

## ASSESSMENT OF DIFFERENT MORPHOLOGICAL PATTERNS OF CUTANEOUS ADVERSE DRUG REACTION AND THEIR RELATIONSHIP IN INDIAN SUBJECTS

Dr. Rakesh Kumar Meena,<sup>1</sup> Dr Amar Singh,<sup>2</sup> Dr Somya Singhal,<sup>3</sup> Dr Prakash Sajja<sup>4\*</sup>

<sup>1</sup>MBBS, MD, Associate Professor, Department of Dermatology, Venereology and Leprosy, Dr. Laxminarayan Pandey Government Autonomous Medical College, Ratlam, Madhya Pradesh, India

<sup>2</sup>MBBS, MD, Assistant professor, Department of Dermatology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh

<sup>3</sup>MBBS, MD, Associate Professor, Department of Dermatology, Venereology and Leprosy, LLRM Medical College Meerut, Uttar Pradesh

<sup>4\*</sup>MBBS, MD, Professor, Department of Dermatology, Venereology and Leprosy, Anna Gowri Medical College and Hospital, Parameswaramangalam, Puttur, Tirupati, Andhra Pradesh

**Address for correspondence: Dr Prakash Sajja**

Email id: [drsajja@gmail.com](mailto:drsajja@gmail.com)

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### ABSTRACT

**Background:** One of the major concerns associated with drug therapy is ADRs (adverse drug reactions) which is also one of the most common concerns of drug therapy. The most common adverse drug reaction is CADRs (cutaneous adverse drug reactions) which vary in different drugs.

**Aims:** The present study aimed to assess different morphological patterns of cutaneous adverse drug reaction and their relationship in Indian subjects.

**Methods:** The present study assessed subjects who were suspected of cutaneous adverse drug reactions and where the drug identity can be ascertained. In all the included subjects, drug history, and clinical profile were assessed. This was followed by the utilization of the Naranjo scale for the assessment of the causality.

**Results:** Drug eruption (fixed drug eruption) was the most common cutaneous adverse drug reaction seen in 49% of study subjects, SJS-TEN spectrum in 17% of subjects, and maculopapular rash in 11% of study subjects respectively. SCARs (severe cutaneous adverse drug reactions) including DRESS, AGEP, SJS-TEN overlap, and SJS was seen in 25% (n=36) subjects. The most common drug-associated was antibiotics followed by NSAIDs and anticonvulsants seen in 54%, 15%, and 12% of subjects respectively. The majority of the cutaneous adverse drug reactions were in the probable category.

**Conclusion:** The present study concludes that the incidence of severe cutaneous adverse reactions is significantly higher in Indian subjects compared to subjects from other countries.

**Keywords:** Antimicrobials, adverse drug reactions, cutaneous adverse drug reactions, fixed drug eruptions, side-effects

## INTRODUCTION

Following the WHO (World Health Organization), ADR (adverse drug reaction) is defined as a response to a drug that is unintended and noxious and is seen at doses that are utilized for therapy, diagnosis, or prophylaxis of a disease or to modify physiological functioning. The most common type of adverse drug reaction is CADR (cutaneous adverse drug reaction) and their reported incidence has increased making them common in the present time. In developing and developed countries, the incidence of CADR ranges from 2-5% and 1-3% respectively.<sup>1,2</sup>

Most of the drug-related reactions in the skin are skin eruptions that are not serious or life-threatening, SCARs (severe cutaneous adverse reactions) include various entities including the AGEP (acute generalized exanthematous pustulosis), DRESS (drug reaction with eosinophilia and systemic symptoms), DIHS (drug-induced hypersensitivity syndrome), TEN (toxic epidermal necrolysis), and SJS (steven-Johnson syndrome).<sup>3</sup> These conditions are associated with fever and systemic symptoms with various complications that are usually life-threatening. The incidence of these severe cutaneous adverse reactions is nearly 2-3 cases per million per year. However, the incidence can vary with the ethnicity.<sup>4</sup>

The pattern of cutaneous adverse drug reactions varies in different drugs. For a better understanding of the accurate nature of the drug reaction, it is vital to identify the drug responsible for the reaction and to have an early diagnosis and prompt drug withdrawal offending drug for the prevention of the mortality associated with cutaneous adverse drug reactions. Also, knowledge concerning drugs that can lead to cutaneous adverse drug reactions can help in selection of the safer drugs.<sup>5,6</sup>

Epidemiological studies are useful in identifying the morphological pattern of various drugs that link cutaneous adverse drug reactions to various classes of drugs. Reporting and identification of unusual reactions to drugs used commonly and reporting the adverse drug reactions to new therapeutic drugs.<sup>7</sup>

Existing literature data is scarce concerning the cutaneous adverse drug reactions in the Indian scenario. Considering this background, the present study was done to assess different morphological patterns of cutaneous adverse drug reaction and their relationship in Indian subjects.

## MATERIALS AND METHODS

The present cross-sectional observational clinical study was done to assess different morphological patterns of cutaneous adverse drug reaction and their relationship in Indian subjects. The study subjects were from the Department of Dermatology of the Institute. Verbal and written informed consent were taken from all the participants before study participation.

The study included 144 subjects from both the genders and all the age ranges. For all the study subjects, detailed history was recorded followed by the physical assessment including the relevant information, provisional diagnosis, other organs involvement, areas involved, rash morphology, duration of eruption, offending drug, gender, and age of the study subjects.

The adequate history for drug intake was also assessed including the ayurvedic, homeopathic, and allopathic medicine along with its temporal correlation with the start of the symptom. After the exclusion of the other possible causes of the similar clinical pictures, the final diagnosis was made in the study subjects, and the subjects were further assessed. In subjects with more than one drug intake, the drug that was considered as offending more likely was noted and the confirmation was made after the rash subsided on the withdrawal of the drug.

After the intake of the history, routine investigations were done in all the study subjects including the complete blood count, microscopic and routine urine examination along with serum electrolytes, liver function tests, serum creatinine, blood urea, and blood sugar assessment in all the participants. Also, HIV 1 and HIV 2 using ELISA, and serum VDRL-like specific investigations were done, if required.

This was followed by the application of Naranjo's Algorithm scale for the assessment of the causality. Naranjo's algorithm scale was used for the assessment of any causal relationship seen an untoward clinical event and a drug with a simple questionnaire that can assign probability scores. Concerning the scoring system, possible, probable, and definitive relationships between drug and clinical event were seen for scores of 1 to 4, 5 to 8, and more than or equal to 9 respectively.

The data gathered were analyzed statistically using the SPSS software version 21.0 (IBM Corp., Armonk, NY, USA) and the chi-square test. The data were expressed as mean and standard deviation and frequency and percentage. Statistical significance was kept at a p-value of <0.05. To evaluate the change in parameters of any group before and after surgery, repeated measurements and ANOVA (analysis of variance) were used.

## RESULTS

The present cross-sectional observational clinical study was done to assess different morphological patterns of cutaneous adverse drug reaction and their relationship in Indian subjects. The study included 144 subjects from both the genders and all the age ranges. There were 2 males and 2 females in the age range of <11 years with a total of 2.77% (n=4) study subjects. In the age range of 11-20 years, there were 12 females and 10 males and 15.27% (n=22) total subjects. In 21-30 years, there were 16 females and 32 males with 33.3% (n=48) subjects. In 31-40 years, there were 18 females and 22 males with a total of 27.7% (n=40) subjects. In 41-50 years, there were 8 females and 6 males with a total of 9.72% (n=14) subjects. In 51-60 years, there were 2 females and 8 males with 6.94% (n=10) subjects in total. In the 61-70 years of age range, there were 2.77% (n=4) subjects and all were males. In 71-80 years, there were 1.38% (n=2) subjects and all were males as shown in Table 1.

On assessing the distribution of various cutaneous adverse drug reactions in the study subjects, it was seen that most common drug reaction was fixed drug eruptions (FDE) seen in 48.61% (n=70) subjects followed by maculopapular rash seen in 11.1% (n=16) study subjects, SJS and TEN in 6.94% (n=10) study subject each, acute generalized exanthematous pustulosis and erythema multiforme in 5.55% (n=8) study subjects each, SJS-TEN, DRESS, erythroderma, and urticaria in 2.77% (n=4) subjects each, and exfoliative dermatitis, drug-induced lichen planus, and angioedema in 1.38% (n=2) study subjects each as summarized in Table 2.

Concerning the common offending drugs that caused the cutaneous adverse drug reactions in the study subjects, the most common drug was antimicrobials which were the offending drug in 54.16% (n=78) subjects followed by NSAIDs in 15.27% (n=22) subjects, anticonvulsants in 12.5% (n=18) study subjects, antifungals in 6.94% (n=10) study subjects, homeopathy in 2.77% (n=40) study subjects, and dapsone, sulfasalazine, antitubercular drugs, and antimalarials in 1.38% (n=2) study subjects each as summarized in Table 3.

## DISCUSSION

The present study included 144 subjects from both the genders and all the age ranges. There were 2 males and 2 females in the age range of <11 years with a total of 2.77% (n=4) study subjects. In the age range of 11-20 years, there were 12 females and 10 males and 15.27% (n=22) total subjects. In 21-30 years, there were 16 females and 32 males with 33.3% (n=48) subjects. In 31-40 years, there were 18 females and 22 males with a total of 27.7% (n=40) subjects. These data were similar to the studies of Posadzki P et al<sup>8</sup> in 2012 and Suthar JV et al<sup>9</sup> in 2011 where authors assessed subjects with demographic data similar to the present study.

In 41-50 years, there were 8 females and 6 males with a total of 9.72% (n=14) subjects. In 51-60 years, there were 2 females and 8 males with 6.94% (n=10) subjects in total. In the 61-70 years of age range, there were 2.77% (n=4) subjects and all were males. In 71-80 years, there were 1.38% (n=2) subjects and all were males. These findings were comparable to the findings of Noel MV et al<sup>10</sup> in 2004 and Sudharani C et al<sup>11</sup> in 2016 where the age and gender distribution similar to the present study was reported by the authors in their respective studies in subjects with cutaneous adverse drug reactions.

The study results showed that for the distribution of various cutaneous adverse drug reactions in the study subjects, it was seen that most common drug reaction was fixed rug eruptions (9fdes) seen in 48.61% (n=70) subjects followed by maculopapular rash seen in 11.1% (n=16) study subjects, SJS and TEN in 6.94% (n=10) study subject each, acute generalized exanthematous pustulosis and erythema multiforme in 5.55% (n=8) study subjects each, SJS-TEN, DRESS, erythroderma, and urticaria in 2.77% (n=4) subjects each, and exfoliative dermatitis, drug-induced lichen planus, and angioedema in 1.38% (n=2) study subjects each. These results were consistent with the studies of Spillers NJ et al<sup>12</sup> in 2023 and Patel T et al<sup>13</sup> in 2014 where authors reported similar cutaneous adverse drug reactions in their study subjects as seen in the results of the present study.

It was seen that for the common offending drugs that caused the cutaneous adverse drug reactions in the study subjects, the most common drug was antimicrobials that were the offending drug in 54.16% (n=78) subjects followed by NSAIDs in 15.27% (n=22) subjects, anticonvulsants in 12.5% (n=18) study subjects, antifungals in 6.94% (n=10) study subjects, homeopathy in 2.77% (n=40) study subjects, and dapsone, sulfasalazine, antitubercular drugs, and antimalarials in 1.38% (n=2) study subjects each. These findings were in agreement with the findings of Pudukadan D et al<sup>14</sup> in 2004 and Al-Raaie F et al<sup>15</sup> in 2008 where authors reported antimicrobials and NSAIDs as the most common drugs causing cutaneous adverse drug reactions.

## CONCLUSIONS

Considering its limitations, the present study concludes that the incidence of severe cutaneous adverse reactions is significantly higher in Indian subjects compared to subjects from other countries. However, the study had limitations of a smaller monitoring period and small sample size warranting further longitudinal studies with larger sample sizes and longer assessment duration.

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**TABLES**

S. No	Age range (years)	Females	Males	Total (n)	Percentage (%)
1.	<11	2	2	4	2.77
2.	11-20	12	10	22	15.27
3.	21-30	16	32	48	33.3
4.	31-40	18	22	40	27.7
5.	41-50	8	6	14	9.72
6.	51-60	2	8	10	6.94
7.	61-70	0	4	4	2.77
8.	71-80	0	2	2	1.38
9.	Total	58	86	144	100

**Table 1: Gender and age distribution in the study subjects**

S. No	Reaction pattern	Number (n)	Percentage (%)
1.	Exfoliative dermatitis	2	1.38
2.	Drug-induced lichen planus	2	1.38
3.	Angioedema	2	1.38
4.	Urticaria	4	2.77
5.	Erythroderma	4	2.77
6.	Erythema multiforme	8	5.55
7.	DRESS	4	2.77
8.	Acute generalized exanthematous pustulosis	8	5.55
9.	SJS-TEN	4	2.77
10.	TEN	10	6.94
11.	SJS	10	6.94
12.	Maculopapular rash	16	11.1
13.	FDE	70	48.61
14.	Total	144	100

**Table 2: Distribution of morphological pattern of CADR in the study subjects**

S. No	Offending drug	Number (n)	Percentage (%)
1.	Antimicrobials	78	54.16
2.	NSAIDs	22	15.27
3.	Anticonvulsants	18	12.5
4.	Antifungals	10	6.94
5.	Antimalarials	2	1.38
6.	Antitubercular drugs	2	1.38
7.	Sulfasalazine	2	1.38
8.	Homeopathy	4	2.77
9.	Dapsone	2	1.38

**Table 3: Common offending drugs causing CADR in study subjects**