

Retrospective analysis of deaths due to drug- induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in inpatients admitted in the dermatology unit of a tertiary care hospital

Sushama A. Bhounsule¹, Laveena V. Bandodkar², Lois James Samuel³
^{1,2,3}(Department of Pharmacology, Goa Medical College, India)

Abstract:

Objective: Stevens –Johnson Syndrome and toxic epidermal necrolysis are two most severe forms of acute drug reactions that are associated with significant morbidity and mortality. An expeditious identification of the offending drug is necessary for the early withdrawal as well as prevention of recurrence of such life threatening illness. The objective of our study was to identify the demography, offending agents, morbidity and mortality of SJS and TEN.

Material and Methods: In this retrospective study, the death statistical records over a period of 10 years from April 2003 to March 2013 were analyzed.

Results: There were 22 deaths in the dermatology department in the 10-year period from April 2003 to March 2013; 5 were due to SJS, 5 were due to TEN, and the remaining 12 were due to causes other than SJS or TEN. Of the 10 (due to SJS or TEN), 6 were female and 4 were male patients. Their ages ranged from 14 years to 69 years.

Conclusion: In our study, we found that the antimicrobials were implicated as the offending drugs in majority of the cases. Our study also showed that some of the patients who were in the 1st, 2nd and 3rd decades of life with SJS/TEN but without any other co-morbid conditions also succumbed to SJS/TEN.

Key words: Retrospective analysis, mortality, cutaneous drug reactions, offending drugs, Stevens-Johnson syndrome, toxic epidermal necrolysis.

I. Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two severe forms of erythema multiforme wherein there is extensive blistering and widespread mucosal involvement in case of SJS, whereas TEN is a more severe form of the reaction; in case of TEN considerable amounts of epidermis may be shed. ¹ Drugs are implicated as important causes of SJS/TEN. Besides drugs, vaccines, radiological contrasts, infections, ulcerative colitis, etc. are the other important causes leading to significant morbidity and mortality.² Several studies and case reports based on SJS/TEN have been published in India as well as abroad.

This retrospective study was carried out to identify the offending drugs causing SJS/TEN as well as to study the demographic pattern of the lesions and the associated morbidity and mortality. In this study, the death statistical records of the SJS/TEN patients who died in the dermatology department of our tertiary care hospital over a period of 10 years were analyzed.

II. Materials and Methods

The ethical clearance for our study was obtained from the Institutional Ethics Committee. The death statistical records of the dermatology department of our hospital were reviewed. The records from April 2003 to March 2013 were analyzed. Our main aims were:

1. To identify deaths that have occurred following SJS, TEN and SJS-TEN overlap.
2. To study the etiology of SJS/TEN.
3. To study the related demography i.e. age, sex, co-morbid conditions.

III. Results

As regards age and gender; out of the 22 patients who died in the 10 year period from April 2003 to March 2013, 10 deaths were either due to SJS or TEN. Drug intake was the etiology in all 10 cases of death. 5 out of the 10 deaths were in SJS patients and the remaining 5 were TEN cases. Out of the 10 who died, 6 were female and 4 were male patients. Females predominated in the SJS group while in the TEN group there were more male patients (see table 1). The SJS cases were in the age group of 14-67 years and TEN cases were in the age group 32 -69 years.

Drugs as an etiology were established in all the 10 cases. The major groups of drugs causing SJS/TEN in our study were antimicrobials followed by NSAIDs, antiepileptics, and allopurinol. Co-morbid conditions for which our patients were taking these offending drugs were infections, chronic obstructive pulmonary disease, seizures, autoimmune deficiency syndrome (AIDS), gout etc. Following is the tabular depiction of our findings (Table 1).

Table 1

	Death from (dermatological manifestations)	Gender	Age (years)	Offending drug/s	Complication	Co-morbidity
1.	SJS	F	20	Clarithromycin	Septic shock	?None
2.	SJS	F	37	Ofloxacin	Septicemia	?None
3.	TEN	M	69	Allopurinol	Septicemia	Hepatitis with DM
4.	TEN	M	55	Amoxicillin+NSAIDs	Septicemia with COPD exacerbation	COPD
5.	TEN	M	33	Carbamazepine	Septicemic shock	Alcoholic liver disease
6.	SJS	F	14	AKT	Pulmonary edema	Tuberculosis
7.	SJS	M	35	Diclofenac+Gentamicin+ Cough expectorant +Omeprazole	Septicemic shock	?None
8.	TEN	F	37	ART(Nevirapine/Zidovudine)	Septicemic shock	HIV
9.	TEN	F	32	Carbamazepine+Fexofenadine+ ?NSAID	Septic shock	?None
10.	SJS	F	67	Etoricoxib+Cefixime	Septicemia with DIC.	DM with hypertension

As seen in table 1, antibiotics (Clarithromycin and Ofloxacin) exclusively were implicated in 2 cases, Allopurinol in one case, antiretroviral therapy (ART) (Nevirapine/ Zidovudine) in one case, antitubercular drugs (AKT) in one case, and the antiepileptic drug Carbamazepine in one case. In most cases, exact causative drug could not be identified as two or more drugs/ classes of drugs were administered simultaneously:

1. Amoxicillin + NSAIDs
2. Diclofenac + Gentamicin + Cough expectorant + Omeprazole
3. Carbamazepine + Fexofenadine +?NSAID
4. Etoricoxib + Cefixime
5. Also as seen in table 1, in case of the patient treated with AKT, it could not be pointed out which of the antitubercular drugs is the offending drug.
6. In case of the patient treated for HIV with Zidovudine and Nevirapine, also, it cannot be pointed out which of the two caused the TEN reaction.

IV. Discussion

Cutaneous drug reactions form a sizeable proportion of the adverse drug reactions³.Stevens-Johnson syndrome and toxic epidermal necrolysis are severe cutaneous adverse reactions (SCAR) to drugs, vaccines etc.; these reactions are associated with significant morbidity and mortality.

Damage to skin in SJS/TEN is thought to be mediated by cytotoxic T lymphocytes and mononuclear cells; these cells induce apoptosis in keratinocytes which express drug derived antigens at their surface⁵. SJS and TEN are potentially serious cutaneous reactions.They are characterized by high fever, widespread blistering exanthema of macules and atypical target-like lesions ; these are accompanied by mucosal involvement^{6,7}.The detachment of the epidermis in SJS is less than 10% of the body surface area, while the detachment is more than 30% in TEN.

More recently, the proposed terminology for SJS and TEN –like dermatological manifestations/lesions is acute disseminated epidermal necrosis (ADEN). Proposed by Ruiz-Maldonado, it reclassifies SJS, SJS-TEN overlap, and TEN as ADEN 1, ADEN 2, and ADEN 3.⁸

In the retrospective study carried out by us in our tertiary care hospital, the analysis of data and records showed equal number of deaths from SJS and TEN (i.e. 5 patients each) during the 10 year period wherein the remaining patients diagnosed as SJS/TEN recovered and were discharged. We had predominance of female patients over males as far as the dermatological manifestations were concerned. However, we had more male patients in the TEN group and more female patients in the SJS group; this is in contrast with the study from West Germany.

In contrast to the general concept that adverse events are more common in extremes of ages due to the fact that hepatic and renal functions are suboptimal in them, in our study there were cases of deaths due to SJS/TEN in young patients in the 1st, 2nd and 3rd decades of life. This finding is similar to other studies in India where the mean age group is seen to be of young individuals. However 2 patients in our study belong to sixth decade, which is in concurrence with the study done in West Germany⁹, which showed a higher age group involvement in TEN (63%). The same study from West Germany also showed more of a lower age group for SJS; this supports our study findings wherein 4 out of 5 cases of SJS belong to lower age group.

As far as the offending agents responsible for these severe cutaneous adverse reactions are concerned, most of our SJS cases were due to antimicrobials as seen in table 1. Ofloxacin, a fluoroquinolone has been implicated for causing SJS/TEN-induced mortality. In an Indian study, it was found that SJS-TEN induced by Ofloxacin has a higher morbidity and mortality compared to anticonvulsants like Carbamazepine, Phenytoin, Phenobarbitone and Sodium Valproate.¹⁰

Carbamazepine can also cause severe and life-threatening rashes including Stevens-Johnson syndrome¹¹ and toxic epidermal necrolysis. The SJS/TEN reaction to Carbamazepine is associated with a particular HLA allele; HLAB*1502. This allele is seen to occur almost only in people with Asian ancestry.¹² The FDA recommends that Chinese patients should be screened for this allele prior to starting treatment with Carbamazepine. People who have developed a reaction to Carbamazepine have a higher probability of developing a hypersensitivity reaction with Phenytoin, thus showing that the same allele is associated with a hypersensitivity reaction to Phenytoin.¹¹

Our study showed one death with SJS associated with AKT (Anti tubercular therapy) and one death with TEN associated with ART (Antiretroviral therapy).

A case of TEN with Allopurinol in our study is in agreement with the findings of a case control study which included 13 patients with such cutaneous reactions who had received Allopurinol¹³. The most common cause of SJS and TEN in Europe and Israel is Allopurinol. The incidence of Allopurinol-associated SJS or TEN has increased possibly because of increased use and dosages of this drug.¹⁴

Almost all of our patients (i.e. 9 out of 10) who had SJS/TEN died of septic shock and most had co-morbid conditions like diabetes mellitus, HIV, tuberculosis and COPD. One patient died due to the development of pulmonary edema.

V. Conclusion

In our study, we saw that the antimicrobials were the commonest offending agents for SJS/TEN. Our study also showed that although patients of SJS/TEN who died mostly had co-morbid conditions, there were also patients in the 1st, 2nd and 3rd decades of life without any other co-morbid conditions who succumbed to SJS/TEN; this reflects the harmful and life-threatening nature of these severe cutaneous allergic reactions.

To conclude, patients with history of drug allergy should proactively protect themselves from similar allergy-related adverse events in future by voluntarily informing the treating physician in advance about the hypersensitivity that he may be harbouring to the particular drug and also by avoiding the use of over the counter medications unnecessarily. Similarly in the hospital setting, pharmacovigilance should be strictly adhered to, to prevent deaths from SJS/TEN, by early identification and prompt withdrawal of the offending drug. In complex medical situations, where multiple drugs are involved, drug reactions can occur and a detailed review of all medications must be undertaken following which the most likely culprits should be discontinued.¹⁵

The major limitation in our study was that the number of cases analyzed were less; further research is therefore required to authenticate our findings and come to a validated and unambiguous conclusion regarding the incidence, prevalence, etiology and demography of SJS/TEN.

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