*Journal of Pakistan Association of Dermatologists*. 2017;**27 (2)**:158-163.

**Original Article**

# Cutaneous adverse drug reactions profile in a tertiary care hospital in North India

**B.K. Brar, Jashandeep Kaur, Sumir Kumar, Naveen Sethi, Raj Kumar***

Department of Dermatology, GGS medical College, Faridkot, Punjab, India
* Department of Pharmacology, GGS medical College, Faridkot, Punjab, India

## Abstract

***Objective*** To document drugs causing the cutaneous adverse effects and the morphology of these reactions.

***Methods*** This observational study was carried out at Department of Dermatology in a tertiary care hospital for two years to study the cutaneous adverse drug reactions (cADRs) and identify the culprit drug or drugs. A total of 188 patients reporting to dermatology department with cutaneous adverse drug reactions were evaluated. Detailed history, as well as, clinical examination findings were recorded along with investigations wherever required and feasible.

***Results*** The commonest drug reaction was found to be fixed drug eruptions (29.2%) followed by urticaria (20.7%). The most common class of drugs implicated was NSAIDs in 37.2% of patients followed by antimicrobials in 30.3% of patients. The males in our study outnumbered the females.

***Conclusion*** The clinical patterns and causative agents observed during our study were similar to those observed in other studies except for few variations. When a patient is exposed to new drugs, each time the pharmacokinetic and pharmacodynamic conditions are different. So outcome of drug intake is unpredictable.

***Key words***
Cutaneous adverse drug reactions, pharmacovigilance, rash.

## Introduction

Drugs are primarily used to cure or to provide relief from various diseases but sometimes they prove wolf in sheep's clothing and themselves result into misery. The definition of adverse drug reactions as given by WHO is 'any response to a drug which is noxious and unintended and which occurs at doses, normally used for prophylaxis or diagnosis or therapy or disease or for modification of physiological function'. It excludes supratherapeutic doses, drug abuse and treatment failure and errors, which occur while drug administration.[1]

Many of the commonly used drugs have reaction rates above one percent.[1] Cutaneous ADRs can range from a transient maculopapular rash to fatal toxic epidermal necrolysis (TEN).[2] Severe drug reactions like SJS/TEN leads to hospitalization. Commonly used drugs that are implicated in causing ACDRs are antimicrobials like penicillins and cephalosporins followed by fluoroquinolones, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants.[3] NSAIDS and antibiotics are commonly used drugs as they are freely available over the counter drugs.

**Address for correspondence**
Dr. Jashandeep Kaur,
Department of Dermatology, GGS Medical College, Faridkot, Punjab, India.
Email: jashanchail@yahoo.com

Reporting of adverse drug reactions(ADRs) is extremely important. It helps to predict the type of drug reaction and the corresponding causative agent in a particular set of population. This information will further help in evaluating if there is any underlying genetic or metabolic susceptibility to a particular drug reaction in a particular population. It further helps in taking measures to reduce the harmful effects to the patients and in turn betterment of the public health. Many new drugs come into existence every day, so reporting of ADRs is extremely important for continuous scrutiny of these drugs and withdrawal as well as replacement of harmful ones.

Present study was undertaken to find out the drugs causing the cutaneous adverse effects and the morphology of these reactions.

## Methods

In this study 188 patients reporting to dermatology department from June 2014 to June 2016 with cutaneous adverse effects of the various drugs were evaluated. An observational, prospective study was conducted. A detailed history regarding age, gender, type of drug intake, dosage, duration, frequency, type of cutaneous rashes, time interval between drug intake and appearance of cutaneous lesions and indications of drug intake were noted.

Improvement in cutaneous eruption after stoppage of drug or decreasing the dosage of drug along with the associated systemic symptoms was also recorded. A detailed clinical examination along with the mucocutaneous examination was conducted on each reporting patient. Morphology of different cutaneous lesions were noted. Routine investigations along with the specific ones like acute eosinophil counts (AEC) and drug allergy tests wherever required and feasible were performed. Any past history of similar kind of eruptions and number of episodes were also noted. At the end of the study the data was analyzed.

## Results

Out of 188 patients, 107 were males and 81 were females. So the ratio was 1.32:1 (M:F). Most common age group affected was 21-40 years (35.6%) followed by age group 41-60 years (27.7%) and least common being less than 20 years (11.2%) as shown in **Table 1**.

The most common class of drugs implicated was NSAIDs (37.2%) followed by antimicrobials (30.3%) with number of patients 70 and 57 in each category respectively as shown in **Table 2**.

The most common cutaneous ADR seen was fixed drug eruptions (FDE), (29.3%), [**Figure 1**] followed by urticaria (20.7%) and maculopapular rash. Severe cutaneous adverse

**Table 1** Incidence of cutaneous adverse drug reactions in different age groups.

| *Age group* | *%* |
|---|---|
| < 20 years. | 11.2% |
| 20-40 years | 35.6% |
| 41-60 years | 27.7% |
| > 60 years | 25.5% |

**Table 2** Different classes of drugs with frequency of cutaneous adverse drug reactions (n=188).

| *Class of drugs* | *%* |
|---|---|
| Nonsteroidal inflammatory drugs | 37.2% |
| Antimicrobials | 30.3% |
| Anticancer drugs | 8.0% |
| Antiepileptics | 5.8% |
| Miscellaneous | 18.6% |

**Table 3** Morphological types of drug eruptions

| *Type of adverse reactions* | *%* |
|---|---|
| Fixed drug eruption | 29.3% |
| Urticaria | 20.7% |
| Maculopapular rash | 16.0% |
| Severe cutaneous adverse reactions | 9.3% |
| Miscellaneous | 24.7% |

**Figure 1** Fixed drug eruption due to nonsteroidal inflammatory drug.

**Figure 2** Toxic epidermal necrolysis due to phenytoin.

**Table 4** Uncommon cutaneous adverse drug reactions.

| *Type of reaction* | *Causative drug* |
|---|---|
| Phlebitis | Vancomycin, ranitidine |
| Segmental purpura | Injection diclofenac |
| Onycholysis | Anticancer drugs |
| Melasma | NSAIDS(chronic use) |
| Photodermatitis | Cetirizine |
| Erythema multiforme | Methylcobalamine |
| Mucositis | Methotrexate |
| Milaria crystallina | Erythropoietin |
| Aggravation of acne | Infusion vitamin B12 |
| Thrombocytopenia | Terbinafine |

drug reactions (SCARs) were noted in 9.3% of patients. 24.7% of patients represent miscellaneous cADRs (**Table 3**). The time interval between drug intake and appearance of cADRs ranged from few minutes to one and a half month.

Individual drugs causing different cADRs were noted, out of which few were rare observations. Some of the interesting and rare drug reactions were reported as given in **Table 4**.

## Discussion

Cutaneous adverse drug reactions have different morphological and distributional patterns. They can be acute or chronic. The common morphologic patterns observed during various studies are exanthematous rashes, urticarial rashes, fixed drug eruption and erythema multiforme.[4] In our study, fixed drug eruption (FDE) was the most common drug eruption (29.3%), followed by urticarial rash (20.7%). The analysis of the data by Chatterjee *et al*.[5] also shows that urticaria and fixed drug rashes were the most common morphological reaction types. An Indian study found FDE in 30% of the total patients enrolled which is in consonance with our study.[6] Our patients being from rural background, usually take treatment from local practitioners which leads to non reporting/underreporting of milder forms of side effects like maculopapular rash and urticaria. Another reason for this variation could be due to difference in the local trends of drug usage in different populations.

The most common class of drugs implicated was NSAIDs (37.2%) followed by antimicrobials (30.3%) in our study. Among NSAIDs, diclofenac was found to be the most common causative agent. Because of lack of awareness among rural masses, they prefer taking over the counter medications as well as visiting local practitioners which usually prescribe them pain killers in form of NSAIDs. These drugs were found to be the most common agents in causing FDE and urticarial rashes in our study (**Figure**

**1**). Among antimicrobials, antibiotics were found to be culprit in 41 cases followed by antifungals in 10 cases. Remaining 6 were due to antitubercular and antiretroviral drugs. Penicillins and cephalosporins were the main antibiotics found to be causing cADRs followed by fluoroquinolones and macrolides. Nandha *et al*.[7] and Naldi *et al*.[8] found antimicrobials as the most common culprit drug class followed by NSAIDs.

The male to female ratio was 1.32:1 in our study, which was in conformity with another study from Gujrat.[9] Sushma *et al*.[10] also found a male preponderance in their study. The majority of our patients belonged to the age group between 21-40 years. However, few other studies reported that the elder people are more commonly affected suggesting that adverse reactions to drugs increase with age.[11,12,13] This may be due to the multiple drug intake by the elderly for multiple diseases concomitantly, more tendency for drug-drug interactions and altered drug pharmacokinetics by the body because of decreased functioning of various systems of the body. Education, socioeconomic status and awareness among people matters and results into variations in health care seeking behavior in different groups of population.[6]

SCARs constituted 9.3% of total cADRs in our study. However, higher incidence of SCARs (14.4%) were reported in the study from Chandigarh.[6] Reason for this difference could be the presence of higher referral center at Chandigarh where severe cases are referred for management. SCARs include Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme major (EMM) and such other severe dermatological reactions. In consonance with earlier study,[6] antiepileptics were found to be the major class implicated in causation of Steven-Johnson syndrome/toxic epidermal necrolysis (**Figure 2**). Two patients in our study were found to be suffering from drug rash with eosinophilia and systemic symptoms (DRESS), out of which one was due to NSAIDS and the other was due to antibiotics. DRESS syndrome is often misdiagnosed to be pyrexia of unknown origin by the attending physician due to presence of fever along with systemic symptoms and because of the time interval between the prescribed drug and the appearance of DRESS syndrome. So it should be kept in mind by the physicians and budding dermatologists while dealing with patients with fever and rash.

Three patients out of 188 was suffering from HIV and two of them presented with exfoliative dermatitis due to nevirapine and one reported with TEN due to nevirapine. Mucosal involvement was also recorded and was seen in 9.0% patients and was mainly in form of ulcers and mucosal candidiasis. All of the patients with SJS/TEN had one or more mucosal area involved.

Another important aspect of cutaneous adverse drug reactions is the medicolegal aspect. The patient should be educated about the ill effects of the drug. History of any sensitivity to drug and to avoid those drugs, as well as, the ones, which can cross-react is equally important.

Severe drug reactions like erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis can prove fatal, so their timely diagnosis and appropriate management is emphasized to reduce the mortality and morbidity. Special care is to be taken of electrolyte balance and aseptic measures in such cases. A physician should advise the patient to carry an information card with complete data about sensitizing medications always with him or her and to show it wherever needed. Clinicians should not advise patient to start any new drug at night until necessary.

Proper history taking about all drugs taken in past few months is very important, as usually drugs taken in remote past turn out to be culprit drugs instead of those taken in recent past, which are often erroneously thought as and are withdrawn.

Complete record of culprit medications are sometimes, not available with the patients. Most of the patients themselves are unaware of type of medications they are using because of illiteracy or lower levels of education. Polypharmacy is another limitation. Despite the limitations, this study stresses that health care providers should realize the importance of reporting cADRs.

Few viral exanthems and bacterial infections may present with morphology similar to drug rash which can pose a difficulty in reaching an accurate diagnosis. So there is need to consider this point while examining a patient. Appropriate present and past history is mandatory. Various laboratory investigations like blood culture and enzyme levels can prove helpful in excluding other differential diagnosis. For example, measles can be easily confused with drug rash. So clinical features and serological laboratory investigations will be helpful in such cases.

The main limitation of this study was that drug rechallenge test was not performed due to ethical reasons. Positive rechallenge tests help in finding the exact etiological drug in a particular reaction. It adds to reliability and helps decreasing false positive cases. Long-term follow-up and monitoring of patients could not be done as patients did not turn up once they got cured.

Various observations made in our study emphasize the need for a strict and efficient pharmacovigilance system. Although the risk of adverse drug reactions is unavoidable, still there is a need to lessen the incidence of this problem in clinical practice. Newer drugs are invented every day. Changing trends in use of drugs makes it necessary that more studies should be conducted to alert the clinicians and curtail the height of this problem. Tests to investigate the underlying genetic and metabolic make up of the patient along with the other details like age, other systemic disorders, multiple drug therapy are as important as the pharmaceutical details of the drug for medical practitioners to avoid these adverse drug reactions to some extent.

## Conclusion

Self-medications and over-the-counter drugs in developing countries such as India are the major hurdle in conduction of studies on cADRs. There is a need of systematic approach to curb this problem. Collective role of the patient, the physician and the manufacturer is necessary to reach the roots. Physicians should update themselves regarding new cADR patterns which are emerging due to discovery of new drugs every year which are basically launched to benefit the people but they bring with them the adverse effects, too. Special attention is to be taken while prescribing high risk drugs like NSAIDs and antibiotics. Patient should be warned to report early if he or she notices any untoward effect of prescribed medications and to stop the drug immediately. Alternates to the known high risk drugs should also be sought out to decrease the sufferings, hence incidence of cADRs.

## References

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;**331**:1272-85.
2. Sharma VK, Sethuraman G. Adverse cutaneous reactions to drugs: An overview. *J Postgrad Med*. 1996;**42**:15-22.
3. Sengupta SR, Das NK. Cutaneous adverse drug reaction to systemic drugs: Recent

updates. In: Ghosh S, editor. *Recent Advances in Dermatology. 1st ed*. New Delhi: Jaypee Brothers Medical Publishers; 2004. P. 88-114.

4. Stern RS, Wintroub BU. Cutaneous reactions to drugs. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, et al, editors. *Fitzpatrick's Dermatology in general medicine. 5th ed*. New York: McGraw-Hill; 1999. P. 1634-42.
5. Chatterjee S, Ghosh AP, Barbhuiya J, Dey SK. Adverse cutaneous drug reactions: A one year survey at a dermatology outpatient clinic of a tertiary care hospital. *Indian J Pharmacol*. 2006;**38**:429-31.
6. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: Clinical pattern and causative agents-A six-year series from Chandigarh, India. *J Postgrad Med*. 2001;**47**:95-9.
7. Nandha R, Gupta A, Hashmi A. Cutaneous adverse drug reactions in a tertiary care teaching hospital: A North Indian perspective. *Int J Appl Basic Med Res*. 2011;**1**:50-3.
8. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E *et al*. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol.* 1999;**48**:839-46.
9. Suthar JV, Desai SV. A study of adverse cutaneous drug reactions in outdoor patients attending to Skin and V.D. Department of Shree Krishna Hospital, Karamsad. *Int J Res Pharm Biomed Sci.* 2011;**2**:2229–3701.
10. Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse drug reactions: A 9-year study from a South Indian Hospital. *Pharmacoepidemiol Drug Saf*. 2005;**14**:567-70.
11. Leape LL, Troyen AB, Laird N, Lawthers AG, Localio AR, Barnes BA *et al*. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med*. 1991;**324**:377-84.
12. Hafner JW, Belknap SW, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. *Ann Emerg Med*. 2002;**39**:258-67
13. Sullivan JR, Shear NH. Drug eruptions and other adverse drug effects in aged skin. *Clin Geriatr Med*. 2002;**18**:21-42.