Analysis of Stevens-Johnson's Syndrome and Toxic Epidermonecrolysis Patients in a Rural Based Medical College with an Emphasis on Steroid Therapy

Venkateshwarlu Nandyala[1], Gandiah P.[2], Govind Das[3], Harish Kumar J.[4], P Anand G. Reddy[5], Sandeep Kumar G.[6]

{[1]Professor, [2]Professor and HOD, [3]Professor and HOD, [4,5,6]P.G. Student}

Department of Internal Medicine, SVS Medical College, Mahabubnagar Andhra Pradesh, INDIA.

[*]Corresponding Address:

venkatetreya@gmail.com

Research Article

Abstract: Thirty cases of SJS-TEN were reported during a seven year period between 01-01-2007 and 31-12-2013 were analysed. Eighteen were males, anti-epileptics were the culprits in 11 cases (Phenytoin sodium was responsible in 6, carbamazepine in 4 while sodium valproate was responsible in 1 case. Ofloxacin was responsible in 4 ciprofloxacin and cefixime in one each case whereas another 8 cases it was NSAIDs. Two ayurvedic medications were also noted in our study. 12 patients received 3 days therapy of pulse dose dexamethasone therapy, 6 patients received pulse dose Methyl Prednisolone 7 patients received regular dexamethasone treatment while remaining 5 did not get any steroid. All cases received supportive therapy, barrier nursing and prophylactic antibiotics. Cases who received Pulse dose steroid treatment recovered fast and hospital stay was reduced, while two patients in non-steroid group died and remaining 3 recovered very slowly. Short term (3 days) pulse steroid therapy is well tolerated and recovery is very fast as compared to regular steroid therapy or therapy without steroid. However as the sample size is small we recommend a large study preferably a double blind study.

Keywords: Stevens-Johnson's Syndrome, Toxic Epidermonecrolysis, steroid therapy

Introduction

Cutaneous drug reactions are the most common type of adverse drug reactions[1]. Adverse cutaneous drug reactions form 2-3% of the hospitalized patients [2]. The percentage of potentially serious reactions is around 2% [2]. Stevens-Johnson syndrome (SJS) was first described in 1922, as an acute mucocutaneous syndrome in two boys. The condition was characterized by severe purulent conjunctivitis, severe stomatitis with necrolysis and macular eruptions. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are cutaneous adverse reactions having an incidence of 0.4-1.2 and 1.2 to 6 million persons per year according to the available data [3]. In 1956, Alan Lyell described four patients with an eruption resembling scalding of the skin which he called toxic epidermal necrolysis or TEN [4]. In SJS, detachment of the epidermis is less than 10% of the body surface area; the detachment is >30 in TEN [5]. In addition to the severe skin symptoms, both diseases are accompanied by complications in numerous organs, such as the liver, kidney, and lung [6]. Incidence of SJS and TEN is 0.05 to 2 persons per million populations per year [7, 8]. Incidence is higher in HIV patients than general population [9]. The reported mortality varies from 3 to 10% for SJS and from 20 to 40% for TEN[10]. Increasingly to date, SJS and TEN are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by their extent of skin detachment.

Materials and Methods

This was a prospective case study of adverse drug reactions that occurred in the last 7 years (2007-01-01 till 2013-12-31) that were admitted to SVS Medical College Hospital, Mahabubnagar A.P. India. SJS-TEN is diagnosed by Bastuji-Garin criteria [5]. We recorded the duration of the rash, drug intake, time period between the drug and reaction, complications, associated co-morbidities. Drug that have been taken within four weeks preceding the onset of symptoms were taken as causal 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 courses of systemic steroids which were gradually tapered. Institutional ethical committee clearance has been taken for the study. SCORTEN, a validated TEN-specific severity-of-illness score, ranking severity and predicting mortality, was calculated retrospectively to assess the efficacy of DPT.

SCORTEN is based on 7 independent risk factors (age, heart rate, malignancy, TBSA, and serum urea, bicarbonate and glucose levels). The predicted mortality progressively depends on the number of factors present [11].

Statistics

Data for primary outcome variable were extracted from the studies and summarized using absolute numbers of cases and percentage. Chi-square test was used to compare the proportion of causative drugs. Data for the complications, co-morbid conditions, abnormal laboratory parameters and mortality were pooled and presented as proportions. Percentage of mortality between SJS and TEN was compared by Chi-square test.

Observations

A total of 30 cases were analysed in the present study. Eighteen patients were males. Mean age in our study was 30.58 years. The figure 1 shows the demographic details.

Table 1: Showing the age and gender distribution

	<20 years	**21-30 years**	**31-40ears**	**41-50 years**	**51-60 years**	**> 60 years**
Male	3	6	6	1	1	1
Female	1	2	4	2	3	0
Total	4	8	10	3	4	1

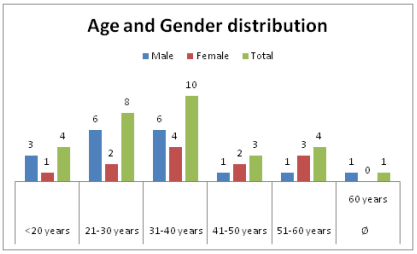

Figure 1: Showing the age and sex distribution among the SJS-TEN patients

Table 2: Co-morbid conditions

HIV	4
Diabetes mellitus	2
Hypertension	2
Tuberculosis	2
Rheumatic heart disease	2
Diabetes mellitus and hypertension	1

Only two patients expired on 5th and 9th day respectively. Mean recovery time was 8.68 days, the earliest being 6 days and the longest one to recover was 16 days. The cases due to carbamazepine and ofloxacin took more time than others. Anti-epileptic agents (11), antibiotics (8) and non-steroidal analgesics (8) were responsible for 90% of the cases. Phenytoin sodium topped the list with 6 cases while carbamazepine, ofloxacin and diclofenac were responsible in 4 each instances; ciprofloxacin aceclofenac were the cause of this calamity in 3 each cases. In two cases the drug history revealed some ayurvedic medications; it was thought to be Isoniazid in one pulmonary tuberculosis patient when the patient was given a challenge later on.

Table 3: Drugs possibly associated with SJS-TEN

Anti-epileptics: Phenytoin	6
Anti-epileptics: Carbamzepine	4
Anti-epileptics: Sodium Valproate	1
Antibiotics : Ofloxacin	4
Antibiotics : Ciprofloxacin	3
Antibiotics : Cefixime	1
Analgesic antipyretic: Diclofenac	4
Analgesic antipyretic: Aceclofenac	3
Analgesic antipyretic: Ibuprofen	1
Anti-tubercular drugs: Rifampicin, Isoniazid, Pyrizenamide and Ethambutol	1 (? Isoniazid)*
Unknown (ayurvedic medication)	2

*known after re-challenge medication after recovery in a pulmonary tuberculosis case

Table 4: Haematological abnormalities

Parameter	Number	Percentage
Leucocytosis	14	46.67
Leucopenia	08	26.67
Anaemia	10	33.33
Thrombocytosis	08	26.67
Thrombocytopenia	12	40.0
Eosinophilia	16	53.33

Table 5: Hepatic abnormalities

Parameter	Number	Percentage
Elevated transaminases	10	33.33
Elevated alkaline phosphatases	06	20.0
Hyperbilirubin	06	20.0
Altered A:G ratio	05	16.67
Prolonged Prothrombin time (PT/INR)	04	13.33

Table 6: Electrolyte abnormalities

Parameter	Number	Percentage
Hypokalemia	09	30.0
Reduced HCO_3^-	08	26.67
Hyperkalemia	05	16.67
Hyponatremia	02	06.67

Table 7: Other abnormalities

Parameter	Number	Percentage
Hyperglycaemia	09	30.0
Hypoglycaemia	08	26.67
Raised blood urea and Serum Creatinine	06	20.0
Dyslipidaemias	04	13.33

Table 8: Complications

Complications	Number	Percentage
Secondary skin infections	11	36.67
Ocular (symblepharon, hypopyon, corneal scarring, viral or bacterial conjunctivitis, blepharitis and corneal xerosis.)	08	26.67
Urinary tract infection	11	36.67
Respiratory tract infection	06	20.0
ARDS	02	06.67
Acute renal failure	02	06.67
Metabolic encephalopathy	02	06.67

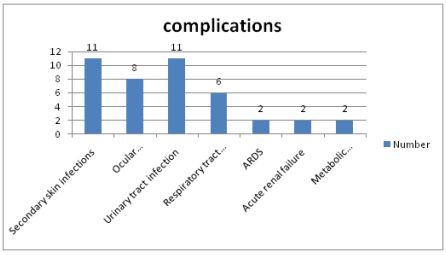

Figure 2: showing complications in our study

Treatment

Except for seven patients, all other patients received definitive therapy in the form of regular dexamethasone (7), 1000mg of methyl prednisolone pulse therapy for 3 days (6), and 100mg of dexamethasone pulse therapy for 3 days (12). Pulse therapy was given along with intravenous broad spectrum antibiotics. Five patients did not receive any steroids as they came very late with complications like sepsis and acute kidney injury. Overall, healing was noticed at 2–18 days after the onset of treatment. For dexamethasone pulse therapy, the onset of healing was on the third day of treatment; for methyl prednisolone pulse therapy, it was on the second day of pulse and for no steroid therapy it was on sixth day. The period of hospitalization ranged from 5 to 30 days, and it was lowest for methyl prednisolone pulse therapy. Apart from

hemoptysis due to gastritis in one patient, we did not record any other complications including sepsis and septicaemia, in patients on dexamethasone pulse therapy.

Table 9: Showing the main stay of treatment apartment barrier nursing and broad spectrum antibiotics and outcome

Group	Number of patients	Earliest day healing	Completion of healing	Mean days
Dexamethasone pulse therapy	12	3	8	3.88
Methyl Prednisolone pulse therapy	6	2	6	3.02
Dexamethasone regular therapy	7	5	12	7.14
No steroid *	5	7 (10)	18	11.67

*Two patients expired on 5th and 9th day respectively.

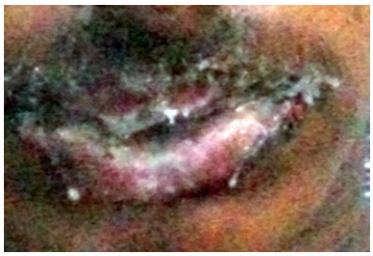

Figure 3: Muco-cutaneous lesions of oral cavity in case no 11

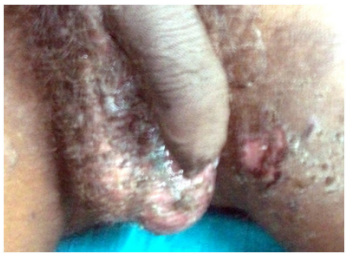

Figure 4: Muco-cutaneous lesions of genitalia in case no: 13

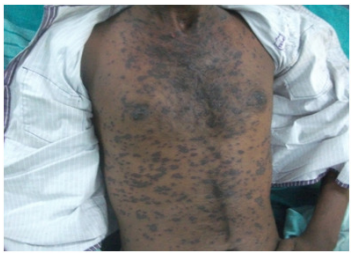

Figure 5: Cutaneous lesions in case number 16

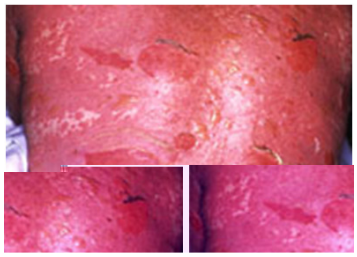

Figure 6: Toxic epidermonecrolysis in case no 22

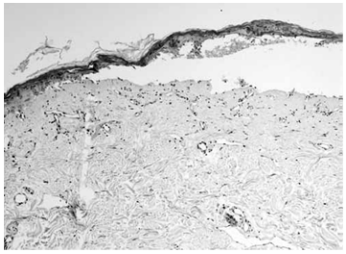

Figure 7: Histopathological examination of case number 22

Discussion

We studied Stevens–Johnson syndrome and toxic epidermal necrolysis, two rare but severe blistering muco-cutaneous diseases that, according to our disease definitions, share common clinical and histo-pathological features but vary in the extent of epidermal detachment. [3,6] Both are frequently associated with drug use [1,2,4]. Slight male preponderance (18 males: 12 females) was noted in our study. This was in agreement with the study done by Barvaliya *et al* [20] and Naveen *et al* [21] which also reported a male preponderance. HIV is the most common co-morbid condition in the patients of SJS/TEN in our study (4 patients/30) which is much lower than South Africa (78.67%) [22], Togo (54.6%) [23] and higher than France (7.3%) [24].[28,45,46] Incidence rate of SJS is 1,000 fold higher in HIV-positive patients as compared to general population in Germany[25]. Patel *et al*[26] reported lower incidence of HIV as in our study. Diabetes mellitus was the next co-morbid condition noted in our series (2 DM cases + one DM and Hypertension). According to SCORETEN raised blood glucose affects badly in the recovery of the patients [27]. There are no generally accepted guidelines for the specific treatment of SJS/ TEN, and few controlled clinical trials have been performed due to the rarity and severity of the disease [28]. The use of corticosteroids in SJS/TEN is controversial [29, 30, 31,32, 33, 34]. The precise action of corticosteroids in inflammatory diseases is still not well understood. They have pleomorphic immune-modulating effects, e.g. through inhibition of numerous cytokines [35]. Nowadays the use of corticosteroids in SJS/TEN is generally not

advocated because of the possibility of delayed healing and the risk of infection[29, 31, 34]. The general negative opinion of corticosteroids is probably because they are often given too late, in too low a dose, and for too long during the process. During the healing phase corticosteroids may indeed impair wound healing and promote sepsis. However, short courses of high-dose corticosteroids in early SJS/TEN have a good rationale, as immune mechanisms are directly responsible for the cascade of events leading to apoptosis. There are only a few case reports describing pulse therapy in TEN[36, 37]. Initially, 1000 mg methylprednisolone was usually used, but recently dexamethasone has often been chosen for pulse therapy because it combines a strong immunosuppressive glucocorticoid with a negligible mineralo- corticoid effect. We studied the effect of dexamethasone pulse therapy (DPT) in 12 patients with SJS/TEN. The patients who received pulse steroid therapy (either methyl prednisolone or dexamethasone) recovered much earlier and with least complications as compared with regular long term steroid therapy or those without any steroid treatment. Our sample size is small and we recommend large double blind controlled study with pulse dose dexamethasone as it is cheaper than methyl prednisolone. This is more relevant at least in developing countries like India where the Medicare is mainly self financed and IVIG (intravenous Immunoglobulin) is very costly so also the plasmapheresis.

Summary and Conclusions

SJS-TEN is rare but not uncommon entity in general practice. Anti-epileptics like phenytoin and carbamazepine are most common culprits followed by NSAIDs. Short term (3 days) pulse steroid therapy is well tolerated and recovery is very fast as compared to regular steroid therapy or therapy without steroid. However as the sample size is small we recommend a large study preferably a double blind study.

Conflict of Interests

The authors declare that they have no conflict of interests.

Disclosure

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