

**Drug-induced cutaneous adverse drug reactions in dermatology in
Dr. B.R. Ambedkar Medical College****C. Kumari Bai^{1*}, L. Padma¹, N. T. Madan Mohan², D. R. Veena¹**¹Department of Pharmacology,
Dr. B.R. Ambedkar Medical
College, Bengaluru,
Karnataka, India,²Department of Dermatology,
Dr. B.R. Ambedkar Medical
College, Bengaluru,
Karnataka, India**Received:** 28 June 2014**Accepted:** 05 July 2014***Correspondence to:**Dr. C. Kumari Bai,
Email: dr.kumaribaic@gmail.
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properly cited.**ABSTRACT****Background:** Cutaneous adverse drug reactions (ADRs) affect 2-3% of hospitalized patients. The severity varies from mild itching to life-threatening Stevens-Johnson syndrome (SJS). Hence, this study was undertaken to emphasize the need to report ADRs.**Methods:** The study was carried out in the Department of Dermatology in Dr. B.R Ambedkar Medical College Hospital from June to December 2012. Naranjo's algorithm was used to determine the causality of an ADR. Informed consent was obtained from each patient, and thorough clinical examination was conducted. All the information was carefully recorded in a pre-designed proforma. To establish the etiologic agent for a particular type of reaction, attention was paid to the drug history, temporal correlation with the drug, duration of the reaction, morphology of the reaction, associated mucosal or systemic involvement, improvement of lesions on withdrawal of the drug.**Results:** In the present study, all the age groups were affected with cutaneous ADRs, with a higher incidence in age group between 31 and 40 years, non-steroidal anti-inflammatory drugs (NSAIDs) (41.66%) were most commonly observed drug, followed by anti-microbials (25%) and anti-convulsants (21.66%). Fixed drug eruptions (FDE) (46.66%) most commonly observed cutaneous reaction, followed by SJS (16.66%), erythema multiformae (16.66%) most commonly observed ADRs.**Conclusions:** ADRs are potentially avoidable causes for seeking medical care. FDE was most common ADR and NSAIDs were most common causative agents in our study. ADRs can be prevented by avoiding polypharmacy, obtaining history of any previous skin reaction and the causative agent.**Keywords:** Adverse drug reaction, Stevens-Johnson syndrome, Fixed drug eruption, Naranjo's algorithm**INTRODUCTION**

Drugs can be remarkably beneficial, lengthen life and improve its quality by reducing symptoms and improving well-being. However, all drugs have adverse effects and carry the potential for causing injury, even if used properly. WHO Defines an adverse drug reaction (ADR) is defined as "a response to a drug that is noxious and unintended and occurs at doses, used in man for prophylaxis, diagnosis or therapy of a disease or for modification of physiological function."¹ The skin and the mucosa are the commonest sites for initial presentation of many ADRs. Cutaneous ADRs affect 2-3% of hospitalized patients.² These reactions can arise, as a result, of immunologic or non-immunologic mechanisms. In addition to their human costs, ADRs are expensive to the health-care system. The severity of the

cutaneous ADRs may vary from mild itching to a life-threatening Stevens-Johnson syndrome (SJS). ADRs can also occur with herbal drugs. The use of herbal supplements has increased dramatically in recent years.³ There are various predisposing factors for the occurrence of an ADR like extremes of age like in neonates and elderly, the liver and kidney enzymes necessary for drug metabolism and elimination are not optimally functional. Women are expected to have a higher incidence of ADRs than men. Patients with past history of ADRs are more likely to develop an ADR. Genetic factors also play a role for pre-disposition to ADR, examples are drug hypersensitivity syndrome to specific human leukocyte antigen (HLA) antigen-abacavir (HLA B*5701), allopurinol (HLA B*5801), carbamazepine (HLA B*1502) are more susceptible to develop SJS-toxic epidermal necrolysis (TEN).

Environmental factors like sun exposure may precipitate severe cutaneous drug reactions. Patient with hepatic disease, renal disease, systemic lupus erythematosus, HIV are prone to develop an ADR.⁴

Aim and objective

1. To study the pattern of cutaneous ADR in the department of dermatology at Dr. B.R. Ambedkar Medical College.
2. To evaluate the incidence of cutaneous reactions from systemic use of drugs.

METHODS

Inclusion criteria

- The diagnosis of the cutaneous ADRs was in accordance with the definition of ADR provided by the WHO.
- No alternate explanation for the reaction.
- A plausible time relationship between the introduction of the drug and the onset of a reaction.
- Improvement in the condition of the patient after dechallenge/withdrawal of the suspected drug.
- Ayurvedic, herbal, homeopathic medicines.
- All age groups.
- Gender-male and female.

Exclusion criteria

- Cases associated with vaccines.
- Drug over dosage.
- Cutaneous manifestation of systemic diseases.

Methodology

The study was carried out in the Department of Dermatology at Dr. B.R. Ambedkar Medical College, Bengaluru from June to December 2012. Institutional Ethics Committee clearance was obtained. Both inpatients and outpatients were included in the study. Informed consent was taken from study subjects. Information regarding the etiological agent, drug history, temporal correlation with the drug, duration of the reaction, associated mucosal or systemic involvement, improvement of the lesion on withdrawal of drug and laboratory investigations were recorded in a carefully pre-designed proforma. Causality assessment was done by using Naranjo's algorithm scale which consists of 10 questions (Table 1). Each question was given a score, and the total score was recorded for each patient and graded as definite, probable, possible, and doubtful.⁵ Naranjo's algorithm scale has wide acceptability as it is simple to follow and nonspecific. Hence, it was used for causality assessment in this study. All values were expressed in percentages (%).

RESULTS

A total number of 60 patients with cutaneous ADRs were included in the study. There were 36 males and 24 females. Mean age of males was 34±36 years (33.94) and females were 35±37 years (35.25) (Figure 1). There were 12 inpatients and 48 outpatients. Majority of the patient were in the age group of 30-40 years (Table 2). Past history of cutaneous ADR was present in six patients (Figure 2). Most common type of cutaneous ADRs in our study was fixed drug eruption (FDE) (46.66%), erythema multiformae (EM) (16.66%), SJS (16.66%), bullous FDE (6.66%), drug-induced urticaria (3.33%), drug reaction

Table 1: Naranjo's algorithm (causality assessment scale).

	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction reappear when a placebo was given?	-1	+1	0	
Was the drug detected in the blood (or the other fluids) in concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

Causality assessment: 0 - Doubtful, 1-4 - Possible, 5-8 - Probable, >9 - Definite

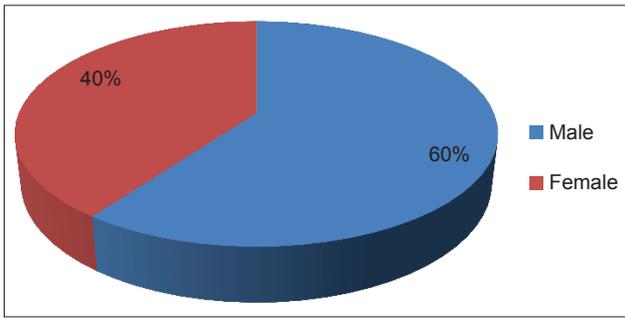


Figure 1: Sex distribution of cases.

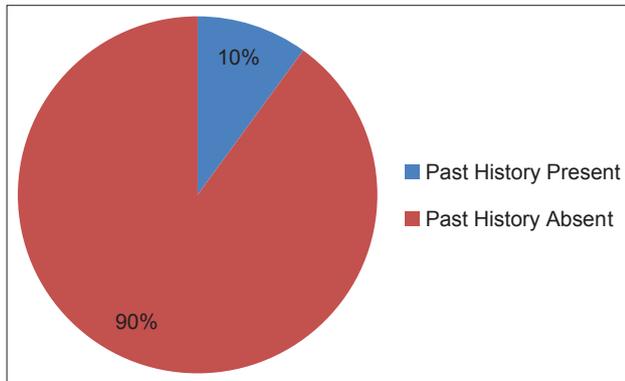


Figure 2: Significant past history.

(or rash) with eosinophilia and systemic symptoms (DRESS) syndrome (3.33%), lichenoid drug eruption (3.33%), TEN (3.33%) (Table 3). The number of cutaneous ADRs associated with individual drug groups were non-steroidal anti-inflammatory drugs (NSAIDs) 25 (41.66%), anti-microbial 15 (25%), anti-convulsants 13 (21.66%), anti-diarrhoeal 2 (3.33%), anti-neoplastic 2 (3.33%), corticosteroids 2 (3.33%), herbal medicine 1 (1.66%). In this study, NSAIDs contributed to the largest number of ADRs followed by antimicrobials (Table 4). Most of the FDE (46.66%) were caused by NSAIDs (Table 5). Causality assessment was done using Naranjo’s scale and 55% of cutaneous reactions were probably due to drugs (Table 6).

DISCUSSION

In the present study, all age groups were affected with cutaneous ADRs, with a higher incidence in adult age group between 31 and 40 years. Few previous studies have shown a higher incidence in 21-40 years of age.^{6,7} There were 24 (40%) females and 36 (60%) males in our study. Male preponderance noticed in our study was similar to the findings of other studies.⁸⁻¹⁰ The diagnosis of cutaneous ADRs involves the analysis of factors such as timing of the drug exposure and the reaction time, the course of the reaction with drug withdrawal/discontinuation, the timing and nature of a recurrent eruption on rechallenge, a history of a similar reaction to the suspected drug, and previous reports of similar reactions to the same drug.¹¹ Past history of ADRs was present in six patients (10%).

Table 2: Age wise distribution of cases.

Age	Frequency	Percentage
1-10	5	8.33
11-20	5	8.33
21-30	16	26.66
31-40	20	33.33
41-50	7	11.66
51-60	2	3.33
61-70	3	5
71-80	1	1.66
81-90	1	1.66
Total	60	100

Table 3: Types of drug reactions.

Type of reaction	Frequency	Percent
Fixed drug eruption	28	46.66
Erythema multiformae	10	16.66
SJS	10	16.66
Bullous FDE	4	6.66
Lichenoid drug eruption	2	3.33
Toxic epidermal necrolysis	2	3.33
Drug induced urticaria	2	3.33
DRESS syndrome	2	3.33
Total	60	100

DRESS: Drug reaction (or rash) with eosinophilia and systemic symptoms, FDE: Fixed drug eruption, SJS: Stevens-Johnson syndrome

Table 4: Commonly incriminated drug in drug eruption.

Drug	Frequency	Percentage
NSAIDs	25	41.66
Anti-microbials	15	25
Anti-convulsants	13	21.66
Anti-diarrhoeal	2	3.33
Anti-neoplastic	2	3.33
Corticosteroids	2	3.33
Herbal medicine	1	1.66
Total	60	100

NSAIDs: Non-steroidal anti-inflammatory drugs

Cutaneous reactions are the most common manifestations of ADRs. Spectrum of cutaneous manifestations ranges from maculopapular rashes to SJS and TEN. The present study which was conducted for a period of 6 months, showed eight types of cutaneous ADRs in 60 cases. Cutaneous ADRs were most commonly observed with NSAIDs (41.66%), followed by anti-microbial agents (25%) and anti-convulsants (21.66%) in our study. Few studies have reported that NSAIDs were the main group of drugs to cause different types of skin reactions, thus supporting our study.^{6,12-15}

Table 5: Morphological types of cutaneous ADRs and the suspected drug.

Types of cutaneous ADRs	Suspected drug with frequency of occurrence	Total number of cases	Percentage
FDE	NSAIDs (19), anti-amoebic (2), corticosteroid (2), anti-convulsant (2), azithromycin (1) quinolone (1), tetracycline (1)	28	46.66
EM	Sulfanamide (2), phenytoin (3), carbamazepine (2) amoxicillin (1), quinolone (1), co-trimaxazole (1)	10	16.66
SJS	Carbamazepine (5), phenytoin (4), herbal medicine (1)	10	16.66
Bullous FDE	NSAIDs (3), co-trimaxazole (1)	4	6.66
Drug induced urticaria	NSAIDs (2)	2	3.33
DRESS Syndrome	Carbamazepine (1), phenytoin (1)	2	3.33
Linchenoid drug eruption	NSAIDs (1), tetracycline (1)	2	3.33
TEN	Cabamazepine (1), sodium valproate (1)	2	3.33
Total		60	100

ADRs: Adverse drug reactions, NSAIDs: Non-steroidal anti-inflammatory drugs, FDE: Fixed drug eruptions, DRESS: Drug reaction (or rash) with eosinophilia and systemic symptoms, TEN: Toxic epidermal necrolysis, EM: Erythema multiformae, SJS: Stevens-Johnson syndrome

Table 6: Causality assessment (Naranjo's scale).

Probability scale	Number of ADRs
Definite	0
Probable	55
Possible	5
Doubtful	0
Total	60

ADRs: Adverse drug reactions

However, previous studies suggests anti-microbial were the most common drugs which cause cutaneous ADRs followed by anti-convulsants.^{16,17} The most common type of ADRs in our study was FDE (46.66%) followed by EM (16.66%), SJS (16.66%), Bullous FDE (6.66%), drug-induced urticaria (3.33%), DRESS syndrome (3.33%), linchenoid drug eruption (3.33%) and TEN (3.33%). Previous studies also suggest FDE as the most common type of cutaneous ADRs.^{3,14,15} The most commonly incriminated drugs in our study are NSAIDs (41.66%), anti-microbials (25%), anti-convulsants (25%), anti-diarrhoeal (3.33%), anti-neoplastic (3.33%), corticosteroids (3.33%) and herbal medicine (3.33%). In the present study, herbal medicine caused 1.66% of cutaneous ADRs which included SJS (one case). NSAIDs responsible for cutaneous ADRs in our study were diclofenac, ibuprofen, paracetamol, and nimesulide. Anti-microbials causing cutaneous ADRs were tinidazole, azithromycin, co-trimaxole, sulphonamides, quinolones, tetracycline, amoxicillin. Anti-convulsant causing SJS and TEN were phenytoin, carbamazepine, and sodium valproate. None of our patients had concomitant illness like HIV, viral or autoimmune hepatitis, diabetes mellitus, as incidence of cutaneous ADRs is more common in immunocompramised patients. Comparison of studies (Table 7).

Strategies to prevent cutaneous ADRs:

1. Avoid polypharmacy.
2. Prescribe drugs, which have been known to cause cutaneous ADRs, only if extremely necessary.
3. Obtain history of skin reactions in the past.
4. Educate the patients regarding common early symptoms of drug reactions (e.g. erythematous rash, edema, urticaria, mucosal erosions, itching, burning of skin etc.) especially during start of a therapy.

CONCLUSION

Cutaneous ADRs are potentially avoidable causes for seeking medical care. Hence, emphasizes the need for setting up a pharmacovigilance unit in each hospital so that all ADRs are reported. Pharmacovigilance is the branch of science and deals with activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. Thus, it improves patient care and safety by promoting rational use of medicines and minimizes the ADR. FDE was most common ADR and NSAIDs were most common causative agents in our study. When a cutaneous ADR is suspected, the causative drug must be identified and withdrawn. Depending on the nature of the drug eruption, symptomatic treatment may be accompanied by local skin care and, if indicated, immunomodulating therapy with corticosteroids to reduce the severity of the skin reaction.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

Table 7: Comparison of studies.

State/Country	Study period	Total number of cases	Common drugs causing cutaneous ADRs	SJS (%)	TEN
Hyderabad ¹⁸	8 months Year 2011	30	Anti-microbials Anti-convulsants	8 (26.6)	0
Chandigarh ¹⁹	3 year 1994-97	123	Anti-microbials NSAIDs	18 (14)	6 (5)
Nepal ²⁰	6 months May-October 2008	25	Anti-microbials Anti-convulsants	3 (12)	1 (4)
St. John's SJMCH, Bengaluru ²¹	1 year 2002-2003	46	Anti-convulsants Anti-microbials	7 (15)	9 (20)
Dr. B.R. Ambedkar Medical College, present study, Bengaluru	6 months June-December 2012	60	NSAIDs Anti-microbials	10 (16.66)	2 (3.33)

ADRs: Adverse drug reactions, NSAIDs: Non-steroidal anti-inflammatory drugs, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis

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