International Journal of Dermatology, Venereology and Leprosy Sciences

**E-ISSN:** 2664-942X
**P-ISSN:** 2664-9411
www.dermatologypaper.com
Derma 2021; 4(1): 107-111
Received: 01-01-2021
Accepted: 05-03-2021

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# Evaluation of dermatological adverse drug reactions, at tertiary care hospital

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**DOI:** https://doi.org/10.33545/26649411.2021.v4.i1b.77

**Abstract**
Cutaneous ADRs are unavoidable and pose a major risk of drug therapy, modulated by several factors, resulting in significant morbidity and mortality. The aim of the study is to analyse various clinical patterns of cutaneous ADRs, to find its causative drugs and assess its causality and severity of reactions.
**Method:** A prospective observational study, was conducted at tertiary care hospital, in Hyderabad for a period of 12 months. Patients presenting with CADRS to the department were included in this study. Causality and severity assessment was done by using WHO UMC system and Modified Hartwig and Siegel scale respectively.
**Results:** Total 58 patients were enrolled. Mean age group was 40.6 years (range 11 to 83 yrs). Out of them, 32 were males and 26 were females. The most commonly manifested CADRs was Maculopapular rash (24.13%) followed by FDE ( 22.4%) and Urticaria (10.34%). About 8 (13.79%) cases were found with severe CADRs. Few cases of Hand - Foot Syndrome, Lichenoid Drug Eruptions were also noted. The most common suspected drug group was Antimicrobials (29.13%) and NSAIDS (29.3%). Most common suspected drug was ciprofloxacin and diclofenac. Conclusion: The health care system can promote spontaneous reporting of cutaneous ADRs to Pharmacovigilance centre's for ensuring safe drug use and patient care.

**Keywords:** cutaneous adverse drug reactions, pharmacovigilance, causality and severity assessment, maculopapular rash, ciprofloxacin

## Introduction
An undesirable change in the structure or function of the skin and its appendages and related to drug eruption regardless of the etiology is called the Cutaneous adverse drug reaction (CADR) [1]. Cutaneous ADRs are unavoidable and pose a major risk of all drug therapy, modulated by several factors resulting in significant morbidity and mortality. Cutaneous ADRs are challenging due to drugs- poorly understood mechanisms, protean morphological patterns, complexicity of therapeutic agents, paucity of laboratory testing and patient factors- genetic predisposition and co -morbidities. Due to high frequency and potential serious consequences, most of CADRs is resulting into discontinuation or switching of drug as well as non – adherence to medication. CADRs may have a dramatic impact in every day clinical practice both from a clinical and economic perspective.
Cutaneous adverse drug reactions are common and comprises (10 % -30 %) of all adverse drug reactions, affecting about 2-3% of all hospitalized patients[2]. CADRs can occur with variable severity. Most of the CADRs are mild and resolve on withdrawing the causative drug. Most common form of drug reactions manifest as transient Maculopapular rash to fatal Toxic Epidermal Necrolysis. [3]. Severe CADRs endangering patient's life include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) occurs in approximately 1 in 1000 hospitalized patients. These carry high risk of morbidity, prolonged hospital stay, diminished quality of life and mortality. Highest mortality is seen in TEN (50%).
In the year 2010, to ensure the availability of safe medicines to the public, Ministry of Health And Family Welfare (MOHFW), government of India, launched National Pharmacovigilance Programme of India.. Multiple centers were established throughout the country under this Programme to ensure safe monitoring of drug reactions, discovering of drug interactions, awareness among people and prevention of ADRs. It helps to address the

problems related with occurrence of adverse drug reactions, derive data, and give away in turn, for framing national regulatory decisions. These measures definitely help pharmacists, pharmaceutical companies regulatory drug authorities, physicians and patients to upgrade the quality of health care in the country [4].

As the pattern of CADRs is changing every year with introduction of newer molecules and evolution of prescription patterns. This study was carried out to analyze various clinical patterns of CADRs Find the causative drugs And to access Causality and Severity of reactions

## Methods And Materials

A prospective observational study was conducted over a period of one year in a Tertiary Care hospital, in Hyderabad. Study was approved by institutional ethics committee. All patients with CADRs attending to clinical OPD, admitted in ward and willing to participate in the study were included in the study. Patients who developed reactions on acute conditions like fever, communicable diseases, any overdose of drugs, those who cannot recall the names of drugs, those on alternative medications like homeopathic, herbal and ayurvedic medications and who were not willing for the study were excluded from the study. Informed and written consent was taken from patients prior to the study. All patients underwent a brief history with relevant questionnaire like age, gender, pattern of cutaneous drug reaction, history of drug intake, reason for the intake, time interval of reaction and past history of any drug reaction, documented in a structured proforma. Details of drugs were recorded in format as per National Pharmcovigilance centre, India.

Assessment of causality systems put forth by World health organization collaborating centre for international drug monitoring, the Uppsala monitoring centre(WHO-UMC) is combined assessment taking into account clinic-pharmacological assessment of the case history and the quality of documentation of observation. It is a method used to estimate the strength of relationship between drug(s) exposure and occurrence of adverse reaction(s). The case were considered “certain” or “definite”, when the event is with plausible time relationship to drug intake,, cannot be explained by disease or other drugs., response to withdrawal plausible (pharmacologically, pathologically)., event definitive pharmacologically or phenomenological (i.e an objective and specific medical disorder or a recognized pharmacological phenomenon) and rechallenge, if necessary, is satisfactory. Probable/Likely: event with reasonable time relationship to drug intake, unlikely to be attributed to disease or other drugs, response to withdrawal clinically reasonable, rechallenge not required. Possible: event with reasonable time relationship to drug intake, could also be explained by disease or other drugs, information on drug withdrawal may be lacking or unclear [5]

The severity of the reaction was accessed by using Modified Hartwig and Siegel scale.

## Results

Total 58 patients were enrolled in a period of one year. The Mean age group suffering was 40.6 years (range 11 to 83 yrs), majority of them were in the age group of 30-40 yrs. Out of them, 32 were males and 26 were females. [table no 1].

**Table 1:** Age distribution of study subjects

| Age group | Females | Males | Total |
|---|---|---|---|
| 11-20 | 1 | 5 | 6 |
| 21—30 | 3 | 1 | 4 |
| 31-40 | 5 | 13 | 18 |
| 41-50 | 5 | 7 | 12 |
| 51-60 | 5 | 2 | 7 |
| 61-70 | 4 | 2 | 6 |
| 71-80 | 3 | 1 | 4 |
| 81-90 | 0 | 1 | 1 |
| 91-100 | 0 | 0 | 0 |
| TOTAL | 26 | 32 | 58 |

### Clinical pattern of cutaneous ADRs.

Wide range of clinical manisfestations of CADRs were observed. The most commonly manifested CADRs was Maculopapular rash ( n = 14, 24.13%) followed by Fixed Drug Eruption ( FDE) ( n= 13, 22.4%) and Urticaria ( n = 6, 10.34%) [table no 2]. About 8 cases (13.79%) of severe CADRs were found with 4 (6.89%) cases of DRESS, 2 (3.44%)cases of SJS and 2 (3.44%) cases of TEN [ table no 2]. Few cases of CADRs reported were Hand- Foot Syndrome (n=4, 6.89%), Lichenoid Drug Eruptions (n= 4,6.89%), Angiodema (n=3,5.17%), Bullous Pemphigoid (n=2, 3.44%), Acute Generalized Eruption of Pustulosis (AGEP) (n=1,1.72%), Drug Induced Vasculitis(n=1,1.72%), Erythema Multiforme (EMF) (n=1,1.72%) and Palmar Desquamation (n=1,1.72%) [table no 2].

**Table 2:** Pattern of CADRs noted.

| Pattern of CADRs | Number of Reactions | Percentage (%) |
|---|---|---|
| Maculopapular Rash | 14 | 24.13% |
| FDE | 13 | 13% |
| Urticaria | 6 | 10.34% |
| DRESS | 4 | 6.89% |
| Hand-foot syndrome | 4 | 6.89% |
| Lichenoid Drug Reaction | 4 | 6.89% |
| Angiodema | 3 | 5.17% |
| SJS | 2 | 3.44% |
| TEN | 2 | 3.44% |
| Bullous Pemphigoid | 2 | 3.44% |
| AGEP | 1 | 1.72% |
| EMF | 1 | 1.72% |
| Drug induced Vasculitis | 1 | 1.72% |
| Palmar Desquamation | 1 | 1.72% |

Mean time interval of reaction was (30- 35 days) with DRESS and 1 day with FDE ( range 1- 35 days ).

Causative drug classes Total of 31 drugs were suspected. The most common suspected drug group was antimicrobials (n= 19,32.75%) followed by NSAIDS (n= 16, 27.5%), anti epileptic drugs (10.34%). Few reactions were reported with chemotherapeutic drugs (n=5, 8.62%) and anti TB drugs (n=4, 6.89 %) [table no 3]. Most common suspected drug was ciprofloxacin (n=5, 8.62%), Diclofenac ( n=5 (8.62%) followed by Phenytoin (n=3, 5.17%) [table no 3]. [ table no 4] [table no 5].

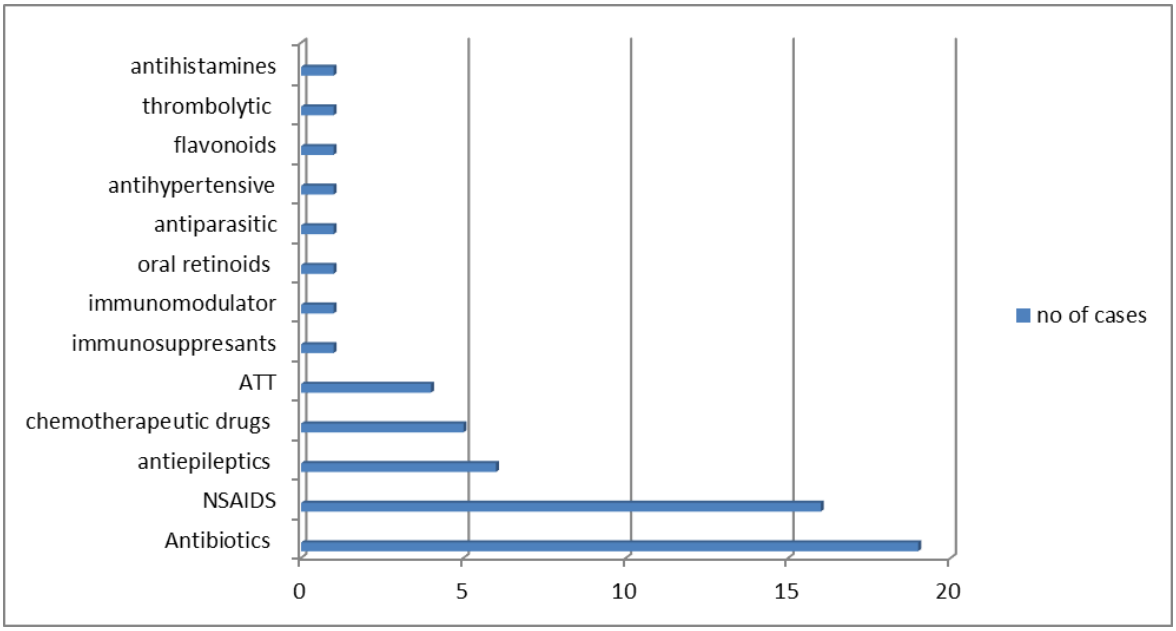


**Fig 3:** Group of drugs causing CADRs

**Table 3:** List of Antimicrobial Drugs with Reaction Details

| Antimicrobials | Reaction Details | Frequency |
|---|---|---|
| Ciprofloxacin | SJS(1),TEN(1),DRESS(1),BP(1),MPR(1) | 5(8.62%) |
| Cefixime | DRESS(1),AGEP(1),MPR(1) | 3(5.17%) |
| Cefpodoxime | Urticaria(1),MPR(1) | 2(3.44%) |
| Ampicillin | Urticaria (1),urticaria with angiodema(1) | 2(3.44%) |
| Amoxicillin | MPR(2) | 2(3.44%) |
| Norfloxacin | FDE(2) | 2(3.44%) |
| Cefuroxime | MPR(1) | 1(1.72%) |
| Cefoperazone | MPR(1) | 1(1.72%) |
| Ofloxacin | MPR(1) | 1(1.72%) |

**Abbrevations –** MPR- Maculopapular Rash, FDE- Fixed drug eruption

In the Study, Table 4 shows - Among Antimicrobials most common group of drugs was Floroquinolones and Cephalosporins. Ciprofloxacin is the common drug causing CADRs.

**Table 4:** List of NSAIDS with Reaction Details

| NSAIDS | Reaction details | Frequency |
|---|---|---|
| Diclofenac | TEN(1),SJS(1),MPR(1),FDE(2) | 5(8.62%) |
| Paracetomol | MPR(1),Urticaria(1),FDE(2) | 4(6.89%) |
| Ibuprofen | MPR(1),FDE(2) | 3(5.17%) |
| Etoricoxib | MPR(1),FDE(1) | 2(3.44%) |
| Nimesulide | DRESS(1) | 1(1.72%) |
| Aspirin | FDE(1) | 1(1.72%) |

Table 4 shows- Among NSAIDS, most common drug causing CADRs is Diclofenac followed by Paracetomol.

**Table 5:** Other drugs causing CADRs

| Suspected Drug | Reaction Details | Frequency |
|---|---|---|
| Phenytoin | Urticaria (1), urticaria with angiodema (1), EMF | 3(5.17%) |
| Lithium | MPR (1), urticaria with angioedema (1), drug induced vasculitis (1) | 3(5.17%) |
| Capecitabine | Hand-foot syndrome | 3(5.17%) |
| Ethambutol | Lichenoid Drug Eruption | 2(3.44%) |
| Isoniazid | Lichenoid drug eruption | 2(3.44%) |
| Carboplatin | MPR | 1(1.72%) |
| Doxorubicin | Hand-Foot Syndrome | 1(1.72%) |
| Sulphasalazine | DRESS | 1(1.72%) |
| Azathioprine | Urticaria | 1(1.72%) |
| Acitretin | Palmar Desquamation | 1(1.72%) |
| Tinidazole | FDE | 1(1.72%) |
| Metoprolol | Bullous Pemphigoid | 1(1.72%) |
| Daflon | urticaria | 1(1.72%) |

| | | |
|---|---|---|
| Teneteplase | FDE | 1(1.72%) |
| Cetrizine | FDE | 1(1.72%) |

Table 5 shows Phenytoin is most common antiepileptic drug causing CADRs. Capecitabine is common chemotherapeutic drug causing CADR.

**Causality assessment**

According to WHO UMC causality assessment system, CADRs were categorised with 29 cases (50%) as probable, 20 cases (34.4%) as possible and 9 cases (6.4%) as definite.

**Severity assessment**

According to Modified Hardwig and Siegel criteria, CADRs were classified as- 32(55.17) mild, 18 (31.03%) moderate and 8 (13.79%) severe.

**Discussion**

Cutaneous ADRs are necessarily inherent risk of all drug therapy distressing to the patient as well as to physician[2]. Identifying the culprit drug specially for severe reactions may be extremely difficult as performing oral provocations would be dangerous and unethical. The development of skin eruption is frequently cited as a reason for discontinuation of treatment without taking the full therapeutic course.

Total of 58 patients were reported with CADRs enrolled during the study period of 12 months. In our study, about 32 males (55.17%) were seen with CADRs showing male preponderance. However, few studies showed female preponderance [6]. In this study, Most of them were in age group of 31-40 years (31%) with mean age group of 40 years, ranging from lowest age 11 years to highest age 83 years. which was similar to study by Ruchita *et al*, were the age group was 31-40 years.[3]

In our study, the most frequently reported Cutaneous Adverse drug reaction was Maculopapular rash (24.13%) followed by FDE (13% ) and urticaria ( 10.34% ) which was contrast with study done by Ankita *et al* who reported most common CADRs as FDE, followed by Maculopapular rash and urticaria.[2] This variation might be due to different drug usage patterns and different ethnic groups in different parts of our country.

The most common offending drug classes were antimicrobials (32%0, followed by NSAIDS (27.5%) and anti epileptics (10.34%). Which was similar to study done by Sharma *et al* [7]. In present study, among antimicrobials floroquinolones (ciprofloxacin) and cephalosporins (cefixime) were the most commonly implicated drugs. Among NSAIDS, (8.62%) of reactions were due to diclofenac sodium followed by paracetomol (6.89%). Phenytoin was responsible for 5.17% cases among epileptics.

Antimicrobilas were the most offending drug class causing Maculopapular rash. which was in concordance with study done by Tejas *et al.* [8]

NSAIDS were major culprit drug group causing FDE in about 8 (13.79%) patients, which showed similar results with study done by Jagruthi *et al.* [9] Out of 13, 2 cases were due to paracetamol. Probability in higher incidence of CADRs with paracemtol could be due to self medication among common people or common prescribing pattern. We had also found one case of FDE each due to Tinidazole, Tenecteplase and Cetrizine.

Hand foot syndrome or Palmar – Plantar Erythrodysesthesia is a well known adverse effect with chemotherauptic drugs. In our study, 3 patients developed Hand foot syndrome while on caepetitabine and one patient with doxorubicin. Results were in accordance with study done by Kriteeka *et al.* [10]

In our study, we reported 4 cases of lichenoid drug eruption associated with anti tubercular drugs. Our study showed Isoniazid and Ethambutol as causative drugs. Similar results were seen in study done by Reena *et al* who found Ethambutol as most common offending drug followed by Pyrazinamide [11].

Severe cutaneous drug reactions like of Stevens Johnson Syndrome (SJS), Toxic Epidermolysis Necrosis(TEN) and Drug Rash with Eosinophilia and Systemic Symptoms(DRESS) were found in our study. Two of them diagnosed as TEN recquired prolonged hospitalization with regular monitoring.

According to WHO UMC causality assessment, in present study, most of CADRs were designated as probable (50%) and possible(43.10%). which was similar to Shah *et al.* (69%). Few cases (6.9%) were classified in the category of " certain".

Though Rechallenge is still matter of debate and difficult to perform on ethical background. We rechalleged 4 patients with ATT drugs, isoniazid and rifampicin were rechallenged first followed by Ethambutol and Pyrizinamide. Out of all, Isoniazid and Ethambutol were found as culprit drugs. Rechallenge was a ray of hope to decrease the burden of TB all over India and decrease the risk of ATT interruption and default.

Severity assessment using Modified Hartwig and Siegel scale relieved majority of CADRs were mild (55.17%), self limiting and dissappered after stopping offending drug followed by moderate (31.08%) and severe (13.7%).

**Conclusion**

The pattern of cutaneous adverse drug reactions and causative drugs were remarkably different in our study. high degree of suspicion, timely diagnosis and identification of the offending drug, is not only mandatory for dermatologists but also to physicians to reduce mortality and morbidity. Self-medication can be a dangerous or serious situation, hence should be avoided. Patients can be educated to avoid self administration of drugs and re- administration of offending drug and carry a card with a list of drugs causing reactions to prevent morbidity in the patients.

The health care system can promote the spontaneous reporting of cutaneous ADRs to Pharmacovigilance centre's for ensuring safe drug use and patient care.

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