

## Evaluation of cutaneous adverse drug reactions in a tertiary care hospital

Rhia Sebastian<sup>1</sup>, Megaravalli R Manasa<sup>2,\*</sup>, Thankappan TP<sup>3</sup>

<sup>1</sup>Assistant professor, <sup>2</sup>Associate Professor, <sup>3</sup>Professor, <sup>1,3</sup>Dept. of Dermatology, <sup>2</sup>Dept. of Pharmacology, <sup>1,3</sup>Pushpagiri Institute of Medical Sciences, Tiruvalla, Kerala, <sup>2</sup>Karwar institute of medical sciences, Karwar, Karnataka, India

**\*Corresponding author: Megaravalli R Manasa**

Email: dr.manasamr@gmail.com

### Abstract

**Introduction:** Skin is one of the most frequently involved organ in adverse drug reactions. A wide spectrum of reactions ranging from maculopapular rashes to toxic epidermal necrolysis can be caused by different classes of drugs.

**Objectives:** To evaluate the cutaneous adverse drug reactions in a tertiary care hospital using standard assessment scales.

**Materials and methods:** A retrospective study was conducted in the Dermatology department of a tertiary care hospital between June 2013 – May 2017. All the inpatient and outpatient records were analysed for Cutaneous adverse drug reactions (CADRs) during the study period.

**Results:** Out of 124 patient case files reviewed, 90 patients were included in the study. Of these 90 patients, 55.6% were males. Maximum number of cases were in the age group of 20-39 years (37.8%). Fixed drug eruption and maculopapular rash were the most common CADRs reported. Type of drug reaction was not significantly associated with age and sex. The most common drugs implicated were antibiotics (33.3%) followed by NSAIDs (21.1%). Most of the patients were managed on outpatient basis (67.8%). Probable association was seen in 86.67% and 13.3% had a possible association. About 92.2% of CADRs were in the moderate category.

**Conclusion:** Commonly used drugs can cause CADRs. Hence careful use of drugs weighing the benefit risk ratio is essential. Pharmacovigilance will play a vital role in monitoring ADRs especially those due to the newer drugs.

**Keywords:** Cutaneous adverse drug reactions, Maculopapular rash, Antibiotics, NSAIDs.

### Introduction

An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug.<sup>1</sup> Studies have found the skin is one of the most frequently involved organ in adverse drug reaction.<sup>2</sup> A wide spectrum of cutaneous manifestations ranging from maculopapular rashes to toxic epidermal necrolysis (TEN) can be caused by different classes of drugs.<sup>3</sup> Studies suggest that roughly a third of drug eruptions require hospital management and are considered as severe, although fortunately only 2% cutaneous drug eruptions are really life threatening.<sup>2</sup> The incidence of adverse cutaneous drug reactions is higher in women than in men and elderly patients have an increased incidence of adverse drug reactions.<sup>4</sup> Viral infections have also been shown to increase the risk of a drug rash. Some intrinsic factors influence the risk of cutaneous drug eruptions. An association between HLA types and susceptibility to drug eruptions has been reported on several occasions.<sup>1</sup> Intercurrent diseases such as systemic connective tissue disease may lead to immune perturbation and enhance the risk of a cutaneous drug eruption. The most important drug related risk factors for drug hypersensitivity concern the chemical properties and molecular weight of the drug. Larger drugs with greater structural complexity are more likely to be immunogenic.<sup>4</sup> Awareness of the cutaneous drug reactions may play an important role in their prevention. Hence this study was conducted to evaluate the cutaneous adverse drug reactions, their types, severity and the drugs causing them.

### Materials and methods

This retrospective study was conducted in the Dermatology department of a tertiary care hospital for a period of four years between June 2013 – May 2017. Approval from the institutional ethics committee was taken prior to the study. All the inpatient and outpatient records during the study period were analysed for Cutaneous adverse drug reactions (CADRs). Patient case files and ADR forms obtained from Central drugs standard control organization (CDSCO) website were used as main sources of data collection. Documented adverse drug reactions were analysed for age and sex of the patient, type of CADR, suspected class of drug and individual drug causing CADR. Management and outcome of CADR was also assessed. Causality of CADR was assessed using WHO UMC scale and severity using Modified Hartwig & Siegel scale.

### Statistical analysis

Data was analysed using GraphPad Prism version 6.05. The results were presented as frequency, percentage and confidence intervals appropriately. Association between type of drug reaction, age and sex, severity was done using Chi-square test. P value < 0.05 was considered significant.

### Results

A total of 124 patient case files of suspected CADRs were reviewed. 90 patients whose relevant details were available were included in the study. Of the total 90 patients studied, 50 (55.6%) were males. The age range of patients was 8 years to 86 years with mean (SD) age being 43.7 (20.7) years. Of all patients, maximum number of cases were in the age group of 20-39 years 34 (37.8%), followed

by >60 years 26 (28.9%), with the least number in age group less than 20 years 10 (11.1%). (Table 1)

Fixed drug eruption (FDE) and maculopapular rash were the most common CADR reported, both seen in 23 (25.6%) each. SCAR reactions were noted in 21 (23.3%) patients of which Stevens Johnson syndrome (SJS) was reported in seven patients. Toxic epidermal necrolysis (TEN) was reported in five patients. SJS-TEN overlap was noted in two. In 10 patients who had SJS-TEN, five were due to anticonvulsants, three due to allopurinol and two due to co-trimoxazole. Five patients had drug hypersensitivity syndrome which included two patients from the SJS TEN spectrum. Acute generalised exanthematous pustulosis was reported in four patients. Eight patients presented with acneiform eruption, five with mucositis, four had urticaria, two each with lichenoid reaction and erythema multiforme, one each with dermatitis medicamentosa and vesicular eruption. (Table 2).

Type of drug reaction was not significantly associated with age group ( $p=0.434$ ) and sex ( $p=0.437$ ).

The most common classes of drugs implicated were antibiotics in 30 (33.3%) followed by NSAIDs in 19 (21.1%), anticonvulsants in 13 (14.4%), steroids in 6 (6.7%), drugs for hyperuricemia in 5 (5.6%), psychiatry medications in 3 (3.3%) and antifungals in 2 (2.2%). Methotrexate and ayurvedic medications were the cause in 2 (2.2%) patients each. Serratiopeptidase, propranolol, glimepiride, cilnidipine and multivitamins were implicated in one patient each. In three patients the causative drug could not be pointed out. (Table 3). Among antibiotics, penicillin group was the most common culprit in 12 (40%) followed by quinolones 10 (33.3%), cephalosporins 3 (10%), sulpha 3 (10%). Sixty (66.7%) patients were on concomitant drugs. (Table 4).

Most of the patients could be managed on outpatient basis 61 (67.8%) whereas 29 (32.2%) were treated as inpatients of which 2 were in the Intensive Care Unit. Of the 90 patients, 21(23.3%) were treated with systemic steroids and i.v. immunoglobulins were administered in 2. There was no mortality.

According to the causality assessment using WHO UMC categories, 78 (86.67%) had a probable association and 12 (13.3%) had a possible association. Severity assessment using Modified Hartwig and Siegel scale revealed that majority that is 83 (92.2%) were in the moderate category of which 58 (64.4%) were in level 3, 21 (23.3%) in level 4b and 4 patients in level 4a. 4 patients (4.4%) belonged to the severe category of which 2 (2.2%) were in level 5 and 2 (2.2%) in level 6. 3 (3.3%) patients were in the mild category.

Severity of drug reactions showed no significant association with antibiotics, NSAIDs, route of administration or causality. (Table 5).

**Table 1: Age and Sex distribution of CADR.**

Age group	Frequency	Percentage	Male	Female
<20	10	11.1	8	2
20-39	34	37.8	16	18
40-59	20	22.2	10	10
>60	26	28.9	16	10
<b>Total</b>	<b>90</b>	<b>100</b>	<b>50</b>	<b>40</b>

**Table 2: Type of CADR.**

Type	Frequency	Percentage
AGEP	4	4.4
FDE	23	25.6
DHS	3	3.3
Lichenoid reaction	2	2.2
Maculopapular rash	23	25.6
SJS	6	6.7
SJS+DHS	1	1.1
SJS/TEN	2	2.2
TEN	4	4.4
TEN+DHS	1	1.1
Urticaria	4	4.4
Others	17	18.9
<b>Total</b>	<b>90</b>	<b>10</b>

**Table 3: Drugs causing CADR.**

Type of drug	Frequency	Percentage
Antibiotics	30	33.3
Anticonvulsants	13	14.4
NSAIDs	19	21.1
Hypouricemic drugs	5	5.5
Steroids	6	6.7
Antifungals	2	2.2
Antipsychotics	3	3.3
Others	9	10
Unknown	3	3.3
<b>Total</b>	<b>90</b>	<b>100</b>

**Table 4: Antibiotic class causing CADR.**

Chemical class	Frequency	Percentage
Penicillins	12	40
Cephalosporins	3	10
Quinolones	10	33.3
Sulpha	3	10
Macrolides	1	3.3
Tetracyclines	1	3.3
<b>Total</b>	<b>30</b>	<b>100</b>

**Table 5: Severity of CADR.**

Characteristic	Severe ADR	Mild to moderate ADR	P value	Odds ratio (95% confidence interval)
<b>NSAIDS</b>				
Yes	1 (5.3%)	18 (94.7%)	0.634	1.204 (0.118 to 12.280)
No	3 (4.4%)	65 (95.6%)		
<b>Antibiotics</b>				
Yes	1 (3.1%)	31 (96.9%)	0.530	0.559 (0.056 to 5.61)
No	3 (5.5%)	52 (94.5%)		
<b>Route of administration</b>				
Oral	4 (5.0%)	76 (95.0%)	0.711	-
Others	0	7 (100%)		
<b>Need for systemic steroids</b>				
Yes	3 (14.3%)	18 (85.7%)	<b>0.038*</b>	11.333 (1.112 to 115.55)
No	1 (1.4%)	68 (98.6%)		
<b>Causality established</b>				
Probable	4 (5.1%)	74 (94.9%)	0.558	-
Possible	0	12 (100%)		

\* Statistically significant

## Discussion

In the present study a total of 90 patients were included. The youngest patient was of 8 years and the oldest 86 years. The maximum number of patients belonged to the age group of 20 to 39 years. Similar findings were noted in the studies by R Sharma et al<sup>5</sup> and Pudukkadan et al.<sup>6</sup> A systematic review of 3671 cases of CADR by T K Patel et al showed maximum (54.42%) of patient distribution in 40 to 60 years of age group.<sup>7</sup> Some studies have reported greater frequency in older age group.<sup>4</sup> In our study 55.6% of patients were males. Similar observations were noted in a study by Sushma M et al.<sup>8</sup> Some studies report higher incidence of drug reactions in females.<sup>4</sup> Reaction rates increased with age and were higher in females (F:M-58: 1) in the data from the Italian spontaneous reporting system.<sup>9</sup>

In this study maculopapular rash and fixed drug eruption were the most common types of reactions, both seen in 23 (25.6%) each. Most of the studies report maculopapular rash as the commonest type followed by fixed drug eruption (FDE).<sup>7</sup> In Pudukkadan et al study FDE was the most common (31.1%) followed by maculopapular rash.<sup>6</sup> This could be due to different patterns of drug usage.

SCAR reactions including Stevens Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity syndrome and acute generalised exanthematous pustulosis were noticed in 23.3% of patients. Of the 2595 reported adverse skin reactions in an Italian study, 17% were serious reactions.<sup>9</sup> In another study on SCAR, of the 106 patients with CADR, 43 required hospitalisation and of this 25 were due to these severe type of reactions.<sup>10</sup>

Another significant type of reaction was acneiform eruption noted in 8.9% of patients. R Sharma et al in their study reported acneiform eruptions in 11.3% of patients.<sup>5</sup>

Among the drugs implicated the most common classes were antibiotics in 33.3% followed by NSAIDs in 21.1% and anticonvulsants in 14.4%. T K Patel et al in their review of CADR in Indian population observed similar findings.<sup>7</sup> In

a 9 year South Indian study of 404 patients, the drug classes implicated were antibiotics (45%) followed by antiepileptics (19%) and NSAIDs (19%).<sup>8</sup> Sharma VK et al in their study found the causative as antimicrobials in 42.6%, anticonvulsants in 22.2% and NSAIDs in 18%.<sup>11</sup> Other important classes of drugs were corticosteroids either topical or systemic and causing mainly acneiform eruptions. In our study, steroids were the causative drugs in 6.7% of patients. In the study done by R Sharma et al corticosteroids were found to be the third most common drug class implicated in CADR accounting for 14.6% of patients.<sup>5</sup> S Ghosh et al in their study reported 4% of cutaneous drug reaction to be due to steroids.<sup>12</sup> Drugs for hyperuricemia caused CADR in five patients of which allopurinol was the causative drug in three cases of TEN. In a study by T K Patel also it was reported as a common offending drug.<sup>7</sup>

Among antibiotics penicillin group was the most common culprit in 40% followed by quinolones in 33.3%, cephalosporins in 10%, sulpha in 10% and 3.3% each for macrolide and tetracycline. In a study by S Thakkar et al CADR due to fluoroquinolones were more frequent than cotrimoxazole and penicillins.<sup>13</sup> In a Korean study of antibiotic related ADRs, quinolones (98 cases, 17%) and penicillins (88 cases, 15.3%) were the most common causative agents for skin and subcutaneous manifestations, followed by third generation cephalosporins in 86 cases (14.9%).<sup>14</sup>

The ultimate goal of management is always to discontinue the offending medication if possible. The therapy for most drug eruptions is mainly supportive and treatment depends on the specific type of reaction.<sup>4</sup> In our study most of the patients could be managed on outpatient basis 61 (67.8%) whereas 29 (32.2%) were treated as inpatients of which two were in the Intensive Care Unit. Of the 90 patients, 21 (23.3%) were treated with systemic steroids. In two patients with toxic epidermal necrolysis i.v. immunoglobulin was given.

According to the causality assessment using WHO-UMC categories, 78 (86.67%) had a probable association

and 12 (13.3%) had a possible association. Causality assessment of ADRs is a method used for estimating the strength of relationship between drug(s) exposure and occurrence of adverse reaction(s).<sup>15</sup> In a study by Amrinder R et al, the implicated drug was found to be a probable cause in 93.3% of patients, possible in 5% and certain in 1%.<sup>16</sup> Severity assessment using Modified Hartwig and Siegel scale revealed that majority that is 83 (92.2%) were in the moderate category of which 58 (64.4%) were in level 3, 21 (23.3%) in level 4b and 4 patients in level 4a. 4 patients (4.4%) belonged to the severe category of which 2 (2.2%) were in level 5 and 2 (2.2%) in level 6. 3 (3.3%) patients were in the mild category. Out of total 120 cases of CADR maximum cases, 109 were of level 3 severity, 10 of level 4 and 1 of level 7 in the previous study.<sup>16</sup> In our study also majority were in the level 3, moderate category. In a study most of cutaneous ADRs (82%) were moderately severe in nature, and 18% were mild in nature.<sup>17</sup>

### Conclusion

Physicians should take proper drug history, maintain records of a patient with CADR and warn the patient regarding the need to further avoid use of the same class of drug. Careful use of drugs weighing the benefit risk ratio is essential especially when used prophylactically. Pharmacovigilance system will be useful to monitor ADRs especially those due to the newer drugs.

### Acknowledgements

We would like to thank the staff of Pharmacology and Dermatology departments of Pushpagiri Institute of Medical Sciences, Tiruvalla for their help and support.

**Funding:** None.

**Conflict of Interest:** None.

**Ethical Approval:** The Institutional Ethics committee has approved this study

### References

- Breathnach SM. Drug reactions. Burns T, Breathnach S, Cox N, Griffiths C. Rook's textbook of dermatology ED 7. Blackwell Science Ltd. 2004; 73.1.
- French LE(ed): Adverse Cutaneous Drug Eruptions. Chem Immunol Allergy. Basel, Karger. 2012;97:ppI-XIV.
- Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacol Rev* 2001;53:357-379.
- Nayak S, Acharjya B. Adverse cutaneous drug reaction. *Indian J Dermatol* 2008;53:2-8.
- Sharma R, Dogra D, Dogra N. A study of cutaneous adverse drug reactions at a tertiary center in Jammu, India. *Indian Dermatol Online J* 2015;6,3:168-217.
- Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. *Indian J Dermatol Venereol Leprol* 2004;70:20-24.
- Patel TK, Thakkar S, Sharma DC. Cutaneous adverse drug reactions in Indian population: A systematic review. *Indian Dermatol Online J* 2014; 5(Suppl 2):S76-S86.
- Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse drug reactions. A 9-year study from a South Indian Hospital. *Pharmacoepidemiol Drug Saf* 2005;14:567-570.
- Naldi L, Conforti A, Venegoni M, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clinical Pharmacol* 1999;48:839-846.
- Sasidharanpillai S, Riyaz N, Khader A, Rajan U, Binitha MP, Sureshan DN. Severe Cutaneous Adverse Drug Reactions: A Clinicoepidemiological Study. *Indian J Dermatol* 2015;60(1):102.
- Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents- a 6 year series from Chandigarh, India. *J Postgrad Med* 2001;47(2):95-99.
- Ghosh S, Leelavathi D, Padma GM. Study on evaluation of various cutaneous drug reactions in Kasturba hospital Manipal. *Indian J Pharm Sci* 2006; 68(2):212-215.
- Thakkar S, Patel TK, Vahora R, et al. Cutaneous adverse drug reactions in a tertiary care teaching hospital in India: An intensive monitoring study. *Indian J Dermatol* 2017;62:618-625.
- Jung IY, Kim JJ, Kim JM. Antibiotic-related Adverse drug reactions at a tertiary care hospital in South Korea. *Biomed Res Int* 2017; 2017:4304973. doi: 10.1155/2017/4304973.
- Smyth R L, Pean M, Turner M A et al. ADRIC: Adverse Drug Reaction In Children- a programme of research using mixed methods. Southampton(UK). *NIHR J Libr* 2014 Jun. Chapter – Causality assessment of adverse drug reaction.
- Amrinder R, Kaur I, Singh J, Kaur T. Monitoring of cutaneous adverse drug reactions in a tertiary care hospital. *J Pharmacovigilance* 2016;4:207.
- Patel NH, Padhiyar J, Shah YB, Dixit RK. Study of Causality, Preventability and Severity of Cutaneous adverse drug reactions in a Tertiary care institute. *GCSMC J Med Sci* 2015 (4)(1)January-June.

**How to cite this article:** Sebastian R, Manasa MR, TP Thankappan, Evaluation of cutaneous adverse drug reactions in a tertiary care hospital, *Indian J Clin Exp Dermatol* 2019;5(1):20-23