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PATTERN OF CUTANEOUS ADVERSE DRUG REACTION IN TERTIARY CARE HOSPITAL TRICHY

Dr. Rajalakshmi T.[1], Gnanasekaran R.[2], Dr. Ann Jenita J.[3], Dr. Dharshini S.[4*]

[1]Postgraduate, Department of Dermatology, Venereology and Leprosy, Trichy SRM Medical College, Trichy, Tamil Nadu, India.
[2]Professor & HOD, Department of Dermatology, Venereology and Leprosy, Trichy SRM Medical College, Trichy, Tamil Nadu, India.
[3]Postgraduate, Department of Dermatology, Venereology and Leprosy, Trichy SRM Medical College, Trichy, Tamil Nadu, India.
[4*]Assistant Professor, Department of DVL, Trichy SRM Medical College, Trichy, Tamil Nadu, India.

***Corresponding Author:** Dr. Dharshini S.,
*Assistant Professor, Department of Dermatology, Venereology and Leprosy, Trichy SRM Medical College, Trichy, Tamil Nadu, India.

ABSTRACT

Background

The World Health Organization defines an adverse drug reaction as unintentional, harmful, undesirable impact of a medicine that occurs at dosages utilized in humans for prophylaxis, diagnosis and therapy. Dermatological signs of adverse drug reactions are more prevalent, and the pattern of cutaneous reactions varies across different medications. Therefore, comprehending the specific characteristics of drug reactions may assist in pinpointing the culpable medication. The main aim of this study is to determine clinical pattern of various CADR's in general population

Methods

Twelve patients who experienced CADRs were the subjects of a descriptive study. Patient demographics, suspected medications, clinical presentation of CADRs, administration route, and causality evaluation were all gathered. The likelihood of drug causation was assessed using the WHO-UMC criteria and the Naranjo Algorithm.

Results

The median age of the patients was 37 years (IQR: 20), with a mean age of 38.33 ± 13.29 years (range: 18–64 years). Of the cases, 58.3% (n=7) of the patients were male, and 41.7% (n=5) were female. Maculopapular rash accounted for 25% of CADR cases, with fluid-filled skin lesions and pruritus following at 16.7% each. Injectable ciprofloxacin (8.3%), injectable cotrimoxazole (8.3%), and injectable penicillin (16.7%) were the medications most commonly linked to CADRs. Oral drugs like ibuprofen, cefixime, paracetamol, and doxycycline were also linked. One patient's Naranjo score was 7, while the others' scores were 6, indicating that all of the reactions were "probable." According to WHO-UMC criteria, all 12 cases were classified as "likely."

Conclusion

ADRs should be identified promptly, and future use should be done with caution. Therefore, it is essential to promote awareness among reporting physicians regarding the necessity of documenting adverse drug reactions (ADRs) through regular sensitization programs on pharmaco-vigilance,

which will motivate healthcare professionals to report adverse reactions associated with pharmaceuticals, vaccines, medical devices, and biological products.

Keywords: Cutaneous adverse drug reactions (CADR), fixed drug eruption, Naranjo Algorithm.

INTRODUCTION

Cutaneous adverse drug reactions (CADR), otherwise known as toxicodermia, are cutaneous reactions resulting from administration of systemic drug. The symptoms vary from severe manifestations, including Lyell's syndrome to modest erythematous skin lesions. They constitute a broad domain encompassing several clinical patterns devoid of distinctive characteristics indicative of drug causality.[1,2] Identifying causal factors is essential. Adverse medication responses frequently present with dermatological symptoms. Research indicates that the prevalence of cutaneous adverse drug reactions (CADRs) in wealthy nations ranges from 1 to 3%, whereas in developing nations, it is elevated, from 2 to 5%.[3]

CADRs is one of the most commonly reported adverse drug reactions (ADRs), accounting for 10-30%, which represents 8% of hospitalizations among dermatology inpatients in India. These reactions adversely impact patients in the form of prolonged hospitalization, systemic complications, mortality, morbidity and economic burden.[4]

Commonly reported CADRs are maculo-papular rash, fixed drug eruption (FDE), and urticarial reaction. A diverse array of pharmacological categories can induce CADRs, and this phenomenon may fluctuate with varying prescribing practices, the introduction of novel medications, self-medication, and referral bias. A broad range of cutaneous adverse medication reactions exists, ranging from transitory maculo-papular rash to toxic epidermal necrolysis. Drug reactions can be categorized as benign or severe CADRs. According to the WHO criteria, roughly 2% of all drug-induced skin responses are classified as "serious."[5,6]

While most cutaneous adverse drug reactions are minor and self-resolving, severe cutaneous adverse drug reactions (SCAR) such as toxic epidermal necrolysis (TEN) ,Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) are linked to considerable morbidity and mortality.[7]

Numerous systemic medications are possible triggers for cutaneous adverse drug responses. Contrast agents and specific categories of pharmaceuticals, including antibiotics, anticonvulsants, anti-neoplastics, non-steroidal anti-inflammatory medications, and allopurinol, are recognized as frequent offenders. Antibiotics and antiepileptic medications induce hazardous consequences in 1% to 5% of cases.[8]

The World Health Organization (WHO) established a pharmaco-vigilance program (PvP) to report all adverse medication reactions following the thalidomide catastrophe identified in 1961. The Pharmaco-vigilance Programme of India (PvPI) was begun by the Government of India on July 14, 2010.[9]

The Adverse Drug Reaction (ADR) Probability Scale, commonly known as the Naranjo Scale, was established in 1991 by Naranjo et al. The Naranjo Algorithm is a systematic approach for evaluating the causal association between a recognized adverse clinical event and a medication, utilizing a straightforward questionnaire to allocate probability scores.[10]

Adverse medication reactions represent a significant clinical issue regarding human suffering and elevated healthcare expenses. Consequently, understanding of potential adverse cutaneous effects of medications and the substances most commonly linked to them is imperative. Identifying the etiology of CADRs necessitates a systematic methodology grounded in clinical characteristics, temporal aspects, and the formulation of a targeted differential diagnosis.

Hence this study aimed to identify the prevalence of different types of CADRs throughout the general population.

OBJECTIVES

- To determine clinic-epidemiological pattern of various CADR's among patients visiting Dermatology department
- To determine common drugs causing CADRs and assess causality and severity.

MATERIAL AND METHODS

An observational study was done to assess the clinical pattern and drugs causing cutaneous adverse drug reactions (CADR) among patients, who presented to Department of Dermatology, Trichy SRM Medical College Hospital and Research Centre. The diagnosis of CDR was made and they are included in this study.

The study was done for six months duration and universal sampling method was adopted for selection of participants. The expected frequency of CADR patients was two per month and 12 patients were included in this study. The patients of age more than eighteen years and patients referred from other departments for the probable diagnosis of CADR were included in this study. The patients who had CADR due to unknown drugs and patients who developed drug reaction flowing intake of Ayurveda, homeopathy, indigenous medicines were excluded from this study.

The study was presented to Institutional Ethical Committee, Trichy SRM Medical College Hospital and Research Centre and it was approved. Informed consent was obtained by the patients to participate in this study after explaining the study protocols. A detailed history, clinical examination, drug therapy were collected using semi - structured questionnaire. The variables like age, gender, duration of ADR were observed and used for analysis. The morphology of cutaneous lesion, mucosal lesion and systemic involvement was observed.

"A response to a drug which is noxious and unintended, and which occurs at normal doses used in patients for prophylaxis, diagnosis, or used for treatment of disease , or drugs used for modifications of physiological function, was taken into consideration.[11] Clinical examination, case record review, pre-ADR drug use history, patient interviews, and dechallenge (impact of drug withdrawal on response) were used to identify CADR. Rechallenge, or reintroducing the suspicious medicine after improvement, was avoided for ethical concerns. To identify probable drugs, however, data on unintentional rechallenges was utilized whenever feasible. Patients were monitored until they recovered from their CADRs.

The causality was assessed using Naranjo's ADR probability scale and WHO causality assessment scale. The use of the WHO-UMC system for standardised case causality assessment, adverse drug reactions are classified into defined terms according to specific assessment criteria. The **"Certain"** category includes an event or laboratory test abnormality that has a plausible time relationship to drug intake, cannot be explained by disease or other drugs, shows a plausible response to withdrawal both pathologically and pharmacologically, is definitive either phenomenologically or pharmacologically-for example, a recognised pharmacological phenomenon or an objective and specific medical disorder-and, if required, demonstrates a satisfactory rechallenge; The **term "Probable/Likely"** describes an occurrence or abnormality that has a plausible temporal correlation to drug usage, is not likely to be brought on by illness or other substances, exhibits a clinically plausible withdrawal response, and doesn't call for a rechallenge; Events that have a plausible temporal correlation to drug use but that may also be explained by underlying illnesses or other substances fall under the **"Possible"** category; information about drug withdrawal may be insufficient or ambiguous. The **"Unlikely"** classification describes events where the time to drug intake makes a causal relationship improbable, though not impossible, and for which disease or other drugs provide a more plausible explanation. The **"Unclassifiable"** category applies when a report suggests an adverse reaction but cannot be judged due to insufficient or contradictory information as well as when the data cannot be supplemented or verified.

The Adverse Drug Reaction Probability Scale, also known as the Naranjo Algorithm, uses a straightforward questionnaire to assign probability scores in order to determine whether a drug and an observed adverse clinical event are causally related.[12] The Naranjo Algorithm, another name for the Adverse Drug Reaction (ADR) Probability Scale, is a structured instrument that evaluates the

possibility that an adverse event is truly caused by a drug and not by other causes. Each of the ten questions is responded with "Yes," "No," or "Do not know," and each response is given a point value of either +1, +2, 0, or -1. The causation is then categorized as certain, plausible, possible, or doubtful based on the sum of the scores from all of the responses, the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less. These inquiries are: (1) Has this reaction been reported conclusively before? (2) After the medication was administered, did the adverse event manifest?(3) When the medication was stopped or a particular antagonist was administered, did the unpleasant response get better? (4) When the medication was given again, did the unpleasant reaction recur? (5) Did the reaction have any other potential causes? (6) Did the unpleasant reaction return after a placebo was given? (7) Were dangerous levels of the medication found in the blood or other bodily fluids? (8) Did the reaction get worse when the dose was increased, or did it get better when the dose was decreased? (9) Has the patient ever experienced a comparable reaction to the medication or a similar agent? (10) Was there any more objective evidence to support the unfavourable event?

Statistical Analysis

Data were entered and analysed using Microsoft Excel 2021 and it was expressed using frequencies and proportions. Drug reactions were compared between the age group and gender using chi square test. Drug reactions due to type of drugs were compared using chi-square test.

RESULTS

This study was conducted among 12 patients who were diagnosed as CADR to assess age and gender distribution and causality assessment. The mean age of CADR patients was 38.33±13.289 years with a minimum age of 18- 64 years, and median age (IQR) was 37 (20).

Figure 1 shows the gender distribution among patients. Seven (58.3%) of them were male and five (41.7%) of them were female.

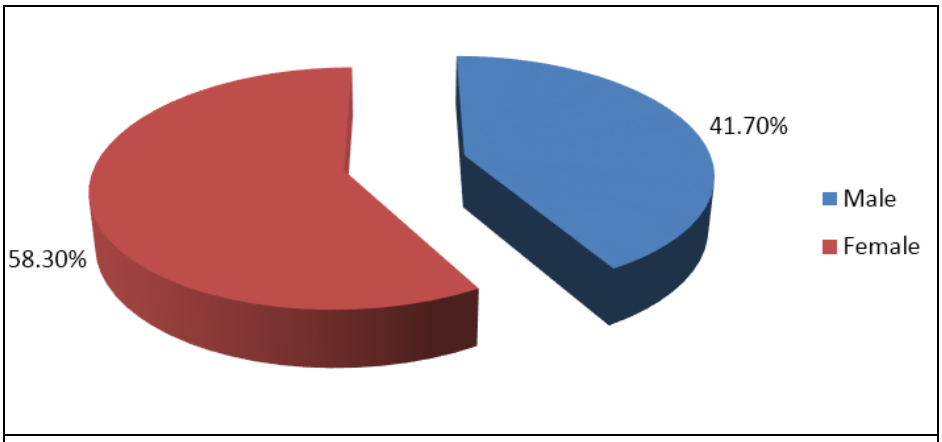


Figure 1: Gender distribution among patients

Table 1 describes the type of lesion occurred among CADR patients. Maculopapular rash was the most often reported kind of CADR, with 3 instances (25%). Following this, two patients (16.7%) had pruritis and fluid-filled blisters on their skin. Additional CADRs that were noted were erythematous plaques, hyperpigmented macules over the perioral area, erosions with bullae, edematous plaques on both palms, and multiple flaccid bullae, all of which occurred in one patient (8.3%). These results demonstrate the variation in the clinical manifestation of CADRs across those who are impacted. The association between gender and Type of lesion was found to insignificant (p = 0.408)

Table 1: Type of CADR among patients			
Sl. No.	**CADR**	**Frequency**	**Proportion**
1	Edematous plaques both palms	1	8.3%
2	Erosions with bullae	1	8.3%
3	Erythematous plaques	1	8.3%
4	Fluid filled skin lesions	2	16.7%
5	Hyper pigmented macules over perioral region	1	8.3%
6	Maculopapular rash	3	25%
7	Multiple Flaccid bullae	1	8.3%
8	Pruritus	2	16.7%

Figure 2 shows the duration of CADR among patients. Two of them reported 2 and 3 days of illness while 8 patients reported to have one day duration. The association between gender and duration of CADR was found to insignificant (p = 0.152)

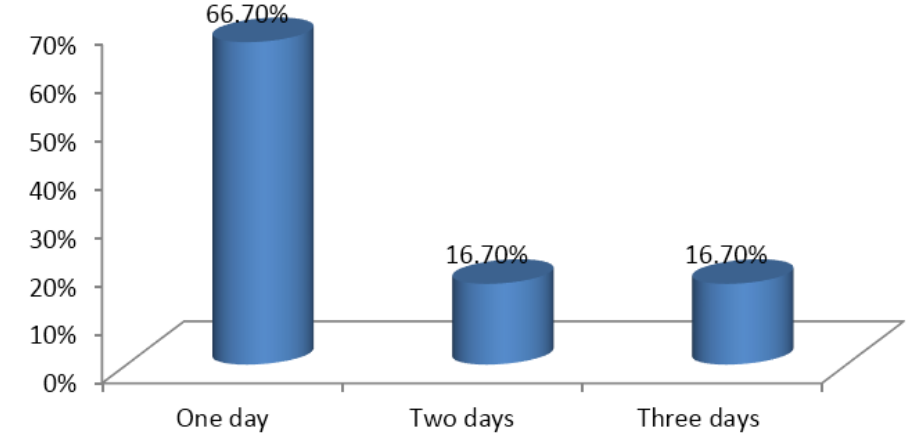


Figure 2: Duration of CADR

Table 2 shows the drug and its route among CADR patients. The most commonly reported medication, injectable penicillin, was linked to two cases (16.7%). Oral doxycycline, cefixime, 650 mg of paracetamol, cefazolin, ibuprofen, cotrimoxazole, and injectable versions of ciprofloxacin, ceftriaxone, and cotrimoxazole were among the medications that were each associated with one CADR case (8.3%). Notably, there were two cases (16.7%) of ciprofloxacin reported in both oral and injectable formulations, each of which accounted for one case (8.3%). The results point to a wide variety of oral and injectable drugs being implicated in CADRs, with injectable antibiotics showing a marginally greater prevalence.

Table 2: Drug and its route CADR among patients			
Sl. No.	**CADR**	**Frequency**	**Proportion**
1	C. Doxycycline	1	8.3%
2	Tab Cefixime	1	8.3%
3	Tab Paracetamol 650 mg	1	8.3%
4	Tab Cefazolin	1	8.3%
5	Ibuprofen	1	8.3%
6	Cotrimoxazole	1	8.3%
7	Inj ciprofloxacin	1	8.3%
8	Inj. ceftriaxone	1	8.3%
9	Inj. penicillin	2	16.7%
10	Inj. Cotrimoxazole	1	8.3%
11	Inj ciprofloxacin	1	8.3%

Figure 3 shows the Naranjo score among CADR patients. Out of 12 patients reported, one had the score of seven and others were reported with sore six. The causality assessment using Naranjo score was probable and Likely based on WHO assessment for all twelve cases.

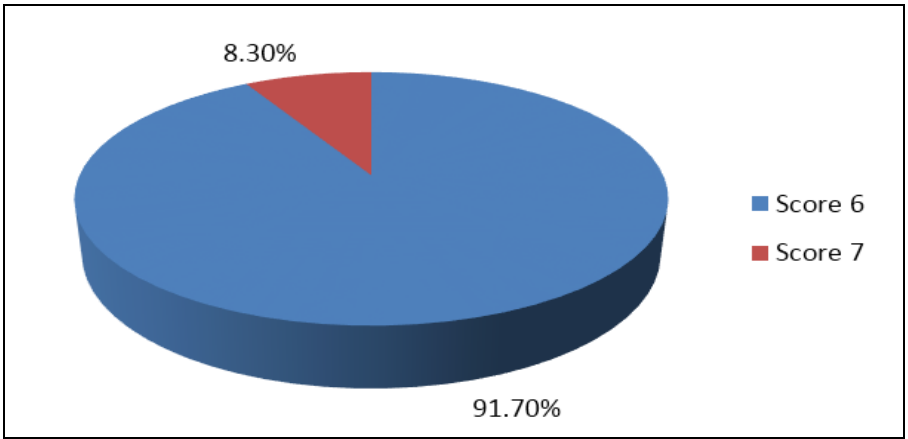
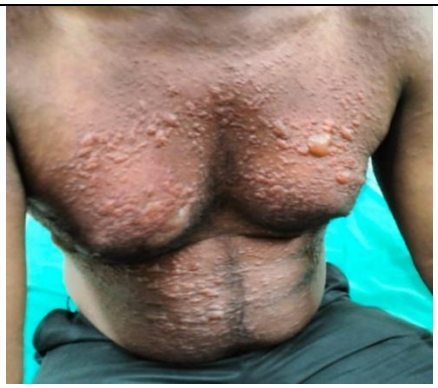


Figure 3: Naranjo score among CADR patients

Picture 1: Multiple erosion with crusting

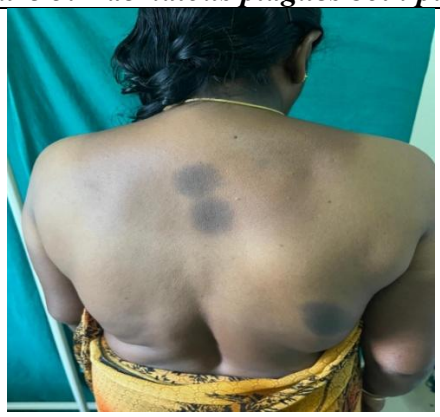
Picture 2: Hyper-pigmented macules over peri-oral region

Picture 3: Erosions with Bullard

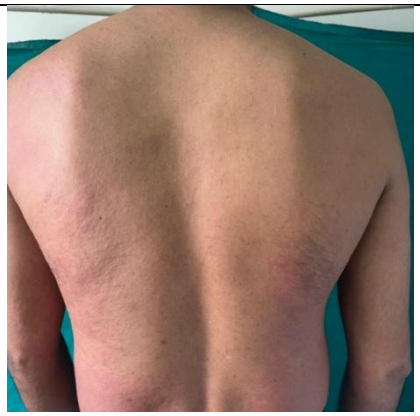


Picture 4: Multiple fluid filled skin lesions

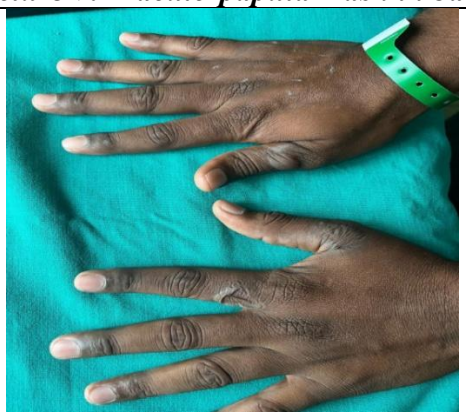
Picture 5: Edematous plagues both palms



Picture 6: Hyper-pigmented macules in back



Picture 7: Maculo-papular rash in back



Picture 8: Fluid filled skin lesions

DISCUSSION

Cutaneous adverse drug reactions (CADRs) continue to provide a considerable challenge in clinical environments owing to their diverse manifestations and related morbidity. Our study report indicated that the average age of CADR patients was 38.33±13.289 years, with an age range of 18 to 64 years. The maculo-papular rash was the most often reported type of CADR, occurring in 3 occurrences (25%). Subsequently, two individuals (16.7%) exhibited pruritus and fluid-filled vesicles on their skin. Injectable penicillin, the most often reported drug, was associated with two cases (16.7%). Oral doxycycline, cefixime, 650 mg of paracetamol, cefazolin, ibuprofen, cotrimoxazole, and injectable formulations of ciprofloxacin, ceftriaxone, and cotrimoxazole were each linked to one incidence of CADR (8.3%). One individual received a score of seven, while others were recorded with a score of six.

Our study report is similar with the research conducted by Modi et al. (2018),[13] which indicated that drug responses are more prevalent among those aged 18-35 years. The most frequently observed cutaneous adverse drug reactions (CADR) were acute exanthem (58.9%), pruritus (10.6%), Stevens-Johnson syndrome (SJS) (4.8%), fixed drug eruption (FDE) (3.5%), and urticaria (3.5%). The predominant medicines associated with responses are mostly antimicrobials (46.3%), followed by NSAIDs (18%) and anticonvulsants (9.7%).

Our study report is also comparable to a study conducted by Padukadan D et al.,[14] which indicates that the predominant age group is 20-39 years. This suggests that individuals in their second to fourth decades have extensive exposure to diverse therapeutic regimens and occupational or environmental factors that contribute to CADR susceptibility. This study indicated that approximately 58.9% of medication responses are attributable to antimicrobials, followed by 15.5% due to anticonvulsants and NSAIDs. The predominant drug reaction is exanthem at 12.2%, succeeded by urticaria at 7.8%.

Sharma et al.[15] conducted a study revealing that maculopapular rash was the predominant cutaneous adverse drug reaction (CADR), comprising 25% of cases, followed by urticaria at 20.1% and

pruritus at 16.1%. The predominant drugs responsible for responses are antibiotics (47.6%), followed by NSAIDs (16.1%) and anticonvulsants (13.7%), which aligns with our study findings.
Our investigation revealed that pruritus and fluid-filled blisters were observed in 16.7% of patients each, which is equivalent to the findings of Sushma et al.[16] These appearances may indicate early urticarial or vesiculo-bullous illnesses and require vigilant monitoring due to the risk of advancing into more serious cutaneous syndromes, such as Stevens-Johnson syndrome or toxic epidermal necrolysis.
Our report indicates that various medications, including oral doxycycline, cefixime, paracetamol (650 mg), cefazolin, ibuprofen, cotrimoxazole, and injectable ciprofloxacin, ceftriaxone, and cotrimoxazole, were each linked to a single case (8.3%). These findings align with multiple studies conducted by Thakkar et al.[17] and Agarwal et al.[18] which assert that nearly all classes of drugs, encompassing antibiotics, NSAIDs, and sulfa medications, may induce CADRs in susceptible individuals.
A systematic review conducted by Patel et al.[18] which aligns with our study findings, indicated that antimicrobials account for 45.5% of medication interactions, followed by NSAIDs at 20.9%, and anticonvulsants at 14.57%. The predominant drug reaction is exanthema, succeeded by urticaria and fixed drug eruption.

CONCLUSION

The findings of our study indicate that the variety of medications and differing clinical presentations require more pharmaco-vigilance and patient education. The primary approach to care is the prompt identification and cessation of the problematic medication. Frequent revisions of hospital formularies and the education of healthcare providers may alleviate the incidence of CADRs.

LIMITATIONS

Single-centered study with a limited sample size.

Conflict of interest: NIL

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