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Original Research Article

Adverse cutaneous drug reactions reporting in a tertiary care teaching hospital in Eastern India: a retrospective study

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ABSTRACT

Background: Any unwanted changes to mucous membrane, skin, its appendages and drug eruptions related adverse events are known as adverse cutaneous drug reaction (ACDR). It has 2-5% incidence in developing countries. The current study was undertaken to analyse adverse cutaneous drug reactions spectrum clinically, drugs responsible, assessment of causality, severity, and preventability in our setup.

Methods: Current study was an observational, retrospective, non-interventional analysis of voluntarily reported ADRs forms, between April 2018 and January 2020. All cutaneous ADRs reported within this period were identified. Data obtained were expressed in numbers, percentages.

Results: 130 cutaneous ADRs was reported during the period of study. Fixed drug eruptions (30%) was the most common cutaneous reaction. The most common causal drug groups were antimicrobials (58.5%). Amongst antimicrobials, ornidazole (8.5%) was the most common drug. The most common drug in NSAID group was paracetamol (14.6%). The major drug causing ACDRs in our study was Paracetamol (14.6%). Assessment of causality revealed 37.7% were probable and 62.3% were possible reactions. Assessment of severity showed 78.5% as mild and 21.5% as moderate. Assessment of preventability showed that 6.1% probably preventable and 93.9% not preventable.

Conclusions: Knowledge of the pattern of cutaneous reactions and the causative drugs guides us in early diagnosis of the condition, better management and associated decrease in morbidity, mortality. In the current study, the most common causal drug group were antimicrobials. The most common morphological pattern and drug causing ACDRs were fixed drug eruptions and paracetamol, respectively.

Keywords: Adverse cutaneous drug reactions, Causality, Preventability, Retrospective study, Severity

INTRODUCTION

WHO defines adverse drug reactions (ADRs) as “any unintended and noxious response to a drug which occurs at doses normally used in human beings for the prophylaxis, diagnosis or therapy of a disease, or for modification of physiological functions”.¹ They are the prime causes of morbidity and mortality, associated with increased hospitalization, socioeconomic burden on patients.² Any unwanted changes to mucous membrane, skin, its appendages and drug eruptions related adverse

events are known as adverse cutaneous drug reaction (ACDR).³

Cutaneous adverse drug reactions are 1-3% and 2-5% in developed and developing countries, respectively.⁴ The practising physician should be well aware of these cutaneous reactions to minimize associated morbidity and mortality. To minimize harm to patients and in order to improve public health, cutaneous reactions have to be detected early, and monitored.⁵ Introduction of new drugs, changing drug usage patterns leads to changes in cutaneous reactions patterns annually.⁶

Hence, the current study was undertaken to analyse the clinical spectrum of cutaneous ADRs, causative drugs, assess their causality, severity, and preventability, with the aim of encouraging the clinicians in voluntary reporting of ADR's and to promote rational usage of medicines.

METHODS

This study was an observational, retrospective, non-interventional analysis of voluntarily reported ADRs forms received at the Pharmacovigilance cell, Department of Pharmacology, IMS and SUM Hospital, Bhubaneswar, which is a designated adverse drug reaction monitoring centre (AMC) between April 2018 and January 2020. All cutaneous ADRs reported within this period were identified.

The study was duly approved by the Institutional Ethics Committee. For additional information, if any, on the reported ADR forms, concerned clinician were contacted.

Data were analysed to find out the total number, clinical presentation of cutaneous ADRs, causal drug groups, and suspected drugs. Causality assessment was done using Naranjo's algorithm.⁷ Modified Hartwig and Seigel scale was used to assess severity.⁸ Modified Schumock and Thornton scale was used to assess preventability.⁹

Inclusion criteria

Patients of either gender, of any age, who developed an ACDR, reported from various clinical departments (outpatient and/or inpatient).

Exclusion criteria

Drug poisoning (accidental or intentional), medication errors; ADR forms with insufficient information; ADR due to medicines of alternate systems like Ayurveda, homeopathy, unani etc.; and transfusion related adverse reactions.

Data obtained were expressed in numbers, percentages, wherever appropriate.

RESULTS

130 cutaneous ADRs reported during the period of the study. 100 (76.9%) are outpatients, and the rest 30 (23.1%) are inpatients. Males (62.3%) were more affected than females (37.7%).

Maximum number of cutaneous ADRs were reported in the age group of 21-30 years and 41-50 years (21.5% each) followed by 31-40 years (14.6%) and 51-60 years (13.8%). Age group of 0-10 years (6.2%) and ≥ 71 years (6.2%) reported the lowest number of cutaneous ADRs as depicted in Table 1.

Table 1: Age and gender distribution.

Age group (yrs)	Male (%)	Female (%)	Total (%)
0-10	5 (6.2)	3 (6.1)	8 (6.2)
11-20	7 (8.6)	3 (6.1)	10 (7.7)
21-30	17 (21.0)	11 (22.4)	28 (21.5)
31-40	10 (12.3)	9 (18.4)	19 (14.6)
41-50	18 (22.2)	10 (20.4)	28 (21.5)
51-60	11 (13.6)	7 (14.3)	18 (13.8)
61-70	8 (9.9)	6 (12.2)	14 (10.8)
>71	5 (6.2)	0 (0)	5 (3.8)

The clinical departments reporting maximum number of cutaneous ADRs were skin and VD (68.5%) followed by medicine (16.2%), paediatrics (6.9%) and psychiatry (5.4%). The most common causal drug groups were antimicrobials (58.5%) followed by NSAIDs (30%) and antiepileptics (5.4%) as depicted in Table 2.

Table 2: Drug class causing ACDRs (≥ 5 ACDRs).

Drug class	N (%)
Antimicrobials	76 (58.5)
NSAIDs	39 (30.0)
Antiepileptics	7 (5.4)

Amongst antimicrobials, ornidazole (8.5%) is the most common drug followed by ornidazole + ofloxacin combination (6.2%) and amoxicillin + clavulanic acid (5.4%) causing cutaneous ADRs. The most common drug in NSAID group is paracetamol (14.6%) followed by diclofenac (12.3%). Fixed drug eruptions (30%), maculopapular rash (15.4%) and pruritus/redness (11.5%) were the common cutaneous reactions. Different clinical presentation of cutaneous ADRs depicted in Table 3.

Table 3: Clinical presentations of ACDRs (≥ 5 ACDRs).

Pattern of reactions	Total number of cases (%)
FDE	39 (30)
Maculopapular rash	20 (15.4)
Pruritus / Redness	15 (11.5)
Bullous eruptions	13 (10)
DRESS	9 (6.9)
Erythematous rash	8 (6.2)
Urticaria	7 (5.4)
SDRIFE	6 (4.6)

The three major drugs causing ACDRs in our study are paracetamol (14.6%), diclofenac (12.3%), ornidazole (8.5%). Other drugs were ornidazole + ofloxacin (6.2%), Amoxicillin + clavulanic acid (5.4%), cefpodoxime + clavulanic acid (4.6%) and itraconazole (3.8%). Fixed drug eruptions (FDE) was the most common reaction with Paracetamol, diclofenac and ornidazole + ofloxacin. Symmetrical drug-related intertriginous and flexural

exanthema (SDRIFE) was most common with Itraconazole, enumerated in Table 4. The common medications causing cutaneous reactions in various studies enumerated in Table 5.

Table 4: Drugs causing ACDRs (≥ 5 ACDRs).

Drugs	Reaction details	Frequency (%)
Paracetamol	FDE (8) erythematous rash (1) urticaria (1) maculopapular rash (3) bullous eruptions (1) papular eruptions (1) dress (2) erythema multiforme (1) hyperpigmentation (1)	19 (14.6)
Diclofenac	FDE (7) pruritus/redness (1) urticaria (2) swelling of lips (1) maculopapular rash (2) bullous eruptions (2) acneiform eruptions (1)	16 (12.3)
Ornidazole	FDE (4) maculopapular rash (1) bullous eruptions (4) papular eruptions (1) hyperpigmentation (1)	11 (8.5)
Ornidazole + ofloxacin	FDE (7) maculopapular rash (1)	8 (6.2)
Amoxicillin/clavulanic acid	FDE (1) pruritus/redness (1) erythematous rash (1) maculopapular rash (2) DRESS (1) erythema multiforme (1)	7 (5.4)
Cefpodoxime/clavulanic acid	Maculopapular rash (1) bullous eruptions (2) DRESS (1) vesicular rash (1) SDRIFE (1)	6 (4.6)
Itraconazole	SDRIFE (5)	5 (3.8)

Table 5: Common medications in various studies causing cutaneous reactions.

Study	Common medications
Our study	Paracetamol, diclofenac, Ornidazole, Ornidazole + ofloxacin, Amoxicillin/clavulanic acid, Cefpodoxime/clavulanic acid
Sharma et al¹²	Tinidazole, fluconazole, paracetamol, amoxicillin, ibuprofen, diclofenac
Modi et al¹⁵	Antiretrovirals, AKT, paracetamol, diclofenac, ofloxacin
Anjaneyan et al¹⁶	Cotrimoxazole, AKT, ciprofloxacin, amoxicillin, carbamazepine, phenytoin, ofloxacin
Dhanani et al¹⁹	Paracetamol, cotrimoxazole, ibuprofen, amoxicillin, phenytoin, vancomycin

Causality assessment by Naranjo revealed 49 (37.7%) were probable and 81 (62.3%) were possible adverse reactions. There were no ADRs which were definite or doubtful. Severity assessment by Hartwig and Siegel scale showed 102 (78.5%) as mild and 28 (21.5%) as moderate. There were no severe cases. Preventability assessment by modified Schumock and Thornton scale showed that 08 (6.1%) probably preventable and 122 (93.9%) not preventable. There were no reactions which was definitely preventable.

DISCUSSION

Current study focussed on the various patterns of adverse cutaneous drug reactions that was reported in our centre. Cutaneous reactions have a varied morphology and distribution. In our study, a total of 130 cutaneous reactions were reported. Cutaneous reactions were more in males (62.3%) as compared to females (37.7%) in our study, similar to the study by Sharma et al, Acharya et al, Gohel et al, Sharma et al, Sasidharanpillai et al, Tejashwani et al, and Modi et al.^{6,10-15}

21-30 years and 41-50 years age group were mostly affected followed by 31-40 years in our study. Similar results were found in the study by Acharya et al, Sharma et al, Tejashwani et al, Modi et al, Anjaneyan G et al and Tabassum N et al.^{10,12,14-17} Paediatric age group in our study had less incidence of cutaneous reactions which may be due to few drugs prescribed and a normal hepatic and kidney functions.

Most of the cutaneous reactions in our study were reported from department of Dermatology (68.5%) and 16.2% from department of Medicine. This was in contrast to department of Medicine (47.7%) followed by department of Dermatology (26.1%) in the study by Dimri et al.¹⁸

In our study, antimicrobials (58.5%) was the common causal drug group followed by NSAIDs (30%) and 5.4% were antiepileptics. This is in contrast to antimicrobials (40%, 46%, 54%, 48%), NSAIDs (35%, 18%, 23%, 30%), and antiepileptics (8%, 10%, 11%, 12%) in the study by Sharma et al, Modi et al, Anjaneyan et al, and Dhanani et al respectively.^{12,15,16,19} Antimicrobials and NSAIDs are commonly prescribed by physicians and general practitioners, hence, higher chances of developing reactions to these groups of medications.

In this study, Fixed drug eruptions (30%), maculopapular rash (15.4%) are common morphology patterns. 66.7% for FDE and 22.2% for maculopapular rash was reported in the study by Nivethitha et al, 31.1% for FDE and 12.2% for maculopapular rash in the study by Pudukadan et al.^{20,21} Similarly, FDE (43.9%) and maculopapular rash are common morphology pattern in the study by Padmavathi et al.²² FDE (33.3%) was also most common in the study by Sharma et al.¹²

Paracetamol is the most common suspected drug causing ACDRs in our study. This could be due to the fact that paracetamol is one of the most commonly co-prescribed medication by the physicians and general practitioners. Gohel et al and Padmavathi et al reported similar results.^{11,22}

Assessment of causality showed that maximum adverse cutaneous reactions had possible (62.3%) relationship and 37.7% had probable relationship with the suspected drug in our study. There were no definite or doubtful cases, which was similar by Modi et al.¹⁵ Other studies demonstrated more probable relationships with the suspected drug.^{11,12,17-19,22}

According to modified Hartwig and Seigel scale in the current study, 78.5% and 21.5% of cutaneous reactions were mildly and moderately severe respectively. Similar results were also reported by Dhanani et al.¹⁹ Most of these patients managed by withdrawing the suspected medication and providing supportive therapy. However, in other studies majority of the cutaneous reactions were moderately severe.^{10,11,15,17,22}

Majority of the cutaneous ADRs were not preventable (93.9%) in our study, which was similar to other studies.^{15,19,22}

CONCLUSION

Reactions to prescribed medications are inevitable in modern day practice. Lack of interest is one of the major factors in nonreporting of ADRs at hospital settings. Early recognition of various morphological patterns is important so that the culprit drug is found out and stopped immediately. Information on the morphology and medications responsible for the reactions would help the clinician by diagnosing the condition early, thereby, reducing the complications associated with these conditions.

In our study, antimicrobials were the most common causal drug group followed by NSAIDs. Fixed drug eruptions and maculopapular rash were the common morphology pattern encountered.

To ensure the safety of medications, healthcare professionals should ensure the voluntary reporting of reactions to prescribed medications.

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