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Original Research Article

Clinico-epidemiological study of cutaneous adverse drug reactions among the in-patients of dermatology department, Goa Medical College, Goa

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ABSTRACT

Background: An adverse drug reaction (ADR) remains often remains underreported and leads to underestimated cause of morbidity and mortality. ADR frequently manifests as adverse cutaneous drug reactions (ACDRs) and manifestations varies from mild acneiform eruption to life threatening events like toxic epidermal necrolysis. Aim was to study clinic-epidemiological pattern of various ACDRs among inpatients in department of dermatology and study common drugs causing ACDRs and assess causality and severity.
Methods: This retrospective observational study was conducted for a period of one year in department of dermatology in Goa Medical College. All patients fulfilling criteria of study were included.
Results: A total of 24 patients were studied. Most common ACDR was observed in age group of 21-40 years. Stevens Johnson syndrome (SJS) (25%) was most common ACDR followed by morbilliform drug rash (20.8%). Other manifestation was DRESS (12.5%), fixed drug eruption (FDE) (12.5%) and angioedema (12.5%), acute generalized exanthematous pustulosis (AGEP) (8.33%); erythroderma (4.16%) and urticaria (4.16%). Antibiotics were commonly implicated drug category in causation of ACDRs accounting for 37.5% followed by NSAIDS (25%). Based on causality assessment, probable cases had higher incidence - 54.2% followed by possible 37.5%. All patients were considered to have severe reaction as patients required hospitalization for management of adverse reactions.
Conclusions: ADRs are under-reported due to various factors and practicing doctors should be encouraged to report ACDRs in order to improve medical therapy for the benefit of healthcare workers and patients worldwide.

Keywords: Cutaneous reaction, Stevens Johnson syndrome, Morbilliform rash, Antibiotics, Naranjo's scale

INTRODUCTION

Adverse drug reactions (ADR) are untoward, unintended effects following intake of drug which is not desired after intake of any particular drug.[1] ADRs are usually underestimated and underreported due to various factors. Cutaneous adverse drug reactions are frequent and it contributes to 10-30% of all reported ADRs, and it accounts for 2-3% of hospitalizations.[2,3] Manifestations of cutaneous adverse drug reaction is varied and can present as mild pruritus to life threatening complications such as Stevens Johnsons syndrome (SJS)/toxic epidermal necrolysis.

Recently various studies have concluded that ADRs are 4th-6th leading cause of mortality.[4] ADR can cause mere inconvenience to disability and sometimes can be fatal. Practicing physicians should be more cautious in reporting adverse drug reactions as lot more new drugs are marketed in last 2 decades.[5]

ADRs should be monitored in hospital set up as it will help to understand nature and severity of adverse reactions to various drugs available. There is no scope of avoiding certain drug reactions but by prescribing drugs more skillfully, physicians can prevent serious and fatal adverse effects.

For example, in a patient with previous history of drug allergy, avoiding other drug belonging to similar class/drug class with similar molecular structure one can prevent the adverse drug reactions.

This study was intended to study adverse drug reaction pattern, common causative drugs, severity and causality among inpatients in department of dermatology, Goa Medical College.

METHODS

Study type

It was a retrospective observational study.

Study place

The study was conducted at the department of dermatology of Goa Medical College.

Study duration

The duration of the study was for one year (December 2020 – November 2021).

Sample size

The sample size was 24.

Study procedure

Patients who were admitted during study period as a case of drug reactions in department of dermatology were included in the study. A thorough history, clinical examination, drug therapy and laboratory parameters were noted in a pre-structured proforma. Precise history of drug intake along with initiation of symptoms was noted. Cutaneous morphology, mucosal and systemic involvement was noted. Causality was assessed according to Naranjo's ADR probability scale. All reactions were considered as severe as patients required hospitalization.

Exclusion criteria

Patients with mild reactions who did not require admission during study period was not included in our study.

Ethical approval

Institutional ethics committee approval was obtained prior to commencement of the study.

Statistical analysis

Results are tabulated as graphs and percentages using Microsoft excel.

RESULTS

A total of 24 patients were admitted in dermatology ward of Goa Medical College as cases of adverse cutaneous drug reaction which were included in the study. The following results were obtained. Demographic and drug intake details are tabulated in Table 1.

Table 1: Demographic and drug history details.

Characteristics	No. of patients	Percentage
Age group (years)		
<20	4	16.7
21-40	11	45.8
41-60	6	25
>60	3	12.5
Gender		
Males	9	37.5
Females	15	62.5
Female: male ratio: 1.66:1		
Mucosal involvement		
Oral	7	29.1
Ocular	4	16.7
Genital	3	12.5
Nasal	0	0
Fever	11	45.8
Time elapsed since drug intake and development of symptoms (weeks)		
<1	15	62.5
1-2	6	25
>2	3	12.5
Past history of drug reactions		
Yes	6	25
No	18	75
Route of drug administration		
Oral	21	87.5
Topical	2	8.33
Injectable	1	4.16
Drug intake for acute illness	20	83.3
Drug intake for chronic illness	4	16.7
Drug intake on prescription	20	83.3
Drug intake over the counter	4	16.7

Maximum patients were in the age group of 21-40 years and the mean age of patients were 38.95 years. The age range was from 7 years to 77 years.

Most common CADR noted was SJS in 6 patients (25%) followed by morbilliform reaction which was seen in 5 patients (20.83%).

DRESS, FDE and angioedema accounted for 3 patients (12.5%) each; AGEP was noted in 2 patients (8.33%); erythroderma and urticaria in 1 patient (4.16%) each (Table 2).

Antibiotics were commonly implicated drug category in causation of adverse cutaneous drug reaction accounting for 37.5% followed by NSAIDS which accounted for 25%. Antiepileptics contributed for 16.66%, allopurinol accounted for 8.33% and itraconazole, dapsone, isosorbide mononitrate, contributed for 4.16% each (Table 3 and Figure 1).

Table 2: Various presentations of cutaneous adverse drug reactions.

Type of reaction	Frequency	
	Number of patients	%
Erythema multiforme	0	0
DRESS	3	12.5
AGEP	2	8.33
Morbilliform reaction	5	20.83
SJS	6	25
TEN	0	0
Erythroderma	1	4.16
Urticaria	1	4.16
Angioedema	3	12.5
FDE	3	12.5

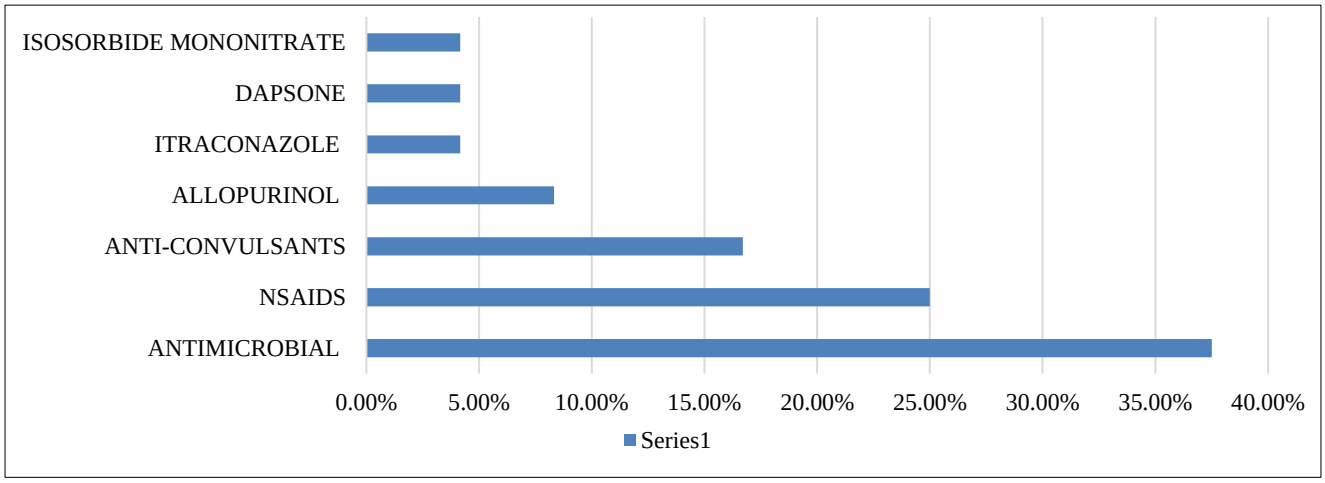

Figure 1: Various classes of drugs causing CADRs.

Table 3: Various drugs implicated in causation of drug reactions in present study.

Drugs	No. of patients	Percentage (%)
Anti-microbials	9	37.5
Beta- lactams	5	20.8
Fluroquinolones	2	8.33
Anti-TB drugs	1	4.16
Sulfonamides	1	4.16
NSAIDs	6	25
Anti-convulsants	4	16.66
Phenytoin	2	8.33
Carbamazepine	1	4.16
Phenobarbitone	1	4.16
Others		
Allopurinol	2	8.33
Itraconazole	1	4.16
Isosorbide mononitrate	1	4.16
Dapsone	1	4.16

According to Naranjo's causality assessment, 54.2% CADRs were categorized as probable, 37.5% were possible whereas 4.16% of CADRs were categorized as definite and 4.16% were categorized as doubtful (Figure 2).

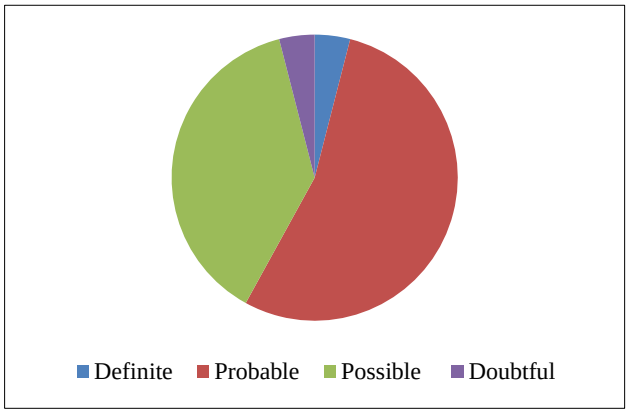

Figure 2: Causality as per Naranjo's scale

All 24 patients (100%) of cutaneous adverse drug reaction who were admitted, recovered from the illness. Among which 41.7% of patients recovered within 1 week; 37.5% of patients recovered in 1-2 weeks and 20.8% of patients took more than 2 weeks for recovery. Along with stopping the offending drugs, patients received supportive care, systemic steroids and immunosuppressants.

DISCUSSION

In a day-to-day clinical practice, almost all practising doctors encounter various manifestations of adverse cutaneous drug reactions. There is no comprehensive studies or data available on adverse cutaneous drug reactions till date. In our study we intended to identify common pattern of cutaneous adverse drug reactions, common drug class implicated in causing drug reactions and causality as per Naranjo's scale. In our study majority of patients belonged to 21-40 years of age group with mean age of 38.95 years. Youngest patient was 7-year-old male and oldest patient was 77-year-old female. In our study female preponderance was seen (F:M ratio 1.66:1) as observed by study done by Lihite and Lahkar et al which was in contrast to other studies done where male dominance was reported.[6-10]

Similar results were obtained by Raksha et al, Sharma et al, Pudukadan et al, and Anjaneyan et al.[7,11,13] However, studies done by Leappe et al and Hafner et al observed that elderly population was commonly affected by adverse cutaneous drug reactions.[14,15] The difference in observations could be due to regional variations in seeking health care. In addition, elderly populations receiving multiple drugs for comorbid diseases are more prone for adverse events due to drug interactions as well as altered drug metabolism.

In present study 62.5% of patients developed symptoms within 7 days of drug intake, 25% developed symptoms in 1-2 weeks and 12.5% of patients developed symptoms after 2 weeks of ingestion of offending drug. As per Anjaneyan et al 55% of patients manifested with symptoms in less than 24 hours and 14% within 24-48 hours of drug intake.[13] A study by Hotchandani et al reported duration of 1-7 days in majority of patients, between the drug intake and development of symptoms which was in concordance with our study.[9] Time period between ingestion of offending drug and development of symptoms serves as a one of crucial data in cases of adverse cutaneous drug reactions. In a patient who develops acute severe life-threatening reaction if treatment is initiated within 3 days it can be life-saving. Early withdrawal of offending drug is associated with the better prognosis. As per available literature it is observed that if referral to higher centre is delayed in severe cases of adverse reactions, it is associated with increased risk of mortality by 416 times.

In our study we reported that 70.8% of patients had more than 30% of BSA involvement, 25% of patients had 11-30% of BSA involvement and <10% BSA involvement was observed in 4.16% of patients. As per Anjaneyan et al 38% of patients had <25% BSA involvement and >75% BSA involvement was observed in 18% patients.[13] Similarly, Pudukadan et al 45.5% of patients had 0-10% of BSA involvement and 3.3% had >40% of BSA involvement.[12]

In present study past history of drug reaction was observed in 25% of patients, however 75% of patients did not have any past history of drug allergy. According to Agarwal et al 18.8% of patients had previous history of drug reaction and 81.3% did not have any past history of drug reaction.[16] Similarly, Patel et al reported past episodes of drug reactions in 18.9% of patients included in his study.[17] In majority of patients i.e., 83.3%, drug intake was for acute illnesses whereas in 16.7% of patients drug intake was for chronic illnesses. In our study 83.3% of drugs were dispensed on prescription, 16.7% of drugs were taken by patients over the counter. ACDRs can have myriad manifestations and distribution and various types reported in our study includes SJS in 6 patients (25%), morbilliform reaction which was seen in 5 patients (20.83%), DRESS, FDE and angioedema accounted for 3 patients (12.5%) each; AGEP was noted in 2 patients (8.33%); erythroderma and urticaria in 1 patient (4.16 %) each.

Table 4 shows comparison of clinical manifestation of drug reactions reported by various studies done in past with the present study. Studies done outside India have also noted that exanthematous reaction as common type of adverse cutaneous drug reaction.[15,18,19] Our study revealed that antibiotics were commonly implicated drug category in causation of adverse cutaneous drug reaction accounting for 37.5% followed by NSAIDS which accounted for 25%. Antiepileptics contributed for 12.5% and itraconazole, allopurinol, sulfasalazine, lignocaine contributed for 4.16% respectively (Figure 1).

Table 5 shows comparison of causative drugs among various studies done in past with the present study.

Table 4: Comparison of cutaneous manifestations among various studies.

Cutaneous reaction	Present study (%)	Anjaneyan et al[13] (%)	Sharma et al[7] (%)	Raksha et al[11] (%)	Jhaj et al[20] (%)
SJS	25	4	3.30	9.83	14.6
Morbilliform rash	20.83	25	34.6	18	50
FDE	12.5	23	30	30.5	13.9
Urticaria	4.16	22	14	18.5	21.5

Table 5: Comparison of causative drugs among various studies.

Drug class	Present study	Anjaneyan et al[13]	Hotchandani et al[9]	Sharma et al[7]	Pudukadan et al[12]	Chatterjee et al[21]
Anti-microbials	37.5	54	61.4	42.6	58.8	34.10
NSAIDs	20.8	23	22.9	22.2	15.5	32.88
Anti-epileptics	16.7	11	10	18	15.5	21.51

As even for mild illness, antimicrobials and NSAIDs are commonly prescribed by physicians and also due to ease of availability over the counter these classes of drugs are associated with higher risk of developing ACDRs.

According to Naranjo's causality assessment, 54.2% CADRs were categorized as probable, 37.5% were possible whereas 4.16% of CADRs were categorized as definite and 4.16% were categorized as doubtful (Figure 2).

Hematological abnormalities were seen in 13 patients (54.16%). Biochemical abnormalities were observed in 10 patients (41.66%).

All 24 patients (100%) of cutaneous adverse drug reaction who were admitted, recovered from the illness. Among which 41.7% of patients recovered within 1 week; 37.5% of patients recovered in 1-2 weeks and 20.8% of patients took more than 2 weeks for recovery. Good prognosis in all cases could be due to prompt diagnosis, stopping offending drug and initiating treatment as soon as possible.

Limitations

Study was done over shorter time period and represented a snapshot of cases at a particular point of time. Also, adverse cutaneous drug reactions reported in other departments were excluded from study. In addition, mild drug reactions which were managed at OPD level during study period was excluded.

CONCLUSION

Cutaneous drug reactions pattern in our study was very similar in many aspects to various other studies conducted in India. In our study life threatening complications like SJS was higher may be due to fact that mild adverse cutaneous drug reactions were treated at OPD level. It is very important to keep diagnosis of drug reactions in all suspected cases as there are varied presentations to various classes of drugs available. All practicing doctors are expected to have sound knowledge of common drug eruptions, diagnose them at the earliest, withdraw the offending drug and refer the patient to the higher centre when indicated.

Also, they should be trained to report ADRs in standard format to the regulatory authorities. Pharmacovigilance is still a budding concept especially in country like India. Most of cases of ADRS go un-noticed and un-reported in the era of emerging pharmaceutical industries where every-day new molecules are being studied and used. Also, for trivial illnesses polypharmacy is utilized by overzealous doctors. Mild or severe, all drug reactions should be reported to regulatory authority, to formulate better preventive measures and help physicians to prescribe more skillfully in a long run.

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

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