the study period, of which 17 were females and 13 were males in the age range of 4–65 years (mean age = 22.3 ± 15.4 years). The duration of cutaneous eruption was 1–40 days (mean duration = 7.04 ± 7.89 days). The mean period between the intake of the drug and the onset of eruption was 24.4 ± 37.0 days. Twenty-six patients had prodromal symptoms in the form of fever, cough, sore throat and headache. Nine patients had underlying seizure disorder while two patients had intracranial pathologies. Two cases had systemic lupus erythematosus. Six patients were classified as SJS, nine as SJS-TEN overlap and 15 as TEN. The duration of hospital stay was 1–41 days (mean = 20.2 ± 15.1 days).

Multiple drugs were implicated in 21 cases while single drug was responsible for the reactions in the remaining nine patients. Fifty-seven drugs have been implicated in the observed adverse events, out of which anticonvulsants were the most common category (35.08%), followed by antibiotics (33.33%) and nonsteroidal antiinflammatory drugs (24.56%). Among the anticonvulsants, phenytoin (45%) and carbamazepine (30%) were the more common drugs. Cephalosporins (26%) were the most common group of antibiotics that caused the adverse reaction. Among the nine patients who reacted to a single drug as the culprit, anticonvulsants (phenytoin in four and carbamazepine in three) were implicated in seven cases. The detailed list of drugs causing adverse reactions is shown in Table 1.

Systemic complications were observed more frequently among the TEN group [Table 2]. Twenty-five patients recovered completely while five patients died (four with TEN, one with SJS-TEN).

Table 1: Drugs eruptions and their causative agents

Drugs	SJS	TEN	SJS-TEN	Total no. of drugs
Antiepileptics				
Phenytoin	1	7	1	9
Carbamazepine	1	3	2	6
Sodium valproate	0	2	0	2
Phenobarbitone	0	1	1	2
Others	1	1	0	1
Antibiotics				
Cephalosporins	4	0	1	5
ATT	0	3	0	3
Ampicillin-cloxacillin	0	2	1	3
Sulfonamides	0	2	0	2
Macrolides	0	0	1	1
Fluroquinolones	0	1	0	1
Others	0	2	2	4
NSAIDS				
Paracetamol	2	1	3	6
Nimesulide	1	2	1	4
Diclofenac	1	0	1	2
Ibuprofen	0	0	1	1
Others	0	0	1	1
Other drugs				
Multivitamins	1	0	1	2
Diuretics	1	0	0	1
Ranitidine	0	1	0	1

Table 2: Complications in our patients

Complications	No. of patients
Hematological	
Anemia	11
Leucopenia	6
Leucocytosis	9
Hepatic	
Transaminitis	11
Hyperbilirubinemia	5
Encephalopathy	1
Ocular	
Symblepharon	2
Hypopyon	1
Corneal opacity	1
Renal	
Raised blood urea nitrogen	4
Urinary tract infection	2
Pulmonary (pneumonitis)	3
Septicemia	6

DISCUSSION

In agreement with other reports, we observed a female preponderance (56% females *vs* 44% males).[4,5] The maximum number of cases were seen to be in their 2nd decade of life. In contrast, Roujeau *et al.* reported the occurrence of these reactions in TEN cases in their 5th decade of life.[5] The mean age in our study was 22.3 ± 15.4 years as compared to 63 and 25 years in TEN and SJS patients respectively, in a report from Germany.[5]

All patients in our study gave a history of drug intake prior to the onset of the reactions. However, Roujeau *et al.*[4] and Schopf *et al*.[5] reported a small number of patients (4.5 and 3%, respectively) with TEN who did not have any history of drug intake preceding the onset. Single drug was found to cause adverse cutaneous reactions in 60, 39 and 14.6% of the patients in our series, a report from Germany[5] and in a series studied by Roujeau *et al,* respectively.[4] The mean numbers of drugs causing the reactions in our study and in a series reported by Roujeau *et al.* were 3.36 ± 2.3 and 4.4 ± 3.4, respectively.[4]

In our 30 cases, of the 57 drugs implicated, the three most common groups of drugs were anticonvulsants, antibiotics and NSAIDS. Anticonvulsant drugs were also the drugs most frequently implicated in SJS-TEN in a six-year series examining drug reactions in 500 patients from Chandigarh, North India.[6] In another survey of the clinical spectrum of drug rashes due to antiepileptics, a significant number of patients had serious rashes of SJS and TEN and these were mostly due to phenytoin and carbamazepine.[7] Carbamazepine was the culprit in all the five cases of SJS and phenytoin in two of the six cases of TEN in a study of adverse cutaneous reactions in children and adolescents.[8] Kamalaiah *et al.* in their report of EM, SJS and TEN in North East Malaysia, also confirm that anticonvulsants were the most commonly implicated group of drugs.[9] In contrast to the Indian and Asian series, antimicrobial drugs were the most common group of drugs resulting in these serious reactions in many of the reports from developed countries.[10-12] In a French Survey, NSAIDS were most commonly involved as culprits causing adverse cutaneous reactions.[4]

The reported mortality rates in the largest series of patients with TEN was found to be 28.6% (10-70%).[13] In our series, the mortality rate was 26 and 9% in the TEN group and SJS-TEN overlap category, respectively. The role of systemic steroids in SJS and TEN is controversial although they may be used in patients with early active disease or with the reappearance of erythema in recovering cases. We have used dexamethasone in most of our patients and the observed mortality rate was comparable with that reported in many series in the literature.[13]

In conclusion, serious adverse reactions such as SJS, TEN and the overlap category of SJS-TEN are mostly caused by anticonvulsants, especially carbamazepine and phenytoin, and also by antibiotics and NSAIDS.

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