A Clinical Study of Severe Cutaneous Adverse Drug Reactions and Role of Corticosteroids in their Management

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Abstract

Background: Various medications are used for the treatment of various diseases. Ironically, adverse drug reactions (ADRs) also accompany the use of these medications and are as old as the medicine itself. These drug reactions can range from mild transient erythema at one end of the spectrum to severe cutaneous ADRs (SCADRS) that include Steven–Johnson syndrome (SJS), toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms complex (DRESS). Aim: This study aims to study the clinical and epidemiological aspects of severe cutaneous adverse drug reactions (SCADRS) at a referral center of Jammu region, with special reference to the role of corticosteroids in the management. Materials and Methods: The study was carried out between July 2015 and December 2015, at a tertiary hospital after permission from Ethical Committee of the institution. A total of 44 patients were included in the study which included outpatients as well as inpatients admitted after written informed consent. The Naranjo ADR probability scale was applied to indicate the causality of the drug with the SCADRS. Results: In the study, a total of 44 patients were included in the study. Males outnumbered the females, and maximum patients were in the age group of 21–40 years. SJS was the most common SCARD found followed by DRESS. Antiepileptic class of drug was found to be most commonly implicated. Immediate withdrawal of the culprit drug and administration of systemic steroids reverted the SCARD in maximum patients. Conclusion: Severe cutaneous adverse drug reactions can be associated with serious morbidity as well as mortality. Their knowledge and prompt recognition are essential for clinicians as early recognition, and immediate withdrawal of the culprit drug/drugs with adequate management can be lifesaving.

Keywords: Acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms complex, severe cutaneous adverse drug reactions, Steven–Johnson syndrome, toxic epidermal necrolysis

Introduction

Cutaneous adverse drug reactions (CADRs) have been reported to be the most frequent ADRs in various studies.1,2 Studies have found the overall incidence of CADRs in developed countries as 1%–3%, while in developing countries, it is thought to be higher between 2% and 5%.3 Out of all CADRs, 2% of these have been reported to be severe and may end in fatal outcome. The term severe cutaneous adverse drug reactions encompasses Steven–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These are severe drug-induced reactions which are unpredictable, so a high index of suspicion is required for their early recognition.4 SCARDS represent mostly an idiosyncratic hypersensitivity reactions with a heterogeneous clinical presentation. This study was undertaken at a referral center of North India for a period of 6 months to assess the patterns of SCARDS among patients and to identify the causative drug/drugs and establish causality using Naranjo scale and also study the role of corticosteroids in their management.1,5

Materials and Methods

In this study, a total of 44 patients including both inpatients and outpatients presenting with SCADRs were taken. The
study was undertaken for a period of 6 months starting from July 2015 to December 2015, at a referral center of North India. A written informed consent was taken from each patient before including them in the study. Patients presenting with SJS, TEN, DRESS, and AGEP were included in the study. The diagnoses of SJS, TEN, AGEP were made on clinical grounds and according to standard definitions while in case of DRESS REGISCAR score was used to establish the diagnosis. Further diagnosis was substantiated by detailed clinical history, detailed general physical examination. A detailed history regarding intake of drug/drugs, cutaneous or mucosal eruption, time gap between drug intake and cutaneous eruption, any associated systemic symptoms, temporal association and improvement after withdrawal of drugs/drugs was noted down.

A detailed general physical examination, cutaneous eruption regarding morphology, pattern and distribution of eruption, and mucosal examination were performed. Causality was assessed using Naranjo probability scale.

Results

During the 6 months period, a total of 44 patients were included in the study. A total of 20 patients were of SJS, 16 patients were of DRESS, 3 patients were of TEN, 3 patients were of AGEP, and 2 patients were of SJS/TEN overlap [Table 1]. The most common class of drug implicated was antiepileptics, and out of it, phenytoin was the most common. There were 27 males and 17 females in the study. The youngest patient was 3 years old and the oldest being 65 years. The duration between drug intake and drug eruption ranged from 3 to 5 weeks. Using the Naranjo probability scale, 22 patients had a probable association, 20 highly probable, and 2 had a possible association.

There were twenty patients of SJS with youngest patient being 4 years old and oldest being 50 years old. Out of 20 patients, 11 patients were on antiepileptics including phenytoin, phenobarbitone, and carbamazepine. A 5 patients out of 20 were on NSAIDS, 2 were on cephalosporins plus clavulanic acid combination. 1 patient was each on sulfonamides and amoxicillin. In 12 patients, drug came out as a probable cause, and in other 8, highly probable. Cutaneous involvement was seen in all the patients with <10% of body surface area involvement. Mucosal involvement was also seen with oral mucosa involvement seen in all 20 patients and eye involvement in 8 patients. Liver function tests were altered in 12 patients and eosinophilia in 11 patients. All the causative and suspected drugs were immediately stopped, and a short course of steroids of 1–2 weeks were given in all patients leading to drastic improvement.

There were 16 patients of suspected DRESS reaction. The youngest patient was 16 years old and the oldest being 65 years old. The duration between drug intake and eruption ranged from 3 to 5 weeks. Phenytoin was the most commonly implicated drug in 12 patients while 2 patients developed DRESS after dapsone intake and the other patient was taking fluconazole and ciprofloxacin, respectively. In three patients, it was seen that after stopping phenytoin, the patient had to be put on levetiracetam - an unrelated antiepileptic of other group, but again the patient’s condition worsened so it too had to be stopped and the patient was then put on lacosamide. All 16 patients presented with fever with rash with facial edema and eosinophilia. Rash was in the form of maculopapular rash in 14 patients and 2 patient presented with SJS like feature. Seven patients had lymphadenopathy, and liver function tests were deranged in all. Renal function tests were deranged in one patient whereas another patient presented with pulmonary involvement. Patients with severe symptoms had greater eosinophilia >1500 and liver enzymes raised to about 20–40 times. There was rapid improvement seen in 15 patients after stopping the offending drug as early as possible, and rapid administration of short course of systemic steroids leads to faster recovery. One patient died because of multisystem involvement.

A total of three patients presented with TEN. The youngest patient was 3 years old and the eldest being 65 years old. The duration between drug intake and onset of eruption ranged from 3 to 6 weeks. Antiepileptics were implicated in all three including phenytoin in two and phenobarbitone in one. There was >30% cutaneous involvement in all three patients with mucosal involvement present. Systemic involvement was seen in all three patients. The offending drug was stopped in all the patients, and all patients were managed under intensive care unit with utmost care. Two patients recovered and one patient (65 years) died.

Two patients presented with SJS/TEN overlap. One was 24 years old, and the other was 30 years old. In one patient, cephalosporin/clavulanic acid was implicated, and in the other, it was gardenal. The time interval between drug intake and eruption was 4 weeks in both. Cutaneous involvement was 10%–30% in both including mucosal involvement. Systemic involvement was also seen in both the patients. Both patients improved after stopping the offending drug and administration of systemic steroids resulted in faster improvement.

Three patients were diagnosed with AGEP. In two patients, the offending drug was terbinafine given for tinea corporis, and in the other, it was azithromycin. The cutaneous lesions were in the form of generalized erythema with pustules which at places were coalescing with petechiae and purpura. Fever with facial edema with eosinophilia was also seen. Liver function tests

| Table 1: Gender distribution of patients among severe cutaneous adverse drug reactions |
|-----------------|-------|-------|-----|
| SCARD            | Number of males | Number of females | Total |
| SJS             | 11     | 9     | 20  |
| SJS/TEN         | 2      | 0     | 2   |
| TEN             | 2      | 1     | 3   |
| DRESS           | 10     | 6     | 16  |
| AGEP            | 2      | 1     | 3   |
| Total           | 27     | 17    | 44  |

SJS: Steven–Johnson syndrome, TEN: Toxic epidermal necrolysis, DRESS: Drug reaction with eosinophilia and systemic symptoms complex, AGEP: Acute generalized exanthematous pustulosis
with enzyme levels raised to 20–40 times were also seen. The offending drug was stopped in both. Biopsy was also taken to differentiate it from pustular psoriasis. Two patients improved with stopping the offending drug and administration of steroids whereas in the one patient, cyclosporine had to be administered for faster improvement.

**Discussion**

A total of 44 patients with SCARDs were taken up for the study, and various SCARDs were observed. Males outnumbered the females which has been reported in various other studies.[5] The patients were in the age group of 21–40 years which has been reported in various other studies also.[6] However, a study from Chandigarh, reported SCARDs in the elderly group. A study also reported that SCARDs to be more common in the elderly due to altered drug metabolism in them.[7] The disparity in the age group presenting with SCARDs could be because of variations in the health-seeking behavior. The most common reaction pattern observed was SJS-TEN spectrum followed by DRESS similar to that reported by various other studies.[8] Two patients were of AGEP.

In our study, antiepileptics came out as the most commonly implicated class of drug in the majority of the patients. This was well in accordance with various other studies where antiepileptics were found to be the causative drugs of SCARDs.[9] Among antiepileptics, phenytoin was the commonly implicated drug whereas antimicrobials constituted the second most common group followed by NSAIDS. Penicillins and cephalosporins were the most commonly offending drugs seen among antimicrobials and addition of clavulanic acid further increased the risk of SCARDS.[10] Two patients presented with terbinafine induce AGEP. Various other studies have also reported AGEP by terbinafine.[11]

Most of our patients were in the SJS/TEN spectrum, and similar findings have been reported in various other studies too. Systemic involvement was seen in twenty patients. Most common organ involved was liver followed by kidneys. This was similar to various other studies which have also reported liver involvement to be common.[11] Marked eosinophilia was seen in 24 patients. On application of SCORTEN scoring system, it was seen that patients with higher scores had severe involvement and eosinophilia more than 1000/mm$^3$.[12] Prompt withdrawal and early administration of systemic steroids resulted in rapid improvement in all but one patient. One patient aged 60 years old died due to multiorgan failure.

Among patients of DRESS, systemic involvement was seen in all patients in the form of altered liver function tests. Lymphadenopathy was seen in 11 patients, and atypical lymphocytes in peripheral blood film seen in 7. It was seen that prompt withdrawal and early administration of systemic steroids resulted in marked improvement in patients. In 4 patients on phenytoin, it was seen that patients had to be put on levetiracetam, an unrelated antiepileptic drug, but this also resulted in worsening of DRESS and patient later had to be put on lacosamide. Various upcoming reports have also reported DRESS due to levetiracetam which is an unrelated antiepileptic drug not belonging to the aromatic group.[13] Less morbidity and rapid recovery were seen in patients of DRESS than in the SJS-TEN spectrum. This finding has also been reported in various other studies.[14,15] The reason being expansion of Treg cells in DRESS and their inhibition in SJS-TEN.

Thus, it was seen that in addition to prompt withdrawal of the culprit drug or drugs, it was seen that systemic corticosteroids resulted in faster remission thus favoring their role as has also been reported in studies.[16]

**Conclusion**

In summary, SCARDs are associated with multiple organ involvement. Early recognition and prompt withdrawal of causative drugs can be lifesaving. Moreover, in a country like India, systemic corticosteroids can play a major role if judiciously used.

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**Conflicts of interest**

There are no conflicts of interest.

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