Clinical Spectrum of Cutaneous Adverse Drug Reactions

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Abstract

Background: Cutaneous adverse drug reactions (CADRs) are common, comprising 10%–30% of all reported adverse drug reactions (ADRs) and its incidence in hospitalized patients is 2%–3%. Aims: The aim is to study the different clinical spectrum of CADRs in outpatient and inpatient and to find out the offending drug. Settings and Design: A prospective observational, nonrandomized hospital-based study was conducted at a tertiary care hospital over a period of 12 months. Materials and Methods: Patients presenting with suspected drug-related cutaneous lesions were included if drug identity could be ascertained. Clinical profiling was done. The severity of the reaction was assessed using modified Hartwig and Siegel ADR severity assessment scale. Statistical Analysis Used: Data were analyzed using Stata Version 13. Results: Out of the total study population, most commonly observed cutaneous ADRs were fixed drug reaction in 28.75%, followed by maculopapular drug rash in 26.3%, and urticarial rash in 20.6%. Few less frequently observed CADRs were a lichenoid eruption, acneiform eruption, and baboon syndrome, generalized pruritus, pityriasis rosea, and vasculitis. Antimicrobials accounted for 37.5% of the total followed by nonsteroidal anti-inflammatory drugs 25%, anti-epileptics 12.5%, and antifungal 6.25%. Anti-retroviral therapy contributed 3.125%, whereas 1.875% were due to Anti-Koch’s therapy. About 28.1% of patients were taking monotherapy, whereas 71.9% of patients were received polytherapy. Conclusions: Wide spectrums of drug reaction were observed in this study. Sound knowledge of these drug eruptions may help the clinician to diagnose and effectively manage their cases. Polypharmacy is a well-known predictor of ADRs in children and adults.

Keywords: Cutaneous adverse drug reactions, drug rash, fixed drug reaction

Introduction

Drug reactions are unwanted reactions that occur following the administration of drugs and are not characteristic of the desired pharmacodynamics effects of the drug. Adverse drug reactions (ADRs) cause a major problem in drug therapy. Most of the reactions often are underreported, and many questions regarding the pathogenesis are yet to be addressed. Despite attempts at monitoring by the government and by the pharmaceutical industry, it is very difficult to obtain proper and detailed information about the incidence of drug reactions. Cutaneous ADRs (CADRs) are common, comprising 10%–30% of all reported ADRs and its incidence in hospitalized patients is estimated to be 2%–3%. They vary from localized and transient erythema to severe forms. The common CADRs are maculopapular skin rash, urticaria, fixed drug eruption (FDE), angioedema, and contact dermatitis. Serious CADRs endangering patient’s life are Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP). SJS has mortality rate <5%, whereas the rate for TEN approaches 20%–30%.

The common offending drugs are antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-epileptic drugs, and anti-gout agents. The morphology of drug-induced lesion gives us a clue for early identification of serious drug reaction, and hence, it is mandatory for a dermatologist or treating physician to pick up these early signs and prompt withdrawal of drug if possible.

The purpose of this study is to identify the pattern of drug-induced cutaneous adverse reactions in patients and establish the causal link between the drug and reaction. A high degree of suspicion is required to make a prompt diagnosis which is crucial in the management of CADR.

Materials and Methods

This prospective, observational study was conducted on patients with CADR to study the most common pattern

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How to cite this article: Agrawal A, Ghate S, Gupta AK, Dhurat R. Clinical spectrum of cutaneous adverse drug reactions. Indian J Drugs Dermatol 2018;4:61-6.
of reaction and offending drug(s). Patients were clinically evaluated and recruited for the study if they fulfilled the inclusion and exclusion criteria and gave willing consent for participation. The study was commenced after acquiring clearance from the Institutional Ethics Committee and conducted between 2015 and 2016. Patients not giving consent for the study, patients who developed drug reactions following intake of homeopathic, Ayurveda, and indigenous medicines were excluded from the study. Confidentiality of the information obtained was assured throughout the study. Information of all the patients including relevant history, clinical examination details, and drug therapy were noted in the pretested proforma. List of drugs taken before the appearance of reaction, whether monotherapy or polytherapy, presenting complaints, period, duration of symptoms, severity, the reason for drug intake, history, and drug-involved were recorded. The WHO causality definitions were used to assess the suspected offending drug. It classifies ADRs into “certain,” “probable,” “possible,” “unlikely,” “unclassified,” or “unclassifiable.”

**Results**

A total of 160 drug reaction patients were included in the study from patients attending the dermatology outpatient department (OPD). The following observations and results were obtained. The mean age of the patients was 30.06 years. Maximum patients \( n = 42 \) were in the age group of 21–30 years, accounting for 26.3% of the total; followed by 31–40 years accounting for 20.6%. The age range was 7 months–73 years. 93 patients (58.1%) were male, 67 patients (41.9%) were female.

Among the various known patterns of CADR [Table 1], most common CADR noted was fixed drug reaction in 28.75% of patients, followed by maculopapular rash in 26.3%, urticaria in 20.6%, erythema multiforme in 8.1%, SJS in 3.8%, angioedema in 1.9%, and AGEP in 1.9%, TEN [Figure 1] in 1.9%, drug induced eosinophilia and systemic syndrome (DRESS) [Figure 2] in 1.9%, exfoliative dermatitis [Figure 3] in 1.3%, lichenoid eruption, acneiform eruption and baboon syndrome, generalized pruritus, pityriasis rosea, and vasculitis in 0.6% of patients each.

The time period between patient ingesting the drug and appearance of symptoms was noted and the mean time period was evaluated. About 45.6% of patients developed symptoms within 2–5 days of drug intake, 32.5% of patients developed in 1 h to 1 day, 10.6% of patients in 6–10 days, 6.3% in <1 h, 3.8% of patients developed reaction in >14 days.

The time periods of development of symptoms after drug intake (lag period) of different types of reaction were noted [Table 2]. The mean lag period of angioedema was lowest, i.e., 10 h followed fixed drug reaction by 21.70 h. Mean lag period for urticaria was 35.27 h, SJS and TEN were 3.69 days and 3.66 days, respectively. Vasculitis and

### Table 1: Distribution of pattern of reaction in study population

| Type of reaction                        | Frequency (%) |
|----------------------------------------|---------------|
| Fixed drug reaction                    | 46 (28.7)     |
| Maculopapular rash                     | 42 (26.3)     |
| Urticarial eruption                    | 33 (20.6)     |
| Erythema multiforme                    | 13 (8.1)      |
| Steven johnson syndrome                | 6 (3.8)       |
| Angioedema                             | 3 (1.9)       |
| Acute generalised exanthematous pustulosis | 3 (1.9)     |
| Toxic epidermal necrolysis             | 3 (1.9)       |
| DRESS                                  | 3 (1.9)       |
| Exfoliative dermatitis                 | 2 (1.3)       |
| Acneiform eruption                     | 1 (0.6)       |
| Baboon syndrome                        | 1 (0.6)       |
| Generalised pruritus                   | 1 (0.6)       |
| Lichenoid rash                         | 1 (0.6)       |
| Pityriasis rosea                       | 1 (0.6)       |
| Vasculitis                             | 1 (0.6)       |
| Total                                  | 160 (100.0)   |

DRESS: Drug reaction with eosinophilia and systemic symptom

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**Figure 1:** Peeling of skin over eyelid, lips, scrotum in case of toxic epidermal necrolysis secondary to nevirapine

**Figure 2:** Drug induced hypersensitivity syndrome (drug reaction with eosinophilia and systemic symptoms) secondary to dapsone
AGEP developed in a mean period of 3 days and pruritus and pityriasis rosea in 4 days. Maculopapular rash and erythema multiforme took 5.66 and 5.73 days. Exfoliative dermatitis and baboon syndrome both developed in 7 days. DRESS in 9.33 days, Acneiform eruption in 10 days and lichenoid drug reaction in 15 days.

History of drug reaction was present in 18.8% of patients and no previous history in 81.3% of patients. In our study, out of 30 patients with past history of reaction, 63.33% of patients developed a mild reaction, 23.33% of patients developed moderate, whereas severe reactions were noted in 13.33%. Among patients with history of drug reaction, FDE was found in a maximum number of patients ~53.33%, followed by urticarial in 16.66%, 13.33% of maculopapular rash, 10% of patients with erythema multiforme, and 0.6% of exfoliative dermatitis and SJS each. In our study group, 36.88% of the patients took medicine for fever.

The severity of drug reaction among patients at the time of the presentation was recorded. Maximum number of patients, 113 (70.6%), had mild reaction; 27 patients (16.9%) had moderate reaction; whereas 20 patients (12.5%) had severe reaction.

Among 160 patients, 60 patients were suspected to have CADRs due to antimicrobials, accounting 37.5% of total; followed by NSAIDS at 25%; anti-epileptics at 12.5%; antifungals at 6.25%; Anti-retroviral therapy (ART) contributed 3.125%; 1.875% were due to Anti-Koch’s therapy; whereas others drug contributed 13.125% of the total [Table 3]. In our study, beta-lactams and diclofenac were the most common implicated drug causing urticaria, followed by fluoroquinolones and ibuprofen. We also found one case each of urticaria due to the sulfa drug, naproxen, and nitroimidazole.

Maculopapular rash was most commonly caused by beta-lactams (n = 10) in our study followed by phenytoin (n = 7). Ibuprofen, fluoroquinolones both caused four cases. ART and diclofenac contributed three cases each of maculopapular rash.

Discussion

Cutaneous ADRs are distressing to the patient and physician. The development of skin eruption is frequently cited as a reason for discontinuation of treatment without taking the full therapeutic course. Furthermore, prescribing medicine to a previously sensitized patient, and prescribing a related medication with cross-reactivity are common medicolegal pitfalls and therefore should not be taken lightly. The rate of adverse reactions increases disproportionately with an increase in the number of

| Type of reaction                  | Mean time period between drug intake and symptoms | Frequency (number of patients) |
|----------------------------------|--------------------------------------------------|--------------------------------|
| Fixed drug reaction              | 0.91 days 21.70 hours                            | 46                             |
| Maculopapular rash               | 5.66 days 135.88 hours                            | 42                             |
| Urticarial eruption              | 1.47 days 35.27 hours                             | 33                             |
| Erythema multiforme              | 5.29 days 127.38 hours                            | 13                             |
| Steven johnson syndrome          | 3.69 days 88.67 hours                             | 6                              |
| Angioedema                       | 0.417 days 10 hours                               | 3                              |
| AGEP                             | 3 days 72.00 hours                                | 3                              |
| Toxic epidermal necrolysis       | 3.66 days 88.00 hours                             | 3                              |
| DRESS                            | 9.33 days 223.92 hours                            | 2                              |
| Exfoliative dermatitis           | 7 days 168.00 hours                               | 2                              |
| Acneiform eruption               | 10 days 240.00 hours                              | 1                              |
| Baboon syndrome                  | 7 days 168.00 hours                               | 1                              |
| Generalised pruritus             | 4 days 96.00 hours                                | 1                              |
| Lichenoid rash                   | 15 days 360.00 hours                              | 1                              |
| Pityriasis rosea                 | 4 days 96.00 hours                                | 1                              |
| Vasculitis                       | 3 days 72.00 hours                                | 1                              |

DRESS: Drug reaction with eosinophilia and systemic symptom, AGEP: Acute generalized exanthematous pustulosis.
The relative incidence rate of CADR among new patients attending dermatology OPD was found to be 6.2 per 1000 in our study. In our study, the mean age of the patient was 30.26 years, which is similar to Pudukadan and Thappa who reported the mean age of 37.06 years. Most patients in our study were of the age group 21–30 years comprising 26.3% of the study population. The youngest age was 7 months and the eldest was 73 years which was in accordance with a study done by Patel et al. most common age group was 21–39 years, accounting for 54.42% of the total. In the present study, patients <10 years of age contributed 10% and only 9.4% of patients were >50 years, which correlates well with study done by Jhaj et al. Hence, according to the studies, it is observed that most of the drug reactions are in the middle age group, coinciding with high Indian population in this age group.

In our study, 58.1% were male (n=93) and 41.9% of females (n=67), which in accordance with the study done by Sharma et al. which had the male-to-female ratio 1.7:1.2. Sushma et al. also found a male preponderance in their study, which matches with gender distribution of the Indian population. This indicates that age and gender do not affect CADRs in the Indian population.

### Table 3: Association of drug with different type of cutaneous adverse drug reaction

| Probable drug      | Maculopapular rash (n) | FDE (n) | EM/SJS/TEN (n) | Urticaria (n) | Others |
|--------------------|------------------------|--------|----------------|--------------|--------|
| **Antimicrobials** |                        |        |                |              |        |
| Beta lactams       | 10                     | 8      | 4              | 7            | 2      |
| Floquinolones      | 4                      | 5      | 1              | 3            | 0      |
| Sulfas             | 0                      | 6      | 0              | 1            | 3      |
| Nitroimidazole     | 0                      | 3      | 1              | 1            | 0      |
| Macrolides         | 0                      | 1      | 0              | 0            | 0      |
| **NSAIDS**         |                        |        |                |              |        |
| Diclofenac         | 3                      | 4      | 1              | 7            | 0      |
| Paracetamol        | 0                      | 9      | 1              | 0            | 1      |
| Ibuprofen          | 4                      | 2      | 1              | 3            | 1      |
| Unspecified NSAID  | 1                      | 1      | 0              | 1            | 0      |
| **Antiepileptics** |                        |        |                |              |        |
| Phenytoin          | 7                      | 0      | 4              | 0            | 3      |
| Carbamazepine      | 2                      | 0      | 3              | 0            | 1      |
| **Antifungals**    |                        |        |                |              |        |
| Terbinafine        | 2                      | 1      | 0              | 0            | 2      |
| Fluconazole        | 1                      | 1      | 2              | 0            | 1      |
| ART                | 3                      | 0      | 2              | 0            | 0      |
| AKT                | 1                      | 0      | 0              | 0            | 2      |
| **Antimalarials**  | 1                      | 0      | 0              | 0            | 0      |

FDE: Fixed drug eruption, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, EM: Erythema multiforme, NSAIDS: Nonsteroidal anti-inflammatory drugs, ART: Anti-retroviral therapy, AKT: Anti-Koch’s therapy

### Table 4: Association of different drug with Stevens-Johnson syndrome/toxic epidermal necrolysis reaction

| Probable drug | SJS/TEN (n=9) |
|---------------|---------------|
| **Antimicrobials (1)** | Beta lactams |
| NSAIDS (2)    | Ibuprofen, paracetamol |
| Antiepileptics (3) | Phenytoin, carbamazepine |
| Antifungals (1) | Fluconazole |
| ART (2)       | Nevirpine |

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, ART: Anti-retroviral therapy, NSAIDS: Nonsteroidal anti-inflammatory drugs

### Table 5: Percentage of body surface area in monotherapy versus polytherapy

| Monotherapy or polytherapy | n   | Mean       | SD          | P   |
|----------------------------|-----|------------|-------------|-----|
| Percentage of body surface area |     |            |             |     |
| Monotherapy                | 45  | 24.8667    | 20.08120    | 0.942 |
| Polytherapy                | 115 | 25.1756    | 25.27099    | NS   |

SD: Standard deviation, NS: Not significant
In our study, 46 patients were of fixed drug reaction (28.7%), followed by 42 patients of maculopapular drug rash (26.3%), 33 patients of urticarial rash (20.6%), which was comparable to the study by Raksha and Marfatia.\cite{10} This is in accordance with the study by, Pudukadan and Thappa\cite{5} who reported 31.1% of patients with FDE, followed by maculopapular rash in 12.2%. Anjaneyan et al\cite{11} in their study found 23% of cases due to FDE and 25% due to maculopapular rash. Radhika et al\cite{12} reported most common reaction as FDE in 36.67% of patients.

In our study, the lag period between starting of the drug and appearance of symptoms varied between 2–5 days in 45.6% of patients. Nandha et al\cite{13} shows a maximum number of patients with a lag period of 2–14 days (80.2%). It is usually considered that chances of saving a life in severely affected patients are more when aggressive treatment is initiated within 72 h. If early withdrawal of the causative drug occurs, it improves the prognosis. Drugs with a long half-life are associated with an increased risk of death. The type of reaction and mean period also varied. In our study, the mean lag period of angioedema was lowest, i.e.,10 h followed by fixed drug reaction (21.70 h). Mean lag period for urticaria was 35.27 h, SJS and TEN were 3.69 days and 3.66 days, respectively. Patel et al\cite{6} reported incubation period for angioedema ranges from few minutes to 24 h, it ranges from 1 day to 4 weeks for urticaria, 1 day to 4 weeks were required for maculopapular rash, for FDE it varies from 1 day to 8 weeks which is similar to our study.

In our study, out of 160 patients, history of similar cutaneous reaction was present in 30 patients (18.8%), whereas 130 patients (81.3%) had no previous history. In the study done by Patel et al., history of CADRs was present in 18.92% of patients which is similar to our study. In our study, out of 30 patients with past history of reaction, 63.3% developed mild reaction and 13.3% developed severe reaction which is similar to Pudukadan and Thappa\cite{5}.

In our study group, most of the patients took medicine for fever accounting 36.88% of total (n = 52) followed by skin disorders (n = 24), seizures (n = 18) which are similar to study done by Saha et al\cite{14} in which medications used for fever accounted for the majority (41.5%). Raksha and Marfatia\cite{10} reported that most of the patients had taken medicine for pain, fever, and infection. The fact that CADR was most frequent in patients with fever and upper respiratory tract infection may be because this condition needs polypharmacy (e.g., antibiotics of different categories, analgesics).

In this study, 28.1% of patients received monotherapy, whereas polytherapy was administered to the remaining 71.9%. A study done by Anderson et al\cite{15} stated that the risk of ADRs was significantly lower in patients receiving monotherapy than those in polytherapy (relative risk: 0.61, 95% confidence interval 0.47–0.79, P<0.0001). In their study, 60% on polytherapy experienced ADRs; in contrast, 21% on monotherapy experienced ADRs. Kumar et al\cite{16} reported combination therapy was associated with significantly high occurrence (P < 0.05) of ADRs as compared to monotherapy. Castro-Pastrana et al\cite{17} study also stated similarly. Therefore, polypharmacy is a well-known predictor of ADRs in children and adults.

In our study, 37.5% of the total reactions were due to antimicrobials. Among antimicrobials, beta-lactams comprised 51.66%, fluoroquinolones 21.66%, sulfa drugs 16.66%. The second most common causative group was NSAIDS. Among NSAIDS, diclofenac was implicated in maximum 15 cases followed by 11 cases each caused by paracetamol and ibuprofen. About 12.5% of cases in our study were due to anti-epileptics; among them, phenytoin was more common as compared to carbamazepine. About 6.25% were due to antifungals, ART contributed 3.125%, whereas others drug contributing 13.125% of the total. This is in accordance with the study by Patel et al\cite{6} who reported 45.46% of cases due to antimicrobials, 20.87% due to NSAIDS. In a study by Sharma et al\cite{18} the most common classes of drugs implicated were antimicrobials in 40% of patients followed by NSAIDS in 35.3%. According to Nandha et al\cite{13}, antimicrobials were implicated as the major causative factor for CADR followed by NSAIDS. Jhaj et al\cite{19} reported antimicrobials to be most frequently associated with cutaneous adverse events. Thus according to the various studies, the results inferred that a variety of drugs caused CADR. Due to growing infections, the use of antibiotics has increased, leading to adverse reactions in almost all the studies quoted above. All drugs are capable of producing any type of reaction in susceptible individuals, but some drugs are more likely to induce certain reaction patterns, and this can also give a clue regarding the likely causative drug and prompt withdrawal. Beta-lactams and diclofenac were the most commonly implicated drugs causing urticaria, followed by fluoroquinolones and ibuprofen. We had also found one case each of urticaria due to the sulfa drug, napsroxen, and nitroimidazole. Jhaj et al\cite{19} found penicillin to be the most common drug among urticaria patients.

In our study, maculopapular rash was most commonly caused by beta-lactams (n = 10) followed by phenytoin (n = 7). Ibuprofen, fluoroquinolones both caused four cases of maculopapular rash. ART and diclofenac contributed to three cases each of maculopapular rash. Sharma et al\cite{18} found maculopapular rash as most commonly reported due to amoxicillin. Our study was also in accordance with the findings of Ghosh et al\cite{18} where a maximal number of maculopapular rashes were due to amoxicillin.

Our study suggests EM/SJS/TEN spectrum were caused commonly by anti-epileptics followed by antimicrobials which form major share for SCAR. Noel et al\cite{19} reported anti-epileptics were responsible for causing a maximum number of maculopapular rash (56%), TEN (55%) and SJS (43%) which correlates well with our study.

In our study, 1.25% of patients worsened and died due to TEN and 98.75% of the patient improved and cured.
showed 71.42% of patients were cured, 27.47% improved and 1.11% died.

In our study, 9 patients of SJS/TEN were recruited. Out of 9, 100% developed conjunctival injection and eye irritation. 66.6% developed synechiae, 11.1% developed iritis and symblepharon, 11.1% developed dry eye as sequelae. Catt et al.[20] reported findings similar in their study. Care should be taken even in mild cases. Appropriate intervention during acute ocular disease may prevent late complications.

The mean BSA for monotherapy was 24.86%, and for polytherapy 25.17%, but the difference was not statistically significant. Our study indicates that polytherapy does not increase the chance of any particular drug reaction as compared to monotherapy, and has no significant effects on BSA. The earlier studies had not mentioned mean BSA involvement in monotherapy versus polytherapy and type of reaction.

**CONCLUSION**

It is our intention that the risk of using drug should be carefully monitored. Awareness must be brought among people so that, the mortality and morbidity related to drug use is reduced. Self-medication can be a dangerous or serious situation, hence avoided.ADR should be reported to the manufacturer and the regulator agency, especially if the skin eruption is rare, serious, or unexpected.

It is incumbent on us as physicians to weigh the benefits and risks of each therapeutic decision carefully. Prescribing a drug to a previously sensitized patient or prescribing a related medication with cross-reactivity are the most common medicolegal pitfalls, therefore should never be ignored.

**Acknowledgement**

The authors would like to thank to all of my juniors and seniors in the Department of Dermatology, LTMMC and GH.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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