Original paper

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS : A PROSPECTIVE STUDY OF EPIDEMIOLOGY AND CLINICAL PATTERN.

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Abstract

Background: Cutaneous adverse drug eruptions are the most common adverse reactions attributed to drugs in which any type of skin reaction can be mimicked, induced, or aggravated. Cutaneous drug reactions are of wide range from mild to moderate to severe life threatening reactions. 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).

Aims: The aims of this study are to evaluate the clinical and epidemiological aspects of severe cutaneous adverse drug reactions (SCADRS) at a tertiary care center from gujarat.

Methods : This is a prospective study which was conducted over period from September 2014 to December 2016. A total 31 patients were included in the study which included outpatients as well as inpatients admitted after written informed consent.The diagnosis 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.

Results : In the study, a total of 31 patients were included in the study,in which 18 were males and 13 were females, and maximum patients were in the age group of 31-40 years. SJS 14(45.16%) was the most common SCADR. Antiepileptic class of drug was found to be most commonly implicated.

Conclusion : Patients can be educated to avoid re-administration of the offending drug(s) to reduce the morbidity associated with CADRs. Early identification of SCADRs can reduce the morbidity and mortality rates.

Key words : Steven–Johnson syndrome, toxic epidermal necrolysis

Introduction

According to the WHO (World Health Organization) definition, an adverse drug reaction (ADR) is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" [1]. Up to 80% of ADRs are dose-dependent and predictable, while about 20% are independent of the administered dose and unpredictable. Frequently, the latter are immunologically mediated reactions, often called "drug allergy", and involve either IgE or T cells. In contrast, non-immunologically mediated reactions are called "idiosyncratic reactions" [2]. As a majority of ADRs involve the skin, epidemiological studies were mainly carried out on the topic of cutaneous manifestations.

However, more often than not, possibility of ADRs is clinically challenging, as there are many other differentials. Roujeau's criteria attempted to simplify defining cutaneous ADRs, (a) other causes for the eruption, such as viral exanthema, should be excluded, (b) a temporal relationship between the drug and onset of rash should exist, (c) improvement should be noted following drug cessation, (d) reactivation upon challenge should be noted, and (e) cutaneous reaction is known to be associated with the drug.[3]

The term, severe cutaneous adverse reaction (SCAR), was proposed for such conditions, as they were (a) severe, (b) unpredictable, and (c) drug induced. SCARs encompass a heterogeneous group of delayed hypersensitivity reactions, which are most frequently caused by drugs.[4] The designation SCAR most commonly includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), SJS/TEN overlap, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, and acute generalized exanthematous pustulosis.[5]

This study aims to evaluate the clinical and epidemiological aspects of severe cutaneous adverse drug reactions (SCADRS) at a tertiary care center from gujarat.

Method

This is a prospective study which is to be conducted over period from September 2014 to December 2016 in the Department of Dermatology, venerology and leprology at a tertiary care hospital at Gujarat.

Conditions included in this study are

- Stevens–Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- SJS/TEN overlap
- Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS)
- Acute generalized exanthematous Pustulosis (AGEP)

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.Patients leaving with HIV/AIDS were not included in this study.

Results and Discussion

Total of 31 patients were included in the study. 18(58.06%) patients were male and 13(41.93%) were female [Table 1] A total of 14 patients were of SJS, 7 patients were of SJS/TEN overlap, 3 patients were of TEN, 3 patients were of AGEP, and 4 patients were of DRESS.[Table 2] The youngest patient was 7 years old and the oldest being 67 years, and maximum patients were in the age group of 31-40 years.

Table 1 : Age distribution

Gender	Number	%
Male	18	58.06
Female	13	41.93
Total	31	100

Table 2 : Severe cutaneous adverse drug reactions

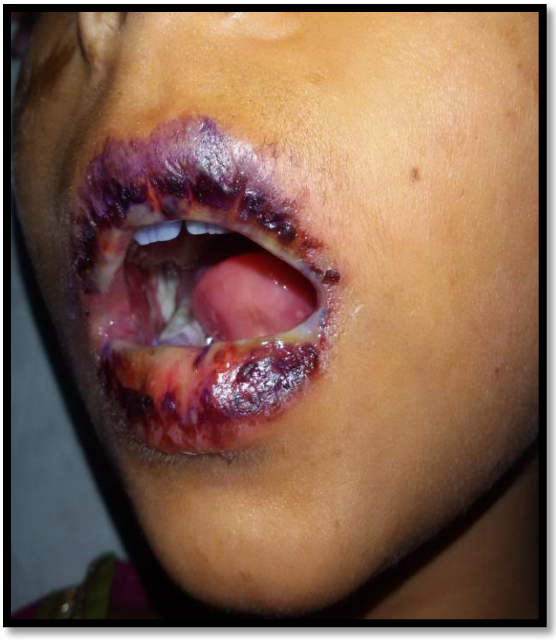
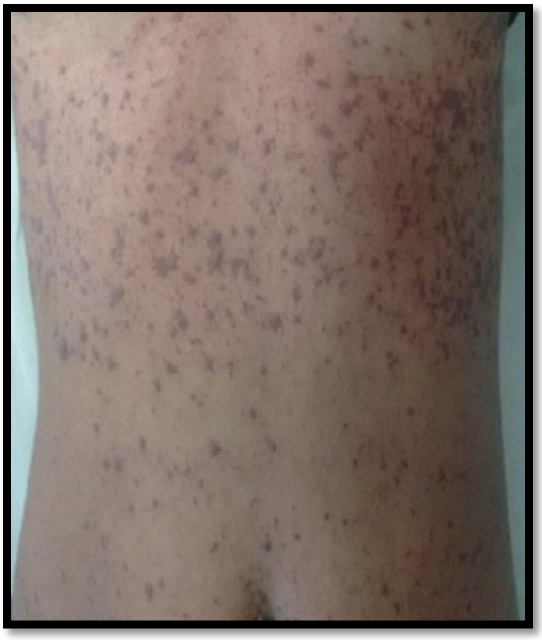
DIAGNOSIS	NO.OF CASES	PERCENTAGE
ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS(AGEP)	3	9.68%
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS(DRESS)	4	12.90%
SJS/TEN OVERLAP SYNDROME	7	22.58%

STEVENS JOHNSON SYNDROME	**14**	**45.16%**
TOXIC EPIDERMAL NECROLYSIS	3	9.68%
TOTAL	**31**	100%

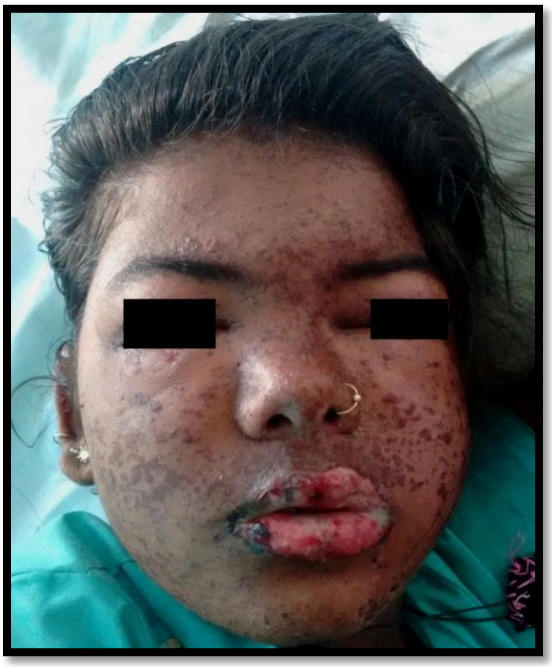
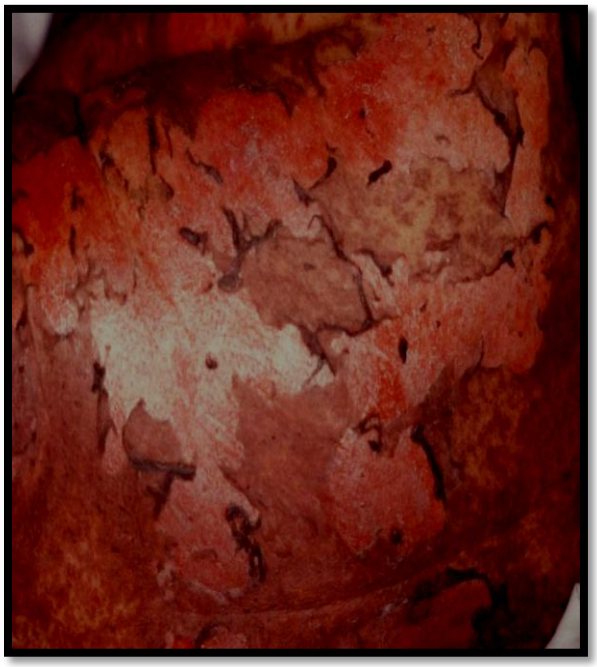
In our study, antiepileptics came out as the most commonly implicated class of drug in the majority of the patients. This was well in accordance with various other studies where antiepileptics were found to be the causative drugs of SCARDs.[8] Among antiepileptics, phenytoin was the commonly implicated 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 clauvulinic acid further increased the risk of SCADRS.[9] Two patients presented with terbinafine induce AGEP. Various other studies have also reported AGEP by terbinafine[10] However patients of old age groups are on polypharmacy and it is very difficult to find out the exact culprit drug sometimes.

SJS-TEN

There were 14 patients of SJS with youngest patient being 7 years old and oldest being 50 years old. Out of 14 patients, 9 patients were on antiepileptics including phenytoin, phenobarbitone, and carbamazepine. A 2 patients out of 14 were on NSAIDS, 1 patient was each on cephalosporins plus clauvulinic acid combination sulfonamides and amoxicillin. 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 10 patients and eye involvement in 6 patients. Liver function tests were altered in 7 patients and eosinophilia in 6 patients. All the causative and suspected drugs were immediately stopped.

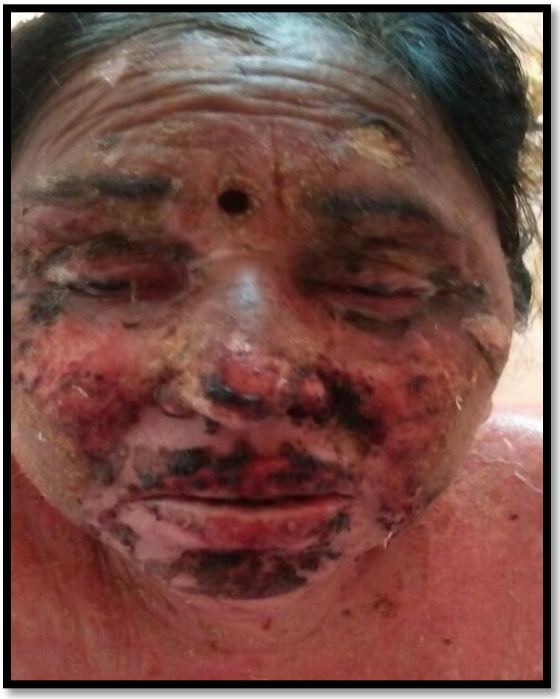



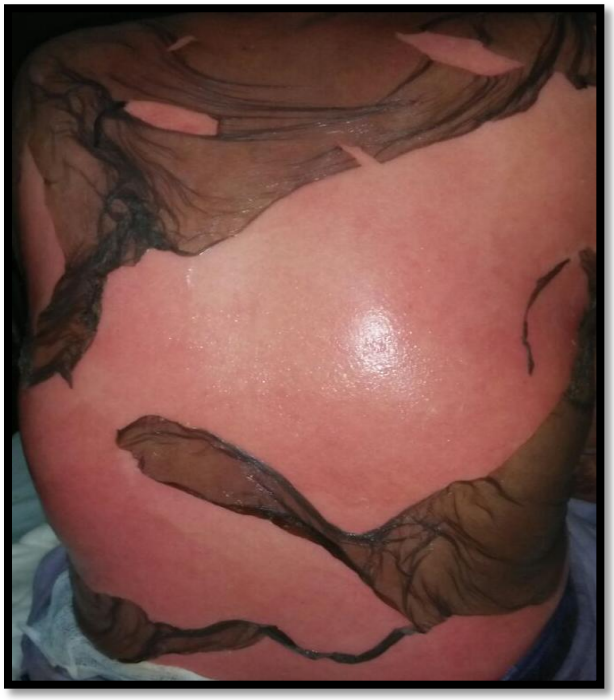
Seven patients presented with SJS/TEN overlap. 3 patients were on antiepileptics phenytoin, Phenobarbita, 3 patients were on NSAIDs. In 2 patient, cephalosporin/clavulanic acid was implicated, The time interval between drug intake and eruption was 2 to 4 weeks.Cutaneous involvement was 10%–30% in all patients including mucosal involvement. Patients improved after stopping the offending drug.

A total of 3 patients presented with TEN. The youngest patient was 14 years old and the eldest being 65 years old. The duration between drug intake and onset of eruption ranged from 3 to 6

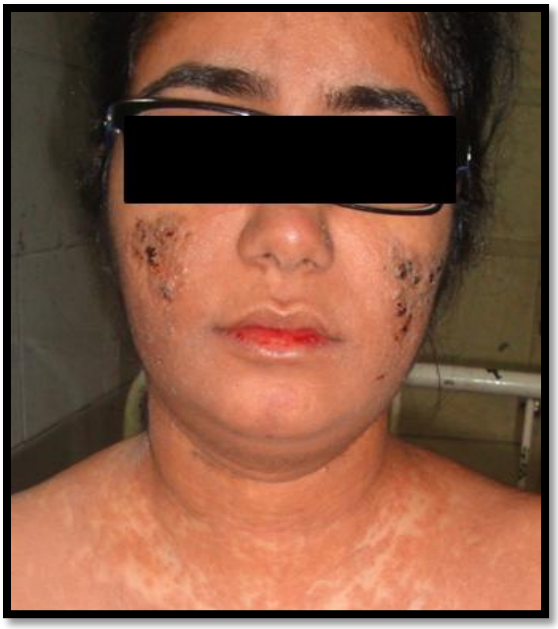
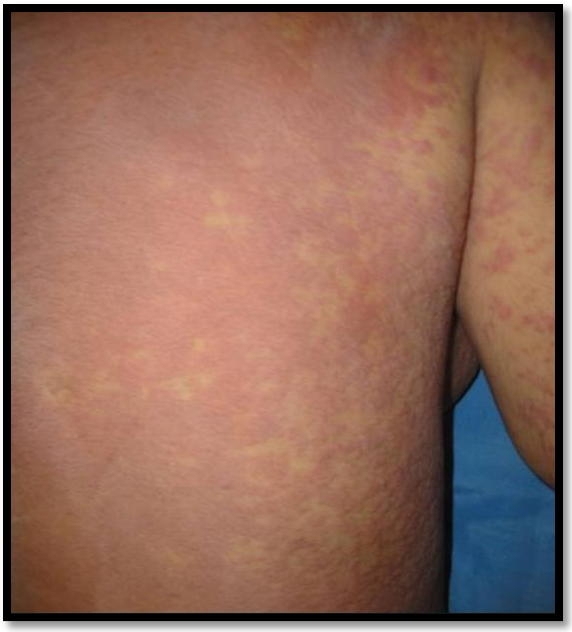
weeks. Antiepileptics were implicated in all three including phenytoin in two and phenobarbitone in one. There was >30% cutaneous involvement in all three patients with mucosal involvement present. Systemic involvement was seen in all three patients. The offending drug was stopped in all the patients, and all patients were managed under intensive care unit with utmost care. Two patients recovered and one patient (65 years) died.





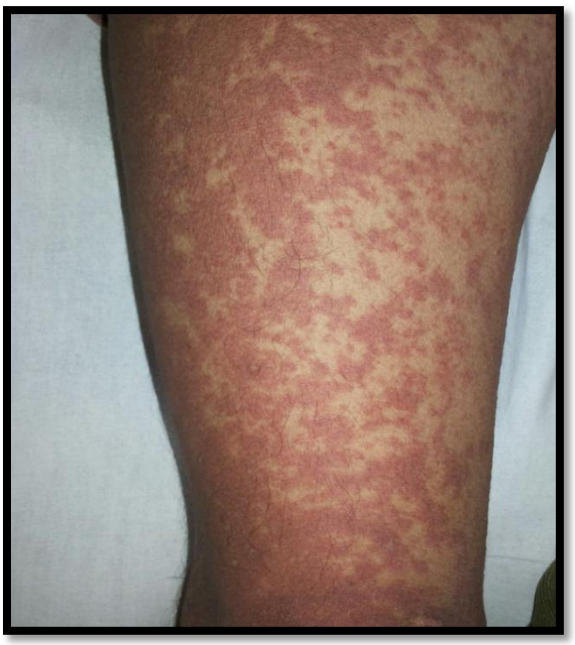
DRESS

There were 4 patients of suspected DRESS reaction. The youngest patient was 16 years old and the oldest being 62 years old. The duration between drug intake and eruption ranged from 3 to 5 weeks. Phenytoin was implicated drug in one patients while 3 patients developed DRESS after dapsone intake. All 4 patients presented with fever with rash with facial edema and eosinophilia. Rash was in the form of maculopapular rash in all. 3 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. There was rapid improvement seen in 2 patients after stopping the offending drug as early as possible.One patient died because of multisystem involvement.

AGEP

3 patients were diagnosed with AGEP. In two patients, the offending drug was terbinafine, and in the other, it was metronidazole. 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 with enzyme levels raised to 20–40 times were also seen. The offending drug was stopped in both. Two patients improved with stopping the offending drug.



Conclusion

No gold standard investigation is available for diagnosing CADR, but taking a proper history such as duration of drug intake, reaction time, response of drug eruption to withdrawal of the suspected drug, rechallenging the drug is very tricky and very stressful for patients' side., and any past history of similar reactions can help in diagnosing CADRs. Advent of newer drug, newer modality of drug delivery, and polypharmacy are throwing newer challenges in the field of CADRs. Continuous learning and careful vigilance can lead to early diagnosis and avoidance of considerable mortality and morbidity.

Acknowlegement : nil

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