Original Article

A Study of Cutaneous Adverse Drug Reactions in a Tertiary Care Center in Punjab

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Abstract

Context: 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. **Aims:** To study the pattern of various types of cutaneous adverse drug reactions (CADRs), to find out the causative drug(s) involved and to determine the response to treatment and outcome in patients with CADRs. **Patients and Methods:** This prospective study was done in the department of dermatology. Patients with suspected drug rash, of either sex and all age groups were included in the study. **Statistical Analysis:** Frequencies and proportions were calculated using Chi-square test and *t*-test as the tests of significance. Data was analyzed using SPSS version 21. **Results:** A total of 258 patients were enrolled in the study. The most common CADR observed in the study was exanthematous drug eruption in 42.63% patients followed by drug induced urticaria in 21.32% patients. Antimicrobials were the most common offending drugs in 64.73% of patients, followed by non-steroidal anti-inflammatory drugs (NSAIDs) in 15.50% patients. In the study, 12 patients (4.65%) were found to have severe cutaneous adverse drug reactions (SCADRs). Stevens–Johnson syndrome (SJS) - Toxic epidermal necrolysis (TEN) was the most common SCADR (50%) and antituberculous drugs were the most common causative group of drugs causing SCADRs. **Conclusion:** The most common CADR observed in the study was exanthematous drug eruption and antimicrobials were the most common causative drugs.

Keywords: *Antimicrobials, cutaneous adverse drug reactions, exanthematous drug eruption*

Introduction

Any drug is capable of causing a drug reaction but the most common ones are penicillin group of drugs, sulfonamides, anticonvulsants, NSAIDs, fluoroquinolones, angiotensin converting enzyme inhibitors, etc.[1]

Approximately 10–30% of adverse drug reactions (ADRs) have cutaneous manifestations out of which 2–3% are seen in hospitalized patients.[2-5] With the introduction of new drugs in the market, intake of multiple medications, self-medication, and availability of over the counter medications, the incidence of ADRs is progressively increasing. CADR is an important clinical entity in dermatological practice.

Drug reactions can be harmless and self-limiting or can be severe and life threatening like toxic epidermal necrolysis (TEN).[4]

Atopy, genetic variations in drug metabolism, HLA variation, comorbidities, underlying disease, active viral infection, immune status of the patient, and concomitant intake of other drugs can alter the rate, presentation, course, and the outcome of CADRs.[3] Only about 50% of drug reactions can be detected in the premarketing trials.[6]

Patients can be educated to avoid re-administration of the offending drug(s) to reduce the morbidity associated with CADRs.[7] Also early identification of SCADRs can reduce the morbidity and mortality rates. Also early identification of SCARDs can reduce morbidity and mortality.

This study was conducted to determine the pattern of various types of CADRs, to find out the causative drug(s) involved and to determine the response to treatment and outcome in patients with CADRs.

Patients and Methods

This prospective study was done in the department of dermatology. The period of study was from 1st December 2014 to

How to cite this article: Jha N, Alexander E, Kanish B, Badyal DK. A study of cutaneous adverse drug reactions in a tertiary care center in Punjab. Indian Dermatol Online J 2018;9:299-303.

Received: March, 2018. **Accepted:** April, 2018.

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_81_18

Quick Response Code:

30th June 2016. A total of 258 patients suspected to have CADR were examined. Patients having moderately severe CADRs with extensive rash or systemic involvement and all patients having SCADR were admitted for further management.

Patients who refused to give consent, patients with generalized pruritus without skin lesions, those patients who developed drug reactions due to intake of indigenous medications and those who could not recall the names of the medicines consumed were excluded from the study.

A detailed history was taken, careful clinical examination was done and significant findings noted.

Final decision of causality was done according to Naranjo adverse drug reaction probability scale.[8]

Culprit drug was determined based on the chronology from the introduction of the drug to the onset of symptoms. If more than one drug was thought to be responsible, then the most likely offending agent was noted and withdrawn.

RegiSCAR criteria was used for diagnosing DRESS syndrome.[9-14] To evaluate prognosis in patients of TEN, SCORTEN criteria was used.[15-18] The severity of the reaction was graded according to the University of Virginia Health System Adverse Drug Reaction Reporting Program criteria as mild, moderate, or severe.[19] Confirmation of the drug rash was done by dechallenging.

Complete blood count, microscopic examination of urine, random blood sugar (RBS), liver enzymes, blood urea, and serum creatinine were carried out in all patients. Biochemical investigations like liver function tests (LFTs), serum electrolytes, and chest x-rays were done in patients with SCADRs to rule out systemic involvement.

Frequencies and proportions were calculated using Chi-square test and *t*-test as the tests of significance and *P* value <0.05 was considered statistically significant. Data was analyzed using SPSS version 21.

Results

A total of 258 patients were enrolled in the study and male: female ratio was 1.32:1. Maximum number of patients were in the age group of 20–40 years (32.94%).

Minimum reaction time noted was 5 min in a patient who developed angioedema after taking Septran (Trimethoprim-Sulfamethoxazole) whereas maximum reaction time was noted to be 2 months in a patient who developed palmo-plantar keratoderma (PPK) after taking imatinib mesylate for chronic myeloid leukemia (CML).

Overall, 5.43% of patients developed fever, 2.33% had abdominal pain, and 7.36% had dyspnea after the intake of the causative drug. Fifty-eight patients (22.48%) with CADR recollected taking same drug or drug of the same pharmacological group previously. One hundred and eighteen patients (45.74%) denied taking the same drug or drug of the same group previously and 82 patients (31.78%) could not recollect if they had taken the same drug (or any other drug of the same pharmacological group) in the past. Thirty-two patients (12.40%) had personal or family history of atopy. No significant association with underlying comorbidities was found.

The most common CADR observed was exanthematous drug eruption in 110 patients (42.63%), followed by drug induced urticaria in 55 patients (21.32%) and FDE in 24 (9.30%) [Figures 1-3]. The common CADRs noted in the study are shown in Table 1.

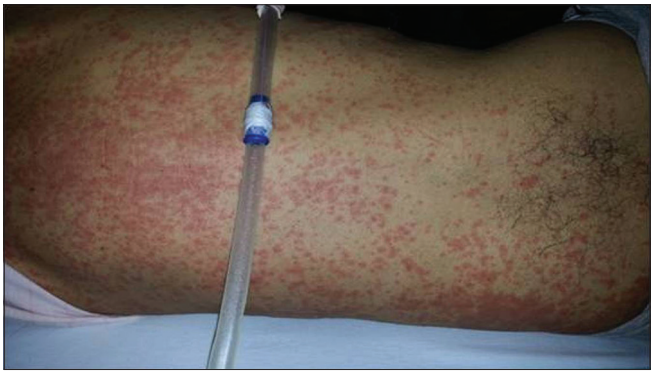

Figure 1: Exanthematous drug rash

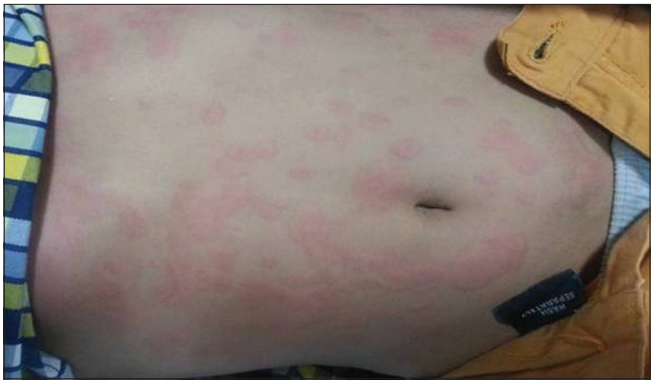

Figure 2: Urticarial drug rash

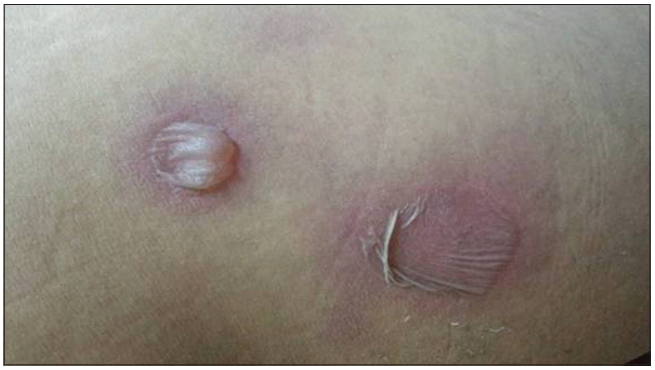

Figure 3: Bullous fixed drug eruption

Table 1: Common clinical types of CADRs

Type of CADR	Frequency	Percentage (%)
Exanthematous drug eruption	110	42.64
Drug-induced urticaria	55	21.32
Fixed drug eruption	24	9.30
Angioedema	23	8.91
Acneiform eruption	21	8.14
Erythema multiforme	9	3.49
Photosensitive dermatitis	8	3.10
SJS-TEN	6	2.32
DRESS syndrome	2	0.77
Exfoliative dermatitis	2	0.77
Acute generalized exanthematous pustulosis	2	0.77

DRESS = Drug reaction with eosinophilia and systemic symptoms

Antimicrobials (64.73%) were the most common offending drugs followed by NSAIDs (15.50%) and antiepileptics (7.36%). Among the antimicrobials, cephalosporins were the most common (16.67%), followed by fluoroquinolones (8.91%) and carbapenems (7.75%).

Fluoroquinolones were responsible for causing CADRs in 23 patients (8.91%). Of the 23 cases, 18 (78.26%) were caused by first generation fluoroquinolones (ciprofloxacin, norfloxacin, and ofloxacin) and the remaining 5 (21.74%) were caused by newer generation fluoroquinolones (levofloxacin mainly).

The most common drug group causing exanthematous drug eruption was cephalosporin (22.73%), followed by carbapenems (17.27%), antiepileptics (11.82%), and beta lactamase inhibitors (11.82%).

P value (for drugs causing exanthematous drug eruption) was found to be statistically significant (<0.05) for cephalosporins, carbapenems, antiepileptics, beta-lactamase inhibitors, and NSAIDs.

Drug-induced urticaria was the second most common drug eruption noted in the study. Most common drug causing urticaria noticed was cephalosporin (27.27%), followed by NSAIDs (23.64%) and fluoroquinolones (14.54%). *P* value (for drugs causing urticaria) was found to be statistically significant (<0.05) for cephalosporins only. 8.14% of patients having urticarial or exanthematous rash had history of atopy.

The third most common drug eruption in the study was FDE. Most common drug causing FDE was NSAIDs (33.33%), followed by fluoroquinolones (29.17%) and nitroimidazoles (16.67%). *P* value (for drugs causing FDE) was found to be statistically significant (<0.05) for NSAIDs, fluoroquinolones, and nitroimidazoles.

Mucosal involvement was seen in 27.52% patients.

Causality assessment was done by Naranjo adverse drug reaction probability scale. Definite drug rash was seen in (30.62%) and probable drug rash in 69.38% patients. Patients suspected to have possible drug rash were not included in the study.

According to the University of Virginia Health System Adverse Drug Reaction Reporting Program criteria, 23 patients (8.91%) had mild reaction and did not require any treatment or prolongation of hospital stay, 223 (86.43%) patients had moderate type of CADR and required treatment and/or prolongation of hospitalization by at least 1 day. Most of these patients responded to antihistamines and topical steroids. Patients with extensive rash or systemic involvement who denied admission were treated with oral corticosteroids. Those patients who were admitted were treated with intravenous corticosteroids (injection hydrocortisone) and injection pheniramine maleate. All patients having moderate type of CADR responded well to the treatment. Drug withdrawal was done in all cases except for cases of acneiform eruption due to antituberculous drugs. Remaining 12 (4.65%) patients had severe type of reaction that was potentially life threatening.

Among 258 cases of CADRs included in the study 12 patients (4.65%) had SCADRs. Among the SCADRs, SJS-TEN was the most common (50%, 6/12) followed by DRESS syndrome, exfoliative dermatitis, and AGEP (16.67%) [Figures 4-6].

Of the 12 cases with SCADRs 6 patients were males and 6 were females (male: female ratio = 1:1).

The shortest reaction time was 1 hr in a patient who developed SJS after taking ciprofloxacin and maximum reaction time noted was 6 weeks in a patient who developed TEN after taking allopurinol.

The most common group of drugs causing SCADR was the antituberculous group (33.33%), followed by fluoroquinolones (25%), cephalosporins (16.67%), and penicillin (8.33%).

Eosinophilia was present in five patients (41.67%) with SCADRs, eight patients (66.67%) had deranged liver enzymes and four patients (33.33%) had deranged renal profile.

Ophthalmological complications (corneal opacities) were seen in two patients. Two patients died (one had developed sepsis and the other developed bronchopneumonia). Other patients of SCADRs responded well to the treatment.

Discussion

In our study, a slight male predominance (male:female = 1.32:1) was seen which is in conformity with the study done by Patel and Marfatia.[7] In contrast, certain studies done by Pudukadan and Thappa and Nandha *et al.* showed a female preponderance.[5,20]

A lower frequency of atopy was found in our study (12.40%), comparable to the findings of Inbaraj

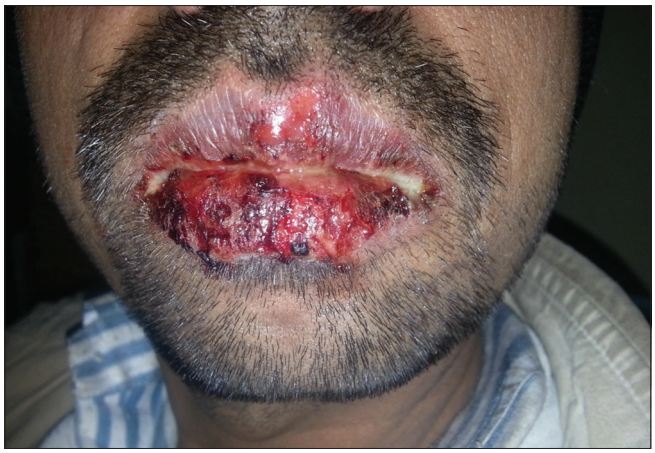

Figure 4: Steven–Johnson syndrome

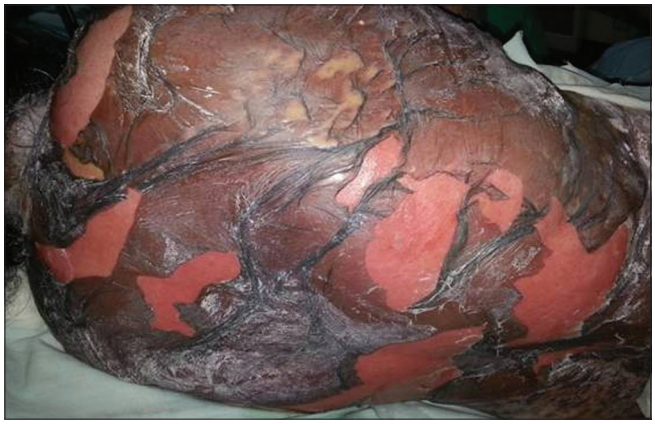

Figure 5: Toxic epidermal necrolysis

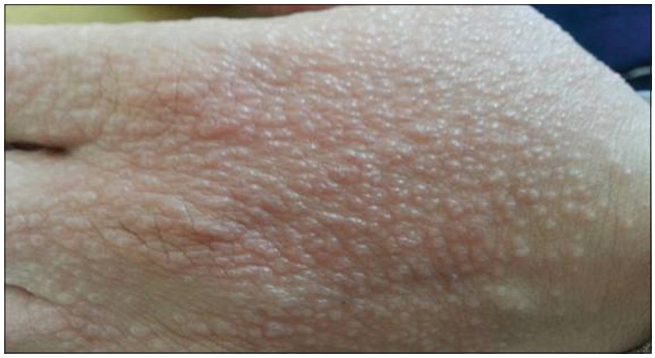

Figure 6: Acute generalized exanthematous pustulosis

et al. where 6.8% patients were found to have bronchial asthma.[21] In contrast, study done by Al-Raaie *et al.* found 21.0% patients to have personal or family history of atopy.[6] In our study, only 8.14% patients presenting with urticarial or exanthemaous drug rash had history of atopy but Al Raaie *et al.* found history of atopy in 44% of cases of urticarial or morbiliform rashes.[6]

Most common presenting symptom in our study was rash (82.55%). This frequency was found to be high in comparison to study by Pudukadan and Thappa (56.7%).[5] This could be because the most common CADR seen in our study was exanthematous type of CADR whereas Pudukadan and Thappa found FDE to be the most common CADR in their study.

Most common CADR noted in our study was exanthematous drug eruption (42.64%) in conformity with the studies done by Saha *et al.* (30.18%), Choon *et al.* (42.3%), Nandha *et al.* (42.85%), Sharma *et al.* (34.6%), Noel *et al.* (35%), and Hiware *et al.* (37.7%).[1,4,20-24] AL Raaie and Banodkar found drug induced urticaria (35%) whereas Pudukadan and Thappa found FDE to be the most common CADR.[5,6] This variation could be due to the difference in the pattern of drug utilization, the reaction rates of the drugs and the pharmacogenetic traits of the population being studied.[5]

Antimicrobials were the most common causative drugs noted in our study (64.73%). This is in concordance with other studies by Choon *et al.* (77.1%), Pudukadan *et al.* (58.88%), and Nandha *et al.* (48.3%).[4,5,20] Al-Raaie *et al.* found NSAIDs to be the most common causative drug, whereas Noel *et al.* found antiepileptics to be the most common offending drug in their study (44%).[6,23] Different patterns of drug usage in different populations studied can explain this variation.

Cephalosporins were the most common antimicrobials causing CADRs in our study, responsible for about 16.67% of cases. This number is much higher than the number published by Thakkar*et al.* which (3.75%).[25] Increased use of antibiotics may be why cephalosporins were found to be the most common offending drug group.

The most common offending drugs group causing exanthematous drug eruption noted in our study was cephalosporins (22.73%). On the contrary, Amrinder et al, found ampicillin to be the most common drug causing exanthematous drug eruption by Amrinder *et al*.[26] Saha *et al.* and Noel *et al.* found antiepileptics to be the most common drugs causing exanthematous type of CADR.[1,23]

We found a higher incidence of mucosal involvement (27.52%) the study by Inbaraj *et al* (5.1%).[21]

A lower frequency of altered LFTS (15.50%) and RFT (12.40%) was found in comparison to the study done by Pudukadan and Thappa.[5]

SCADRs accounted for 4.65% of the total CADRs which is much lower than the incidence noticed by Saha *et al.* (32.04%) and Sasidharan Pillai *et al.* (13.20%).[1,10] Lower incidence of SCADRs in our study can be explained by early recognition of drug eruption, early withdrawal of the suspected drug, and proper management of patients, halting progression of the drug eruption.

SJS-TEN was the most common SCADRs (2.32%), which is in conformity with studies by Choon *et al.* (30.39%) and Patel *et al.* (6.84%).[4,27]

Most of the studies have reported antiepileptics to be the most common drugs causing SCADRs.[4,10,23] But we found anti tuberculous drugs to be the causative agent in most of the SCADRs which may be explained by the increased burden of tuberculosis in this region.

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, response to rechallenging (not done in our study) with the suspected offending drug, and any past history of similar reactions can help in diagnosing CADRs. Early identification of CADRs can reduce the morbidity and mortality. Patients can be educated to avoid self administration of drugs and readministration of the offending drug(s) to prevent further morbidity in the patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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