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Research Article

CURRENT TRENDS OF CUTANEOUS ADVERSE DRUG REACTIONS IN A TERTIARY CARE HOSPITAL IN NORTH INDIA: A RETROSPECTIVE STUDY

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ABSTRACT

Objectives: The objectives of this study were as follows: (1) To analyze the reported cutaneous ADRs in a tertiary care hospital for their pattern and suspected medications. (2) To assess the causality and severity of the CADR.

Methods: A retrospective study of cutaneous adverse drug reactions (CADRs) reported from July 2020 to August 2023 was conducted. The modified Hartwig and Siegel scale was utilized to evaluate the severity of the reactions, and Naranjo's causality evaluation scale was employed to determine causality.

Results: A total of 187 cases were reported. Maximum cases (48.12%) were between 21 and 40 years age group. The most prevalent CADR pattern was maculopapular rash (57.21%) followed by fixed drug eruption (24.06%). The most common offending drug was diclofenac (9.90%) followed by paracetamol (7.2%). Overall, antimicrobial medicines accounted for the greatest number of CADRs (24.59%).

Conclusion: There was a broad range of clinical manifestations of CADRs, from maculopapular rash to severe Steven–Johnson syndrome. Overzealous use of the drugs should be avoided, and proper ADR monitoring should be done for patient safety.

Keywords: Cutaneous adverse drug reactions, CADR to vaccines, CADR to anti-fungal.

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INTRODUCTION

The skin is a frequent site of adverse drug reactions (ADRs). The World Health Organization (WHO) defines an ADR as "Any unpleasant, unexpected, or undesirable consequence of a medicine that occurs at dosages used in people for prevention diagnosis, treatment, or alteration of physiological processes" [1]. A cutaneous medication reaction occurs when the skin, its appendages, or mucous membranes experience an unwanted change. This comprises all negative effects related to drug release, regardless of etiology [2]. Cutaneous adverse drug reactions (CADRs) impact 2–3% of hospitalized patients, accounting for roughly 30% of all adverse pharmaceutical responses [3]. Fatal adverse cutaneous reactions account for just 2% of cases [4].

Different reactions occurred more frequently in different research on cutaneous ADRs conducted in India, according to an analysis of those studies. The most commonly reported responses are urticaria, fixed drug eruptions (FDE), and maculopapular rash [5].

Every year, different medications are licensed, which cause a shift in both the drugs' prescribing patterns and the frequency of CADRs [6,23].

As a result, it is imperative to keep a close eye on CADRs and the offending medications.

This study intends to assess the severity and etiology of CADRs in a tertiary care hospital, including probable medication and pattern.

METHODS

This was a retrospective study based on the cutaneous adverse medication responses that were recorded in the dermatology department of a tertiary care hospital in North India between July 2020 and August 2023, both for outpatients and inpatients. The Institutional Ethics Committee gave its clearance before this study could be carried out.

Information about the patient, the event's description, suspected drugs, and the use of concurrent medications were all taken from the ADR form. The study covered CADRs in patients of both sexes and all age groups.

The study excluded cutaneous ADR forms that lacked any of the Pharmacovigilance Program of India's mandated fields, such as patient initials and the date the reaction started. The modified Hartwig and Siegel scale was used to gauge the reaction's severity, and Naranjo's causality evaluation scale was employed to determine the reaction's cause.

Statistical analysis

A descriptive analysis of the data was done using Microsoft Excel 365, and the results were expressed as numbers and percentages.

RESULTS AND DISCUSSION

Out of 173,324 patients attending the skin department from July 2020 to August 2023, 187 patients were presented with CADRs. ADRs were most commonly reported among those aged 21–40 (48.12%) followed by those aged 41–60 (23.52%). The male-to-female ratio was 1.01.

The most prevalent CADR described by patients was a maculopapular rash (57.21%) followed by a FDE in 24.06%. Serious CADRs such as Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) accounted for 2.67% of all cases.

Other forms of CADRs reported are urticaria, vasculitis, lichen planus, photoallergic rash, eczematous rash, lupus erythematosus, and conjunctival hemorrhage (Table 1).

Diclofenac was the common culprit drug causing CADR in 9.90%, followed by paracetamol in 7.4 %, ofloxacin in 5.9%, ornidazole in 3.77%, and amoxicillin in 3.2% and followed by many other drugs, as mentioned in Table 2.

Antimicrobial agents (24.59%) were identified to be the leading cause of cutaneous adverse medication responses. NSAIDS (23.52%), antifungals (6.4%), anti-epileptics (4.2%), vaccinations (4.2%), antitubercular medicines (3.7%), and other drug types were less commonly involved (Table 3).

Among the anti-fungal group, fluconazole and itraconazole constituted an equal number of CADRs, 2.67% each.

Sodium valproate was the most common offending drug among the anti-epileptics in 2.13% of cases.

In our investigation, CADRs related to anti-rabies and COVID-19 vaccines were recorded in 2.1% and 1.6% of cases, respectively.

The most prevalent CADR associated with diclofenac, paracetamol, and ofloxacin was maculopapular rash followed by FDE (Table 4).

Serious cutaneous adverse reactions like SJS were reported with the intake of terbinafine and carbamazepine, SJS/TEN with Na valproate, and TEN with diclofenac and injection iron sucrose. Maculopapular and urticarial rash were reported with vaccines.

Most of the CADRs had onset between 24 h and 1 week (56.68%) followed by <24 h in 22.45% of the cases.

It was observed that, as per the modified Hartwig and Siegel scale, the majority of the cases (56.14%) were mild in severity, followed by moderate severity in 41.17% cases and severeness in 2.67% cases.

Table 1: Types of cutaneous ADR

Type of cutaneous ADR	Number (%)
1. Maculopapular rash	107 (57.21)
2. Fixed drug eruption	45 (24.06)
3. SJS/TEN	5 (2.67)
4. Vasculitis	1 (0.53)
5. Urticarial rash	10 (5.34)
6. Conjunctival hemorrhage	1 (0.53)
7.Drug-induced lichen planus	3 (1.6)
8. Photoallergic rash	1 (0.53)
9. Eczematous rash	1 (0.53)
10. Lupus erythematosus	2 (1.63)
Total	187 (100)

Table 2: Drug groups causing cutaneous ADR

Drug group	Number (%)
1. Anti-microbials	46 (24.59)
2. NSAIDS	44 (23.52)
3. Anti-fungal	12 (6.4)
4. Anti-epileptics	8 (4.2)
5. Vaccines	8 (4.2)
6. Anti-tubercular drugs	7 (3.7)
7. Anti-retroviral drugs	2 (1.06)
8. Anti-hypertensives	3 (1.60)
9. Anti-gout drugs	2 (1.06)
10. Anti-histaminic	4 (2.13)
11. Anti-diarrheal	1 (0.53)
12. Multivitamins	4 (2.13)
13. Anti-scabietic	1 (0.53)
14. Anti-psoriatic (Topical)	2 (1.60)
15. Miscellaneous drugs	44 (23.52)

According to Naranjo's causality assessment score, probable association was found in 70.05%, followed by possible in 27.21% of cases, and definite association in only 2.67% of cases.

Retrospective analysis of spontaneously reported cutaneous ADRs between July 2020 and August 2023 was done. During this time frame, 187 cases of CADRs were documented.

In 48.12% of the cases in our current study, the age group most frequently impacted was 21–40 years old. According to Padukadan *et al*. (52.22% of cases between 20 and 39 years), Brar *et al*. (35.6%) of cases between 21 and 40 years, and Rath *et al*. (48% of cases belonged to 21–40 years), our study's results are similar with those of those studies [19,22].

The increased incidence of ADRs in this group could be related to the certitude that the majority of patients visiting the OPD or admitted to wards were between the ages of 21 and 50, which corresponds to the large Indian population in this age range.

Males showed a slight predominance in this study (male-to-female ratio = 1.01), which coincided with Rana *et al*., in which the male-to-female ratio was 1.7:1 and was not similar to studies by Padukadan *et al*. (0.87:1) and Qayoom *et al*. (0.97:1), respectively [10,19,21].

A modest male prevalence in our analysis could be accredited to chance alone.

In this study, 56.68% of patients exhibited a reaction within 24 h to 1 week, whereas 22.45% had a reaction within 24 h.

Table 3: Drugs causing cutaneous ADR

Drug groups	Drugs	Number (%)
1. Anti-microbials	1. Ofloxacin	11
	2. Ornidazole+ofloxacin	7
	3. Amoxicillin	6
	4. Amoxiclav	6
	5. Cotrimoxazole	5
	6. Azithromycin	5
	7. Norfloxacin	4
	8. Cefixime	1
	9. Cephalexin	1
2. NSAIDS	1. PCM	14
	2. Diclofenac	17
	3. Acelofenac	5
	4. Piroxicam	2
	5. Nimesulide	2
	6. Naproxen	1
	7. Ibuprofen	1
	8. Etoricoxib	1
	9. Mefenamic acid	1
3. Anti-fungal	1. Fluconazole	5
	2. Itraconazole	5
	3. Terbinafine	2
4. Anti-epileptics	1. Na-valproate	4
	2. Carbamazepine	2
	3. Clonazepam	1
	4. Levetiracetam	1
5. Vaccines	1. Anti-rabies	4
	2. COVID	3
	3. Polio	1
6. Anti-tubercular drugs		7
7. ART		2
8. Anti-histaminic	1. Dextromethorphan	1
	2. Levocetirizine	1
	3. Fexofenadine	1
	4. Ebastine	1
9. Anti-gout	1. Febuxostat	2

This aligns with the research lead by Mahatme *et al*., who described reaction time of 24 h to 1 week in 52% of cases [9].

The literature offers an approximate time frame for developing various types of CADRs: Maculopapular rash <7 days, urticaria 7–21 days, SJS, TEN in 1–3 weeks, drug hypersensitivity syndrome in 2–6 weeks, photodermatitis up to 1-year, exfoliative dermatitis in 1–6 weeks, and FDE within 30 min to 16 h [12,15].

The distribution and morphological patterns of CADRs differ. The most frequent drug eruption in the present study was maculopapular rash (57.21%), which was followed by FDE (24.06%) and the results are consistent with the studies conducted in India and abroad [8,11,13-15,17]. However, in some studies, FDE was the most frequently reported cutaneous ADR [16-18].

Urticarial rash constituted 5.34% of the cases, more commonly caused by vaccines, NSAIDS, and antimicrobials (Fig. 1). A study done by Padukadan *et al*. showed a similar incidence of urticarial rash (7.2%) [7].

Antimicrobials accounted for the largest percentage of the drug category implicated in this study (24.59%), with NSAIDS coming in second (23.52%). Still, there was not much of a difference between the two groups. Our study's findings are in line with those of Bhanushali *et al*.'s investigations (anti-microbials: 27%, NSAIDs: 19%). and Mahatme *et al*. (NSAIDS: 24%), and anti-microbials: 48% [4,9,13].

Our study's findings are at odds with those of Nagraju *et al*., who found that NSAIDs were used in 31.2% of cases and anti-microbials in 26.25%) [12-14]

Table 4: Types of drug rash caused by most common implicated drugs

Drug group	Drugs	Types of cutaneous ADR
1. Anti-microbials	1. Ofloxacin	Maculopapular -4 FDE-3 Urticaria -1
	2. Ornidazole+ ofloxacin	Maculopapular-5 FDE-2
	3. Cotrimoxazole	Maculopapular-4 FDE-4
	4. Amoxyclav	Maculopapular rash- 2 Urticarial rash -1 FDE -2
	5. Azithromycin	FDE-1 Maculopapular -1
2. NSAIDS	1. Diclofenac	Maculopapular - 9 FDE- 7 TEN- 1
	2. PCM	Maculopapular - 10 FDE- 3 Vasculitis-1
	3. Nimesulide	Lichen planus -1 Maculopapular -1
3. Anti-fungal	1. Fluconazole	Maculopapular -4 FDE-1
	2. Itraconazole	Urticaria- 1 FDE-1 Maculopapular-1
	3. Terbinafine	SJS-1
4. Anti-epileptics	1. Na valproate	SJS/TEN-1 Urticaria-1 Maculopapular -1
	2. Levetiracetam	Maculopapular -1
	3. Carbamazepine	SJS -1 Maculopapular -1
5. Vaccines	1. Anti-rabies vaccine	Maculopapular-3
	2. COVID	Urticaria-2 Maculopapular-1
	3. Anti-polio vaccine	Maculopapular -1

The results indicated that fluoroquinolones (8%), beta-lactams (6.4%), macrolides (2.67%), combinations of fluoroquinolone and nitroimidazole (3.7%), and sulfur groups (2.67%) were the anti-microbial classes most frequently found to be objectionable.

Our study's findings are in line with those of Rana *et al*., where the most prevalent anti-microbial class was detected to be fluoroquinolones [21]. However, cotrimoxazole is still often utilized as an antibiotic in research conducted in other regions of India [22]. This might be explained by the fact that β-lactam antibiotics are widely used in our system or by the fact that antimicrobial usage varies by location.

Among NSAIDS, diclofenac (9.09%) was the most common offender, followed by paracetamol (7.48%), respectively (Fig. 2). Our findings are congruent with those of Badar *et al*. [3].

Maculopapular rash was the most prevalent drug rash caused by anti-microbials and NSAIDs followed by FDE. A case of TEN was reported with diclofenac. Vasculitis was reported in a case with PCM.

In our study, anti-fungal constituted 6.4% of cases, among which both fluconazole and itraconazole had similar incidences, followed by a single case with terbinafine. Our findings differ significantly from those of Nagaraju *et al*., who reported an incidence of antifungal-related ADRs of 2.5%.

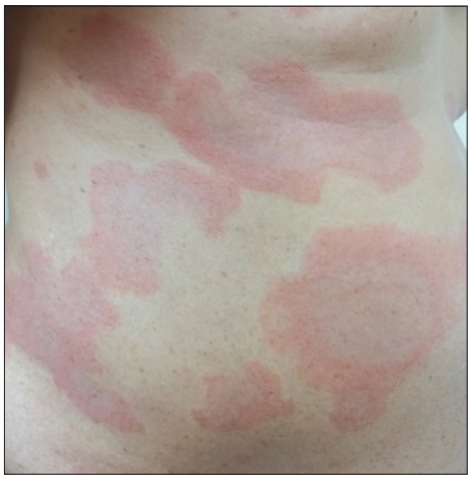

Fig. 1: Fifty-five years old male patient having urticarial rash following paracetamol intake

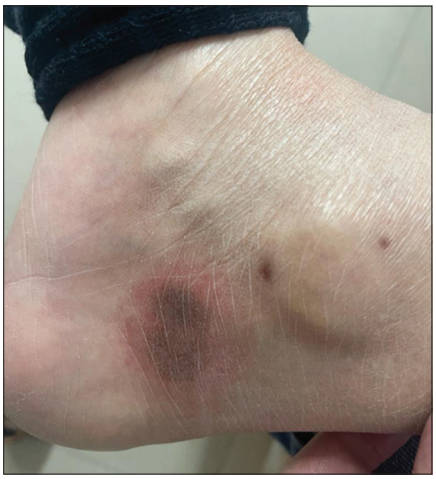

Fig. 2: Twenty-three years old male developed FDE within 8 h of diclofenac intake

FDE was the most prevalent pattern in our sample followed by lichenoid eruptions [20]. This could be explained by regional differences in the prevalence of fungal infections.

In our study, a case of SJS was reported with terbinafine.

Anti-epileptic medications were the culprit drugs in 4.2% (n=8) of the instances. Our investigation found a lower incidence of anti-epileptics compared to previous studies by Brar *et al*. (5.8%) and Bhanushali *et al*. (7%) [4,6].

Among anti-epileptics, sodium valproate was the most frequently implicated, followed by carbamazepine and levetiracetam. The results of our investigations are dissimilar to those of Patel *et al*. and Bhanushali *et al*., in which the most common accredited drug was carbamazepine, followed by phenytoin [4,17].

A case of SJS/TEN was reported with sodium valproate and a case of SJS with carbamazepine. According to the study by Tejas *et al*., maculopapular rash and SJS/TEN are common with antiepileptics [17].

In our study, vaccines are responsible for 4.2% of CADRs. Studies are lacking on CADRs caused by vaccines.

The anti-rabies vaccine was most implicated followed by the COVID vaccination. Maculopapular rash was reported with the rabies vaccine, whereas urticarial rash was more common with the COVID vaccine. Studies are lacking on CADRs caused by the rabies vaccine. However, Ma *et al*. (2018) reported the first case of SJS by rabies vaccination [8].

The meta-analysis included 32 studies totaling 946,366 persons. Following COVID-19 immunization, 3.8% reported cutaneous complaints. Injection site reactions can result in cutaneous symptoms such as urticaria (72.16%), rash (14%), and rare adverse reactions such as flare-ups of pre-existing dermatoses (0.07%) and delayed inflammatory reactions to tissue filler [25].

According to Naranjo's scale, in our study, most of the reported ADRs were probable (70.05%), followed by possible (27.21%), and only 2.6% were definite.

The results of our investigation are similar to the study by Bhanushali *et al*., in which 72% comprised probable ADRs, whereas possible ADRs were 28% [4].

Following mild (56.14%) and moderate (41.17%) ADRs, severe ADRs were detected in just 2.6% of instances, according to the Hartwig severity evaluation scale.

Following treatment, most ADR patients made a full recovery. Our study's findings are consistent with research conducted by Badar *et al*. and Rath *et al*. Most of the adverse events (ADRs) in both studies were moderate [3].

CONCLUSION

The clinical pattern and spectrum of CADRs were studied in 187 subjects. CADRs range from maculopapular rash to severe SJS. The predominant patterns of reactions observed were maculopapular rash followed by FDEs. Antimicrobials were the most common drug group incriminated in 24.5% of patients, followed by NSAIDs in 23.5% of cases. This study also sheds light on the ADRs caused by vaccines. Adverse drug reactions are a definite challenge for the treating physician. The pattern of CADRs is changing every year due to physician and patient preferences or the emergence of new drugs on the market. It emphasizes the need for more extensive ADR monitoring in the hospital and will be useful in generating more data about ADR.

AUTHORS' CONTRIBUTIONS

Dr. Tejinder Kaur formulated the concept, design of the project and reviewed the manuscript, Dr. Nikita Margam assisted in preparation of the manuscript, data acquisition and data analysis, and Dr. Gurpreet Kaur Randhawa helped in conceptualizing and reviewed the manuscript.

CONFLICTS OF INTEREST

Nil.

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Nil.

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