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Original Research Article

Decoding dermatologic dilemmas: Assessment of cutaneous adverse drug reactions at a tertiary care hospital in South India - A retrospective study

Nafeesath Jafna[1], Dhivya Palaniappan[1]*, Seethalakshmi Ganga Vellaisamy[1], Navakumar Manickam[1], Kannan Gopalan[1]

[1]Dept. of Dermatology, Venerology, Leprosy, Vinayaka Missions Kirupananda Variyar College Medical College, Salem, Tamil Nadu, India

Abstract

Background: The incidence of adverse cutaneous drug reaction (cADR) varies from 2-3% among hospitalized patients. Around 2% of all cADR may be severe and end in fatalities.
cADR can range from mild, exanthematous rash to severe, life-threatening reactions.
Objective: This study aimed to draw association between potential offensive drugs and the ensuing cutaneous adverse reactions, and to assess the various morphological patterns and severity of reported adverse reactions.
Materials and Methods: This was an observational study conducted between February 2023 and March 2024 in a tertiary care hospital in Tamil Nadu. A total of 63 patients with cADR were evaluated for a period of one year. Detailed history, clinical examination and relevant investigations, along with treatment outcomes were analysed.
Results: We noted a wide spectrum of cADR ranging from maculopapular eruption and fixed drug eruption to severe cutaneous adverse reactions (SCARs) like SJS/TEN. Antimicrobials were identified as the major factor associated, followed by NSAIDs. The most common presentation of cADR was fixed drug eruption (46%) followed by maculopapular eruption (17.5%). SCARs accounted for 26.9% of the total cADR in our study. SJS/TEN overlap (12.7%) was the most common SCAR we observed in our study, the most frequent drugs implicated in SCAR were antiepileptics (25%).
Conclusion: The most common cADR observed in this study was FDE and antibiotics were the most commonly associated agents.

Keywords: Cutaneous adverse drug reaction, Pharmacovigilance, Severe cutaneous adverse reactions

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1. Introduction

The skin is one of the most common target organs for adverse drug reactions, constituting 10-30% of all drug reactions.[1] The incidence of adverse cutaneous drug reaction (cADR) varies between 2-3% among hospitalized patients. Around 2% of all cADR may be severe and end in fatalities.[2,3]

cADR can range from mild, exanthematous rash to severe, life-threatening reactions like Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). The most common types of cADR include maculopapular rash and urticarial eruptions.[4]

Antibiotics, anticonvulsants, antineoplastic drugs, nonsteroidal anti-inflammatory drugs, and allopurinol are the most frequent incriminating drugs associated with cADR. Drugs like antibiotics and anticonvulsants may lead to toxidermia complications in 1-5% of patients treated.[5,6]

Mechanisms that account for drug reactions can be broadly classified into two: immunological and non-immunological.[5,7] Most (75-80%) cADR are due to non-immunological effects while around 20-25% are caused due to immunological causes.[3]

Some important risk factors for cADRs include (i) patient related factors, like age of patients, female sex, viral

*Corresponding author: Dhivya Palaniappan
Email: dhivyamedical@gmail.com

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infection, genetic variations in the metabolism of the drug and association with human leucocyte antigen (HLA) and (b) drug related, viz number of drugs taken, route of administration, duration of intake, dose and variation in metabolism.[4,7]

Severe cutaneous adverse reactions (SCAR) usually include Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). TEN, also known as Lyell syndrome may occur in continuum with SJS.[5] SJS and TEN can lead to severe morbidity and mortality, with a mortality rate of 5-10% for SJS and 25-30% for TEN.[4] The warning signs of imminent SCAR include skin pain, epidermolysis and positive Nikolsky's sign.[4]

A systemic study of cADR, regarding possible risk factors, patterns of drug eruption and drug eruption-related factors influencing prognosis, is of crucial clinical significance.

2. Aims and objectives

1. To identify the incidence of common drug eruptions and their associations with potential causative drugs in a hospital-based setting
2. To determine the most common drugs implicated in severe cutaneous adverse reactions (SCAR)
3. To assess the outcome and prognosis in patients with SCAR

3. Materials and Methods

This was an observational study conducted between February 2023 and March 2024 at the Department of Dermatology in a tertiary care hospital in Tamil Nadu. The department of dermatology keeps a database of all patients with cADR since 2014. All suspected cases of cADR were evaluated by two qualified dermatologists from our department.

A total of 63 patients with CADR were evaluated for a period of one year, out of a total caseload of 11,230 patients. Information, regarding baseline demographic characteristics, precipitating and predisposing factors, drug history, clinical examination and relevant investigations, along with treatment outcomes, was collected from the clinical records of the patients.

All cases of cADR were broadly classified into minor and severe reactions. Severe reactions included SJS-TEN, DRESS, AGEP and erythroderma. Minor reactions were composed of maculopapular rash, FDE, urticarial and angioedema, EMF, acute cutaneous necrosis and allergic contact dermatitis-like.

The severity of the reaction was graded based on the Naranjo Adverse Drug Reaction Probability Scale.[8]

3.1. Statistical analysis

The data gathered was compiled, coded and entered in a Microsoft Excel data analysis sheet. Analysis of data was performed using SPSS version 27.0. Descriptive statistics, e.g., mean, median, minimum, maximum and percentages was calculated to describe the demographic data.

4. Results

A total of 63 patients were studied among 11,230 patients over a period of one year, yielding an incidence rate of 0.56% and the following observations were made.

The majority of patients belonged to the age group of 21-30 years, with the mean age being 41.14 ±17.90 (**Table 1**). The youngest patient in this study was 10 years old and the oldest 80 years old.

Among the affected cases, 55.6% were males and 44.4% were females. The male to female ratio was 1.25:1 (**Table 1**). A previous history of cADR was found in 19 of our patients, comprising 30.2% of the total population. Many of our patients (60.3%) had comorbidities such as diabetes mellitus, hypertension, epilepsy and a previous history of tuberculosis.

Fixed drug eruption (46.0%) was the most common type of reaction pattern observed among our patients, followed by maculopapular exanthem (17.5%). This was followed by Steven-Johnson syndrome/toxic epidermal necrolysis overlap (12.7%), and Steven Johnson syndrome alone (7.9%). (**Table 2)(Figure 1)**

Mucosal involvement was observed in 50.8% patients. It was predominantly seen in FDE (40.6%), (**Figure 2**) SJS/TEN (25%) and SJS (15.6%).

The most frequent time taken for the onset of rash was 2-5 days (46%), followed by 6-10 days (22.2%). Average time taken for the onset of FDE was 2-5 days (68.9%), while it was one day for both maculopapular rash (50%) and urticarial with angioedema (100%).

Among the drug groups implicated, antibiotics (25.5%) were the most common, succeeded by NSAIDs (22.2%), and polypharmacy (15.9%) where the patient was on multiple drugs, making it unfeasible to identify a single culprit drug. Among antibiotics, fluoroquinolones (12.7%), penicillins (4.8%) and cephalosporins (4.8%), were most frequently implicated (**Table 3**). Antifungals were found to be the incriminating drug in 4.8% of patients. Ciprofloxacin (7.9%) and carbamazepine (7.9%) were the most common individual drugs implicated.

The frequency of drugs implicated in each cADR was summarized (**Table 4**). NSAIDs were the most frequent drugs implicated in fixed drug eruption while penicillins and fluoroquinolones were the predominant causative agents in maculopapular eruption.

SJS/TEN was mainly due to NSAIDs and carbamazepine.(**Figure 3**)

Seventeen patients (26.9%) developed SCAR, out of which eight had SJS-TEN overlap, five had SJS alone, and two patients each developed DRESS and erythroderma. The most frequent drugs implicated in SCAR were antiepileptics (25%), polypharmacy (19%), NSAIDs (12.5%) and cephalosporins (12.5%).

Figure 1: SJS in a patient on analgesics

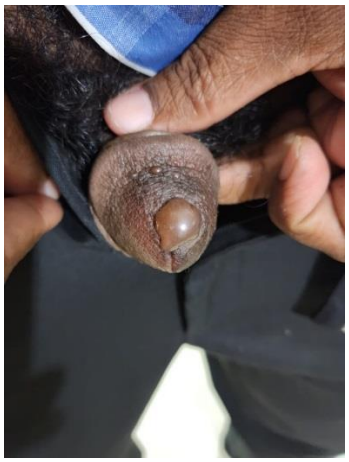

Figure 2: Bullous FDE over penis caused by NSAIDs

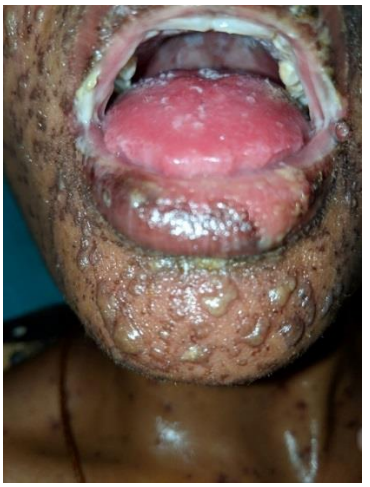

Figure 3: SJS-TEN overlap caused by Carbamazepine (oral involvement)

The shortest reaction time noted was 5 days in a patient who developed SJS/TEN after ingesting a combination of drugs and the longest time taken was 21 days in a patient who developed SJS after taking chloramphenicol. Eight among these patients had life-threatening disease while the other eight were hospitalized. No patient succumbed to death.

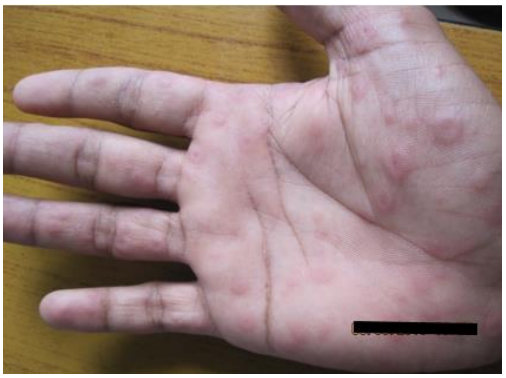

Figure 4: Erythema multiforme caused by Ciprofloxacin over palms

Table 1: Clinico-demographic profile of the study population

S.No	Explanatory variable	Parameter	n (%) n = 63
1	Age Mean age: 41.14 ±17.90	≤ 10 years	1.6
		11-20 years	12.7
		21-30 years	23.8
		31-40 years	14.3
		41-50 years	17.5
		51-60 years	14.3
		> 60 years	15.9
		Total	100
2	Sex M:F – 1.25:1	Male	55.6
		Female	44.4

		Total	100
3	Severity of reaction	Minor	74.6
		Severe	25.4
		Total	100
4	Presence of past history	Present	30.2
		Absent	69.8
		Total	100
5	Presence of mucosal involvement	Present	50.8
		Absent	49.2
		Total	100
6	Time taken from drug intake to onset of symptoms	1 day	23.8
		2-5 days	46.0
		6-10 days	22.2
		11-14 days	6.3
		>14 days	1.6
		Total	100

Table 2: Types of drug eruption

S.No	Type of rash	Frequency	Percent
1.	Fixed drug eruption	29	46.0
2.	Maculopapular rash	11	17.5
3.	Steven-Johnson syndrome/Toxic epidermal necrolysis	8	12.7
4.	Steven-Johnson syndrome	5	7.9
5.	Urticaria and angioedema	2	3.2
6.	Erythema multiforme (**Figure 4**)	2	3.2
7.	Drug rash with eosinophilia and systemic symptoms	2	3.2
8.	Erythroderma	2	3.2
9.	Acute cutaneous necrosis	1	1.6
10.	Contact dermatitis-like	1	1.6

Table 3: Drugs implicated in cutaneous adverse drug reactions

Drug implicated	Frequency	Percent
NSAIDs/analgesics	14	22.2
Polypharmacy	10	15.9
Ciprofloxacin	5	7.9
Carbamazepine	5	7.9
Unknown drugs	5	7.9
Penicillins	3	4.8
Cephalosporins	3	4.8
Other fluoroquinolones	3	4.8
Antifungals	3	4.8
Antihistamines	3	3.2
Other antiepileptics	2	3.2
Olanzapine	1	1.6
Amitriptyline	1	1.6
Anti-tuberculosis therapy	1	1.6
Nitrofurantoin	1	1.6
Cotrimoxazole	1	1.6
Tranexamic acid	1	1.6
Lignocaine	1	1.6
Total	63	100

Table 4: Frequency of drugs implicated in cutaneous adverse reactions

S.No.	Type of Rash	Drug implicated	No. of patients
1.	Fixed drug eruption	NSAIDs (38%)	11
		Polypharmacy (17.3%)	5
		Unknown (13.7 %)	4
		Ciprofloxacin (3.4 %)	1
		Other fluoroquinolones (3.4 %)	1
		Cephalosporins (3.4%)	1
		Cotrimoxazole (3.4%)	1
		Levocetrizine (3.4 %)	1
		Carbamazepine (3.4%)	1
		Antifungals (3.4%)	1
2.	Maculopapular eruption	Penicillins (18.2%)	2
		Ciprofloxacin (18.2%)	2
		Other fluoroquinolones (18.2%)	2
		Polypharmacy (18.2%)	2
		Carbamazepine (9%)	1
		Olanzapine (9%)	1
		Amitriptyline (9%)	1
3.	Steven-Johnson syndrome/Toxic epidermal necrolysis	NSAIDs (25%)	2
		Carbamazepine (25%)	2
		Polypharmacy (25%)	2
		Other antiepileptics (12.5%)	1
		Cephalosporins (12.5%)	1
4.	Steven-Johnson syndrome	Penicillins (20%)	1
		Cephalosporins (20%)	1
		Chloramphenicol (20%)	1
		Other antiepileptics (20%)	1
		Unknown (20%)	1
5.	Urticaria and angioedema	Antifungals (50%)	1
		Tranexamic acid (50%)	1
6.	Erythema multiforme	Montelukast-levocetrizine (50%)	1
		Unknown (50%)	1
7.	Drug rash with eosinophilia and systemic symptoms	Anti-tuberculosis therapy (50%)	1
		Polypharmacy (50%)	1
8.	Erythroderma	Carbamazepine (50%)	1
		Antifungals (50%)	1
9.	Acute cutaneous necrosis	Lignocaine (100%)	1
10.	Contact dermatitis-like	Nitrofurantoin (100%)	1

Table 5: Frequency of rash and sex distribution

Type of rash	Males	Females	Total
FDE	17	12	29
Maculopapular rash	6	5	11
SJS/TEN	3	5	8
SJS	4	1	5
Urticaria and angioedema	0	2	2
EMF	1	1	2
DRESS	1	1	2
Erythroderma	0	2	2
Acute cutaneous necrosis	1	0	1
Contact dermatitis-like	1	0	1

Table 6: Comparison of data between current study and existing studies

Author	Year of study	Place of study	Commonly implicated age group	Commonly implicated gender	Most common type of rash	Most common drug group
Current study	2024	TN, South India	21-30 years	Males	FDE	Fluoroquinolones
R Lakshmi et al.[10]	2021	South India	40-60 years	Males	Maculopapular rash (31.5%)	Penicillins
Niharika Jha et al.[15]	2018	Punjab, India	20-40 years	Males	Maculopapular rash (42.63%)	Cephalosporins
Raja Amrinder et al.[9]	2016	Punjab, India	31-40 years	Females	FDE (33.3%)	Fluoroquinolones
Siew-Eng Choon et al.[1]	2012	Johor, Malaysia	20-59 years	Females	Maculopapular rash (42.3%)	Penicillins
Ruchika Nandha et al.[16]	2011	North India	21-30 years	Females	Maculopapular rash (42.85%)	Sulfonamides
Pudukkan and Thappa[11]	2004	JIPMER, Pondicherry	20-39 years	Females	FDE (31.1%)	Sulfonamides

5. Discussion

Cutaneous reactions are the most common manifestations of adverse drug reactions.[9] It is imperative for the treating doctor to have a clear knowledge of the clinical spectra of CADRs and the drugs which are frequently involved in such adverse reactions. As there are no specific tests for diagnosing cADR, taking a proper history is crucial. History must include duration of drug intake, reaction time, the response of drug dechallenging and rechallenging of the suspected drug, and any past history of similar reactions.[10]

Most epidemiological studies show a wide variation in the prevalence rate of cADR, ranging from 0.36% to 12.2%.[1,11-14] The current study included 63 cases over a period of one year, yielding an incidence rate of 0.56%. This may not be indicative of the actual prevalence of cADR during this period as patients with unsure diagnosis and deficient history were not included. Furthermore, underreporting by patients and indifference towards minor reactions due to lack of awareness are thought to have contributed to the reduced incidence of cADR in this study.

A slight male preponderance was noted in our study, which is in accordance with studies conducted by Rajendran et al,[10] Niharika Jha et al[15] and Siw-Eng Choon et al[1] while some other studies[9,11,16] showed a female preponderance. This disparity could be due to the descriptive analysis of gender distribution among patients without adjusting it to that in the overall population.

Most of our patients were in the age group of 21-30 years (23.8%) and 41-50 years (17.5%), in concordance with the studies conducted by Choon et al, Jha et al and others.[1,9,11,15,16]

The incidence of cADR was significantly less among patients aged 10 and less, and more in patients over the age of 20 years (**Table 1**). The risk of adverse cutaneous reaction escalates with age due to increased use of drugs, altered drug handling by the body and a higher potential for drug interactions.[1]

The most common clinical pattern of cADR observed in our study was fixed drug eruption (46%), which was in conformity with studies conducted by Raja Amrinder et al,[9] and Pudukkan and Thappa.[11] In contrast, authors like Choon et al, Rajendran et al and others noted maculopapular eruption as the most common pattern of drug rash.[1,10,15,16] This variation could be due to dissimilarities in the pattern of drug usage and reaction rates of the drugs, and different pharmacogenetic characteristics along with geographic variations of the study populations.[10,11]

Antibiotics (25.5%) were the most commonly associated factor in our study, thus confirming the results produced by other authors like Choon et al, Rajendran et al, Jha et al, Nandha R et al, and others.[1,9-11,15,16] This was closely followed by NSAIDs (22.2%), which are already established offenders in cADR (**Table 3**). Fluoroquinolones (12.7%) were the predominant incriminating antibiotics in our study, as was the case in the study conducted by Raja Amrinder et al.[9] This was followed by penicillins (4.8%) and cephalosporins (4.8%). Other studies conducted by Rajendar et al[10] and Siew-Eng Choon et al[1] showed penicillins to the be the most frequently implicated antibiotics while cephalosporins were most commonly incriminated in the study conducted by Jha et al.[15]

Ciprofloxacin and carbamazepine were the single most commonly implicated drug in our study. The majority of cADR caused by ciprofloxacin was FDE, and that of carbamazepine was SJS/TEN.

It was noted that 30.2% our patients had a previous history of similar complaints in the past (**Table 1**). Many of our patients (60.3%) gave a history of known comorbidities

such as hypertension, diabetes mellitus, epilepsy and previous history of tuberculosis. Co-existing systemic illnesses increase the risk of developing adverse drug eruptions.[17]

SCARs accounted for 26.9% of the total cADR in our study, which was higher than the numbers encountered by Rajendran et al[10] and Jha et al.[15] This could be due to referral bias, wherein patients with severe manifestations would have been identified and referred more frequently than those with minor illnesses as this is a tertiary care centre.

We observed that antiepileptics were the predominant causative agent in SCAR, which was consistent with the findings in most other studies conducted by Choon et al, Rajendran et al and Jha et al.[1,10,15,18] Carbamazepine was the most common antiepileptic implicated in SCAR (Table 4). SCAR due to carbamazepine has been associated with HLA-BFNx011502.[19]

Minor cADR usually subside with withrawal of the associated drug, and only require symptomatic management at best. They resolve within 1-2 weeks and show excellent prognosis, except for residual hyperpigmentation in FDE. SCAR on the other hand, require prompt treatment with intensive care support and immunosuppressive therapies like high dose corticosteroids, cyclosporine and intravenous immunoglobulins. Recovery takes a longer duration of weeks to months, based on the severity of presenting symptoms. Clinicians must identify red flags such as high fever, targetoid and purpuric lesions, blistering with epidermal detachment, elevated liver enzymes, renal dysfunction and hypotension.

This study helps identify high-risk drugs and severe reactions, thereby strengthening pharamacovigilance and clinical preparedness for early diagnosis and treatment. It also lays the groundwork for future research and policy in drug safety.

6. Limitations

This was a single center study and the sample size was small. Long-term follow-up and drug re-challenge were not done, hence treatment outcomes were not assessed.

7. Conclusion

A wide spectrum of cADR was noted, ranging from maculopapular eruption and FDE to SCARs like SJS/TEN. Antimicrobials were identified as the most commonly associated agents, followed by NSAIDs. The most common presentation of cADR was FDE followed by maculopapular eruption.

cADR may significantly impact the quality of life of patients, deterring them treatment adherence and may subsequently lead to treatment failure. It also poses a medico-legal threat to the treating doctors. Hence, early identification of cADR is imperative as it may significantly reduce morbidity and mortality. SCAR is a medical emergency in dermatology where immediate management is crucial to prevent fatality.

Patients must be educated to avoid self-treatment and re-administration of implicated drugs. Prevention and early detection of cADR can be facilitated by closely monitoring the patients when a new drug is introduced.

8. Conflict of Interest

None.

9. Source of Funding

None.

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Annexure

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			