

## Cutaneous drug reactions notified by ADR monitoring centre in a tertiary care hospital of Bihar

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### ABSTRACT

**Background:** Cutaneous drug reactions are most frequent drug related adverse events which lead to early treatment discontinuations, high treatment cost and leading cause of morbidity and mortality. The aim of this study is to analyze the clinical patterns and offending drugs as well as their causality, severity and preventive strategies.

**Methods:** All adverse drug reactions (ADRs) forms filled from May 2015 to April 2016 were scrutinized and forms with cutaneous drug reactions were analyzed and assessed for causality, severity and preventability.

**Results:** Out of 300 ADR forms, 160 (53.34%) included cutaneous drug reactions. 68 (42.50%) patients were male and 92 (57.50%) were female. Maculopapular rash 58 (36.25%), fixed drug eruption (FDE) 31 (19.37%), pruritus 27 (16.87%) and urticaria 19 (11.87%) were the common clinical patterns of cutaneous drug reactions. Most common offending drug classes included antibiotics, anti-inflammatory and steroidal agents. Causality assessment was done by using Naranjo's algorithm. The result showed that out of 160 cutaneous drug reactions 141 (88.12%) ADRs were probable, 15 (9.37%) were classified as possible; 2 (1.25) doubtful and 2 (1.25%) were definitely related to the drug.

**Conclusions:** The present study shows cutaneous drug reactions are commonly reported at ADR monitoring centre of this tertiary care hospital. Our study suggests that there is a need of intensive monitoring for ADRs in tertiary care hospital for early detection and to ensure the patient safety.

**Keywords:** Cutaneous drug reactions, Fixed drug eruption, Maculopapular rash, Naranjo's algorithm

### INTRODUCTION

The WHO defines ADRs as 'any response to a drug which is noxious, unintended and which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological function'.<sup>1</sup> None of the drug is free from adverse effects. Drugs are an integral part of healthcare system. Patient safety is the most important concern for health care professionals while prescribing a drug. It is therefore important for prescribers to be aware of adverse effects of drugs before prescription. Clinically important

ADRs are diverse but cutaneous drug reactions are most common among the various adverse reactions and attributed by the drugs.<sup>2</sup> Cutaneous drug reactions is defined as any undesirable change in the structure or function of skin, its appendages or mucous membranes, encompassing all adverse events related to drug eruption regardless of etiology.<sup>3</sup> Of the various adverse reactions to drugs, cutaneous drug reactions are the most frequent, with an incidence of 10-30% of all the reported ADRs.<sup>4,5</sup> Cutaneous drug reactions are also responsible for approximately 3% of all disabling injuries during hospitalisation.<sup>6</sup> In 2010, Central Drugs Standard Control Organization (CDSCO) under the aegis of Govt. of India,

Ministry of Health and Family welfare has established Adverse Drug Reaction (ADR) Monitoring Centres in pharmacology department of various hospitals in all over India (Pharmacovigilance Programme of India (PvPI), 2010). ADR Monitoring Centres (AMCs) under PvPI play a vital role of collection and follow-up of ADR reports from the patients. These hospital-based adverse drug reaction monitoring programmes are aims to identify and quantify the risks associated with the use of drugs in patients. In view of this, Pharmacovigilance plays a vital role in establishing the safety profile of marketed drugs.<sup>7</sup> Cutaneous drug reactions are the commonly reported type of ADR.<sup>8</sup> Although such cutaneous reactions are common, information regarding their incidence, severity and ultimate health effects are often not available as many go unreported. Cutaneous drug reactions patterns and the drugs causing various reactions are changing every year, which may be due to the emergence of newer molecules and changing trends in the use of drugs. However, the early identification of the condition and identifying the culprit drug and omit it at earliest holds the keystone in management and prevention of a more severe drug reaction. Therefore, not only the dermatologist, but all practicing physicians should be familiar with this condition to diagnose them early and to be prepared to handle them adequately. The wide spectrum of presentation of cutaneous drug reactions ranges from transient maculopapular rash to severe Stevens-Johnson syndrome (SJS), hence, there is a continuous need to carry out studies in this field with a closer scrutiny of the clinical spectra of cutaneous drug reactions as well as offending drugs.

**METHODS**

This was an observational and analytical study conducted over 1 year period at Indira Gandhi Institute of Medical Sciences, (IGIMS) Patna, Bihar, which has an ADR monitoring centre (AMC) under Pharmacovigilance Programme of India (PvPI). 300 suspected ADR forms filled from May 2015 to April 2016 were scrutinised and forms with cutaneous drug reactions (160) were analysed and assessed with the help of Technical Associate of ADR monitoring centre, IGIMS and the faculty members of the Department of Pharmacology. Prior permission was taken from Institutional Ethics Committee to conduct the study. Data extracted from ADR form includes patient details (age, sex, weight, initials, etc.), description of the event (date of start and recovery, other relevant history, seriousness, outcomes, relevant laboratory tests, etc.), suspected medications (dates of prescription, dosage, frequency and route of administration, duration and indication of use) and use of concomitant medications. In order to improve the accuracy of our assessments, individual causality assessments were undertaken using the Naranjo’s causality assessment scale which classifies drug reactions into definite, probable, possible and doubtful ADR.<sup>9</sup> Severity of the reaction was assessed using ADR Severity Assessment Scale (Modified Hartwig and Siegel) which classifies

ADR into mild, moderate and severe.<sup>10</sup> Preventability assessment was done by using Schumock and Thornton scale<sup>11</sup> which classifies the ADRs into definitely preventable, probably preventable and not preventable.

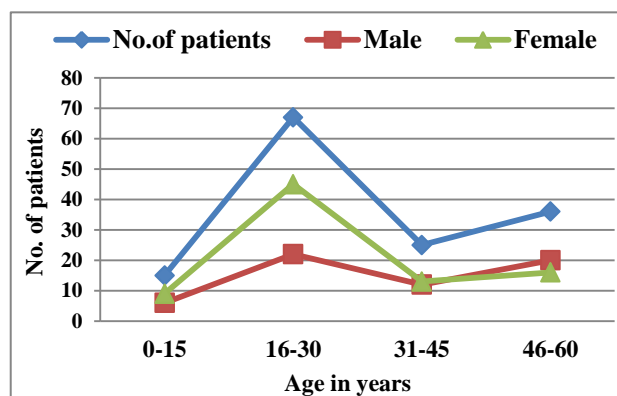
**Statistical analysis**

A descriptive analysis of the data was done using Microsoft Excel and results were expressed as percentage.

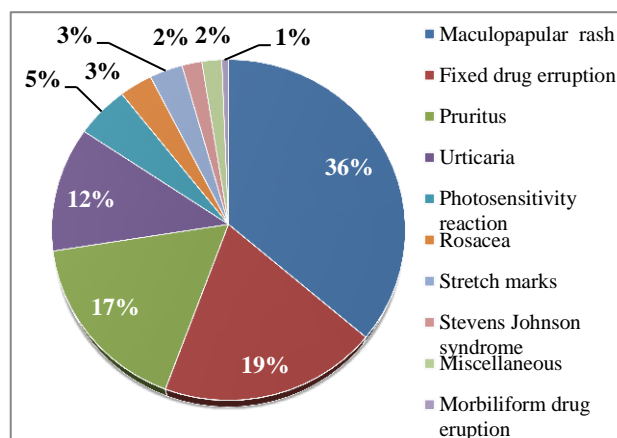
**RESULTS**

A total of 300 ADR forms collected from May 2015 to April 2016 were scrutinised of which 160 (53.34%) included cutaneous drug reactions. The majority of the patients belonged to the age group of 16-30 years 67 (41.8%) followed by 36 (22.5%) in 31-45 years. Females comprised 57.5% of the total population (male/female: 68/92).

The age group by total number and sex distribution of patients is represented in Figure 1. The various types of cutaneous drug reaction have been shown in Figure 2 and the commonly implicated drugs have been shown in Table 1.



**Figure 1: Age and sex distribution of patients.**



**Figure 2: The distribution (%) of various cutaneous drug reactions in the studied population.**

**Table 1: Drugs causing various cutaneous drug reactions.**

Sr. No.	Offending drugs	Clinical presentations	Total no. of patients (n)
1.	Antimicrobials (Ceftriaxone/Azithromycin/Piperacillin/Ampicillin)	Maculopapular rash (28), Pruritus (16), Urticaria (19)	63
2.	Fluoroquinolones (Ofloxacin/Norfloxacin)	Maculopapular rash (13), Pruritus (5), FDE (18), Photo allergy (8)	44
3.	Antiepileptic (Phenytoin/Carbamazepine)	SJS (3), Maculopapular rash (8), FDE (5), Lichenoid reaction (1), Pompholyx (1)	18
4.	NSAIDS (Diclofenac/Nimesulide)	Maculopapular rash (9), Pruritus (4), FDE (1)	14
5.	Steroids (Prednisolone/Beta methasone)	Acneform eruption (1), Stretch marks (5), Rosacea (5)	11
6.	Nitroimidazole (Tinidazole/Ornidazole/ Metronidazole)	FDE (7), Hyper pigmented patch (1)	8
7.	Antidiabetic (Metformin)	Morbiliform drug eruption (1)	1
8.	Antigout (Allopurinol)	Papular pruritic eruption (1)	1

**Table 2: Route of administration of offending drugs.**

Route of administration	Frequency	Percentage (%)
Oral	99	61.87
Parenteral	45	28.12
Topical	16	10
Total	160	100

**Table: 3 Causality assessments by Naranjo's algorithm.**

Scoring	Frequency	Percentage (%)
≥9 = definite	2	1.25
5-8 = probable	141	88.12
1-4 = possible	15	9.37
0 = doubtful	2	1.25
Total	160	100

Causality assessment was done by using Naranjo's algorithm. The result showed that out of 160 cutaneous

drug reactions 141 (88.12%) ADRs were probable, 2 (1.25) doubtful; 15 (9.37%) were classified as possible and 2 (1.25%) were definitely related to the drug (Table 3).

**Table: 4 Severity assessments by modified Hart wig and Siegel Scale.**

Assessment	Frequency	Percentage (%)
Mild	106	66.25
Moderate	52	32.5
Severe	2	1.25
Total	160	100

**Preventability assessment using Schumock and Thornton scale**

38 (23.75%) cases were found to be definitely preventable whereas 122 (76.25%) were probably preventable.

**DISCUSSION**

In the present study 160 patients with cutaneous drug reactions were studied with the maximum number of patients from the age group of 16-30 years followed by 31-45 years. These findings were in concordance with the study done by Balpande.<sup>12</sup> The females in our study outnumbered the males. Mahapatra also showed female preponderance in his study.<sup>13</sup>

Among various types of cutaneous drug reactions seen in this study, maculopapular rash (36.25%) are the commonest one followed by fixed drug eruptions (19.37%), pruritus (16.87%), urticaria (11.87%), photoallergy (5.0%), rosacea (3.12%), stretch marks (3.12%), SJS (1.87%) and miscellaneous (1.25%) which were supported by Pudukadan D et al.<sup>14</sup>

The drugs which commonly produced cutaneous drug reactions in our study were antimicrobials/antibiotics like (fluoroquinolones; cephalosporins and penicillins). This was followed by NSAIDS (Diclofenac and Nimesulide); corticosteroids (oral and topical) and antiepileptic drugs (Phenytoin, Carbamazepine) which was similar to previous study done by Sharma.<sup>15</sup> Anticancer, antitubercular, oral hypoglycemic agents and blood transfusion also produced cutaneous drug reactions.

Fixed drug eruption (FDE) was reported mainly due to Nitroimidazoles (Tinidazole, Metronidazole, Ornidazole); NSAIDS (Paracetamol, Nimesulide) and fluoroquinolones (Ofloxacin, Norfloxacin and Levofloxacin). Tinidazole was found to be main culprit among Nitroimidazoles inducing FDE, multiple lesion FDE and hyperpigmentation patch (Figure 3 and Figure 4). Phenytoin and Carbamazepine induced Stevens Johnson Syndrome (SJS) were reported. Phenytoin induced SJS was reported with 100 mg of Phenytoin

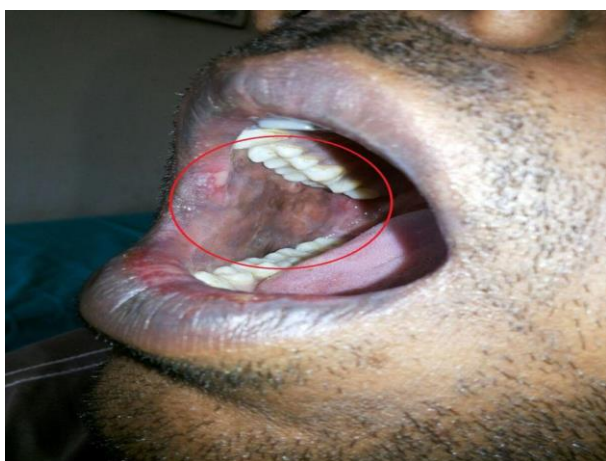
thrice daily after 2-3 weeks of therapy.<sup>16</sup> Phenytoin usage also caused oral FDE and lichenoid reaction (Figure 5).



**Figure 3: Multiple FDE due to Nitroimidazole drugs.**



**Figure 4: Old Hyperpigmented patch of FDE due to Tinidazole.**



**Figure 5: Oral FDE and lichenoid reaction due to Phenytoin.**

In this regard, Carbamazepine induced SJS has already been recommended by PvPI to Central Drugs Standrd

Control Organization (CDSCO) for regulatory interventions for label change (source-PvPI performance report 2014-15).<sup>17</sup> Signal review panel of PvPI recommended screening of HLA-B \*1502 prior to initiating the carbamazepine treatment because of risk factor for carbamazepine induced Stevens Johnson Syndrome. It was observed by the Committee that association between Stevens Johnson Syndrome and HLA-B \*1502. So, it was recommended that all the drug manufacturers should include the same in the prescribing information (label/leaflet) and the same should be available on the official website of all the firms manufacturing carbamazepine in India.

Cutaneous drug reactions due to oral corticosteroids (Prednisolone) were acneform eruptions and topical corticosteroids (Betamethasone, Mometasone furoate) produced rosacea and stretch marks (Figure 6). Corticosteroids produce cutaneous drug reactions mainly if used for long term and interrupted usage. Demelanizing cosmetic creams used for fairness (e.g. - Melacare, skin lite, No scars containing potent steroid Mometasone furoate, Hydroquinone and Isotretinoin) also caused rosacea. Maculopapular rash was most commonly reported due to amoxicillin in the study done by Sharma.<sup>15</sup> Levofloxacin fast I/V infusion was more likely to produce cutaneous drug reactions than slow infusion.



**Figure 6: Acneform eruption and stretch mark due to Prednisolone.**

Out of 160 cases of cutaneous drug reactions studied the dechallenge was done in all cases. In some definite cases of cutaneous drug reactions, route of administration was changed from oral to topical formulation (e.g. Metronidazole tablet to Metronidazole topical cream) for confirmation and results were found positive. After causality assessment using Naranjo's algorithm, the offending drug was found to be a probable cause in 88.12% of patients, possible in 9.37% of patients, definite and doubtful in 1.25% of patients. Chowdhury found that the majority of cases were either probable (41.5%) or possible (39.6%).<sup>18</sup> The assessment might vary with the type of scales/ algorithms used for the assessment of ADRs in different regions.

### Limitations

Cutaneous drug reactions are considered in our study has some limitations like difficulties in causality assessment due to polypharmacy. Only dechallenge was done, rechallenge was not done due to ethical issue and patient concern. Since our study was observational and analytical, we were able to provide only a snapshot of cutaneous drug reactions provided by dermatologist of this institute.

### CONCLUSION

Cutaneous drug reactions are among the most frequent adverse reactions to drugs. Most are benign, but a few can be life threatening. Prompt recognition of severe reactions, drug withdrawal and appropriate therapeutic interventions can minimize toxicity. This study focus on adverse cutaneous reactions to systemic medications; it covers their incidence, patterns, offending drugs, assessment of causality, severity and future use of drugs. The common class of drugs known to cause cutaneous drug reactions were antimicrobial/antibiotics, NSAIDs, Corticosteroids and anti-epileptic. This study effectively throws light on important aspects of cutaneous drug reactions, which would be helpful in creating awareness among physicians and curtailing the damage associated with doctor prescribed drugs.

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