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Clinico etiological study of adverse cutaneous drug reactions

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ABSTRACT

Background: Adverse cutaneous drug reactions (ACDR) are the most frequent ADRs (30-45%) and are responsible for about 2% of hospital admissions and few can result in significant morbidity, health care costs, hospitalization, and death. To study different clinical patterns of ACDR, assess the cause and identify the offending drug and to study the relationship of ACDRs to age and sex among patients referred to the department of DVL, NRI General Hospital.

Methods: This is a retrospective study of 70 cases of colorectal carcinoma analysing incidence, clinicopathological features and outcome after different therapies including surgery, radiotherapy and chemotherapy. It was a descriptive hospital-based case series study. All out-patients and in-patients referred to the department of DVL, NRIGH, Chinakakani and in whom a diagnosis of ACDR is made, form the subjects for this study. The study was conducted over a period of two years.

Results: 100 patients with adverse cutaneous drug reactions were included in the study. 42 (42%) were males and 58 (58%) were females. The age group ranged from 6 to 80 years with a maximum (43) belonging to 21 to 40 years. Maculopapular rash was most common followed by urticarial drug reaction, FDE, acneiform eruptions, EMF, erythroderma, DRESS, SJS, SJS/TEN, TEN and drug-induced hyperpigmentation. NSAIDs were the commonest culprits followed by antibiotics, antiepileptics and ATT.

Conclusions: The commonest ACDR was maculopapular rash followed by urticaria, FDE and acneiform eruption. Antimicrobials as a group were the most common offending agents followed by individual drugs like diclofenac (13%), isoniazid (11%), efavirenz (9) and prednisolone (8%).

Keywords: Adverse cutaneous drug reactions, Etiology, Maculopapular rash

INTRODUCTION

Adverse drug reactions (ADRs) are unexpected or dangerous reaction to a drug and are a major clinical problem in terms of human suffering. Adverse cutaneous drug reactions (ACDRs) are the most common ADRs (30-45%) and are responsible for about 2% of hospital admissions. ACDR occur with variable severity. A few can result in significant morbidity, health care costs, hospitalization, and death. The mortality rate in toxic epidermal necrolysis (TEN) can be high.

The incidence of ACDRs among in-patients in developed countries and in developing countries such as India is 1-3% and 2-5% respectively. Incidence among outpatients is 2-6%. ACDRs are responsible for approximately 3% of all disabling injuries during hospitalization. The incidence of acute cutaneous drug reactions among all drug reactions is between 24-29%. The Incidence of drug eruptions in our country varies between 6 to 30 % and about 8% hospital admissions are due to drug eruptions. The large majority of cases were in the age group of 21-40 years with female preponderance.

Although ACDRs are common, detail information regarding their incidence, severity and ultimate health effects are often not available as many cases go unreported. In India, drug reactions are uncommonly reported on a regular basis, except by a few departments of dermatology or pharmacology affiliated to tertiary health care centers. Determining the cause, particularly for severe reactions with conviction may be extremely difficult as conducting oral provocation tests would be dangerous and unethical.⁵

ACDRs are potentially avoidable reasons for seeking medical care. Besides, drug reactions are a common reason for litigation. In this background, it was thought appropriate to undertake a clinico etiological study of ACDRs.

The main aim and objective was to study different clinical patterns of ACDR, assess the cause and identify the offending drug and to study the relationship of ACDRs to age and sex among patients referred to the department of DVL, NRI General Hospital and in whom a diagnosis of ACDR is made.

METHODS

It is a descriptive hospital-based case series study with a total of 100 out-patients and in-patients of and referred to the Department of DVL, NRIGH and in whom diagnosis of ACDR is made, form the subjects in a two year study period from December 2016 to November 2018. Ethical clearance has been taken from the institute. Inclusion criteria-All cases of ACDR with a causal relationship of "Certain," "Probable" and "Possible" with drugs according to WHO-UMC guidelines⁶ and willing to participate were included in the study. Patients with ACDR with drug abuse and incomplete history were excluded. Informed written consent was obtained from the patient. Detailed history including the complete medication list was collected. Clinical examination and relevant laboratory investigations were done. The steps furnished by Nayak et al were followed to trace the offending drug.² Causality assessment was done using WHO-UMC guidelines. Data was entered in a specially designed case record form and subjected to statistical analysis. Qualitative data like sex, sites involved and quantitative data like age, gap between drug intake and onset of rash was recorded.

RESULTS

It was an institutional based prospective observational study. 100 patients with adverse cutaneous drug reactions were included in the study. 42 (42%) were males and 58 (58%) were females. The male to female ratio in the study was 0.72:1. The age group of patients ranged from 6 years to 80 years with a maximum number of patients (43) belonging to the age group of 21 to 40 years. Reaction time (RT) was commonly found to be within one day 39 (39%) patients. The reaction time of <1 day was common in cases of urticaria and maculopapular rash. RT of 60 days was seen in cases of DRESS. Maculopapular rash is the most common ACDR observed followed by an urticarial drug reaction, FDE, acneiform eruptions, EMF, erythroderma, DRESS, SJS, SJS/TEN, TEN, drug-induced hyperpigmentation.

Table 1: Various types of adverse cutaneous drug reactions (n=100).

S. no.	Cutaneous ADR	No.of cases (N)	%
1	Maculopapular rash	25	25
2	Urticarial drug reaction	21	21
3	FDE	15	15
4	Acneiform eruptions	14	14
5	Erythema multiforme	7	7
6	Erythroderma	6	6
7	DRESS	4	4
8	Stevens-Johnson syndrome (SJS)	4	4
9	SJS/TEN	2	2
10	Toxic epidermal necrolysis (TEN)	1	1
11	Drug-induced hyperpigmentation	1	1

Of the various ACDRs, maculopapular rash is seen in majority of the cases followed by urticarial drug reaction, FDE and acneiform eruptions.

Table 2: ACDR patterns with respect to age, gender, time and mucosal involvement.

ACDR pattern	Mean age (in years)	Gender (male to female ratio)	Mean reaction time (in days)	Presence of mucosal involvement (%)
Maculopapular rash	38.16	0.66:1	7.01	36
Urticarial drug reaction	32.08	0.9:1	0.62	0
Urticarial drug reaction with angioedema	33.75	1:7	1.10	100
Acneiform eruptions	31.28	1.8:1	16.57	0
FDE	34.53	1:2.75	1.64	13.3
Erythema multiforme	37.85	1:2.5	2.42	14.28
Erythroderma	44.33	5:1	7.33	16.66

Continued...

ACDR pattern	Mean age (in years)	Gender (male to female ratio)	Mean reaction time (in days)	Presence of mucosal involvement (%)
DRESS	41.25	1:1	28.5	75
SJS	41.5	1:1	3.5	100
SJS/TEN	34.5	0:2	17.5	100
TEN	50	0:1	18	100
Drug induced hyper pigmentation	44	0:1	7	100

Table 3: Drugs causing severe cutaneous adverse drug reactions (SCAR).

Drugs	SJS	TEN	SJS/TEN	DRESS	Erythroderma
Diclofenac	1	-	1	-	1
Eptoin	1	1	1	1	-
Cefixime	1	-	-	-	
Metoclopramide	1	-	-	-	
Carbamazepine	-	-	-	1	
Levetiracetam	-	-	-	1	
Ethambutol	-	-	-	1	
Isoniazid	-	-	-	-	2
Methotrexate	-	-	-	-	1
Allopurinol					1
Cephalexin	-	-	-	-	1
Total	4	1	2	4	6

Table 4: Various drugs causing ACDRs (n=100).

Drugs	No. of patients	(%)
NSAIDs	26	26
Antibiotics	25	25
Antiepileptics	13	13
ATT	12	12
Steroids	9	9
ART	10	10
Others	5	5

No. of ACDRs

7
6
5
4
3
2
1
0
Phenytoin Carbamazepine Levetiracetam Clobazam

Figure 1: Anti-epileptics and ACDRs.

Of the various patterns, mucosal involvement is seen in all cases of urticarial drug reaction with angioededma, SJS, SJS/TEN, TEN and drug induced hyperpigmentation.

Table 5: NSAIDs causing ACDRs (n=26).

Drug	No. of ACDRs	(%)
Diclofenac	13	50
Ibuprofen	7	26.92
Aceclofenac	3	11.54
Naproxen	1	3.85
Ultracet	1	3.85
Paracetamol	1	3.85

Table 6: Anti-microbial drugs causing ACDRs (n=47).

Drugs	No. of ACDRs	(%)
Isoniazid	11	23.40
Efavirenz	9	19.15
Augmentin	5	10.64
Ofloxacin	5	10.64
Cotrimoxazole	5	10.64
Ciprofloxacin	2	4.26
Ceftriaxone	2	4.26
Cefixime	2	4.26
Cephalexin	1	2.13
Linezolid	1	2.13
Ampicillin	1	2.13
Norfloxacin	1	2.13
Nevirapine	1	2.13
Ethambutol	1	2.13

Erythroderma is the most common SCAR in the present study.

NSAIDs and antibiotics are the most common drugs implicated in the development of ACDRs.

Among NSAIDs diclofenac was the commonest followed by ibuprofen. When individual drugs were considered diclofenac was the commonest followed by Isoniazid.

Most common anti-microbial drug causing ACDRs in the present study is isoniazid. Phenytoin is the most common anti-epileptic causing ACDRs.

DISCUSSION

100 patients were evaluated of which 42 were males, and 58 were females. Female preponderance was seen with the M:F ratio of 0.72:1. Our study showed female preponderance 0.72:1 similar to the study done by Pudukadan et al (0.87:1) and Nandha et al (0.94:1). 9 In our study, the age group of patients ranged from 6 years to 80 years, with the maximum number of patients (43) within 21-40 years age group. This is similar to studies done earlier. 9 Pediatric and geriatric age showed decreased incidence. Most common age group observed in our study is between 21-40 years which included 43% of patients similar to study by Nandha et al.

Reaction time is the period between the drug intake and onset of symptoms. Reaction time ranged from 15 minutes to 60 days in our study. In our study, 39% of cases were seen within 24 hours of drug intake and 72% of cases within seven days of drug intake. These findings are similar to the study done by Gor et al, where they observed 77.78% of reactions occurring within the first ten days of intake of the implicated drug. ¹⁰

In our study, urticarial drug reactions occurred within 15 minutes to 2 days similar to the study done by Sushma et al (1-3days). But Saha et al observed it to be 1-28 days. Maculopapular rash occurred within 1 day to 30 days similar to the study done by Saha et al (1-30 days). Sushma et al observed it to be 2-7 days. Erythroderma was observed to occur within 1-15 days in contrast to the study done by Saha et al (1-42 days).

Maculopapular rash was the commonest, seen in 25 (25%) patients similar to the study done by Saha et al (30.18%).¹² Urticaria is the second most common and is observed in 2 (21%) patients similar to the study done by Patel et al.³ Fixed drug eruption is the third most common observed in 15 (15%) patients similar to the study done by Hiware et al (17.2%).¹³

Acneiform eruption was observed in 14 (14%) cases similar to the study done by Sharma et al (11.3%). Mucosal involvement is not seen in patients presenting with an acneiform eruption. Morphologically acneiform eruption cases presented with monomorphic inflammatory lesions like papules and pustules.

Erythema multiforme was observed in 7 (7%) cases similar to the study done by Sharma et al (11.3%). Mucosal involvement was seen in 14.28% of patients with EMF. Most of the cases presented with typical targets, characterized by a central dusky area or a central crust, a pale zone and a peripheral reddish zone. Atypical target lesions with only two zones were also seen.

Exfoliative dermatitis (6%) observed in 6 (6%) cases correlated with the study done by Saha et al (7.5%). ¹² Mucosal involvement in the form of erosions and ulcers over the buccal mucosa is seen in 16.66% of patients presenting with exfoliative dermatitis.

Maculopapular rash in our study was caused by antibiotics in 40% of cases and is similar to the studies done by Sharma et al.¹⁵ Anti-epileptics in 28% of cases and these findings are similar to the studies done by Sharma et al (22.2%) and NSAIDs in 16% of cases.¹⁵

Urticarial drug reaction was the second commonest reaction pattern with 21 cases (21%). In our study, the most common offending drugs for urticaria were non-steroidal anti-inflammatory drugs with 9 cases followed by antibiotics, ATT, antiepileptics (phenytoin), ART (efavirenz) and anticoagulant (warfarin).

FDE was the third commonest reaction with 15 cases (15%), and these findings are in correlation with the previous study done by Hiware et al (17.2%). ¹³ Drugs Implicated are: NSAIDs in 9 cases followed by antibiotics and antiepileptics.

The acneiform eruption was seen in 14 (14%) cases similar to study done by Sharma et al. ¹⁴ Common offending agents in our study were corticosteroids followed by ATT.

Erythema multiforme was seen in 7 (7%) cases and the commonest drug implicated being non-steroidal anti-inflammatory drugs.

Erythroderma was seen in 6 (6%) cases and these findings correlated with a study by Saha et al (7.54%). Drugs implicated in erythroderma include isoniazid (2), cephalexin (1), allopurinol, methotrexate, and diclofenac (one each case).

Among severe cutaneous adverse drug reactions (SCARs) anti-epileptics were the commonest drugs observed. This observation was similar to the findings in a study done by Sasidharanpillai et al.¹⁶

In our study antimicrobials is the commonest drug group causing ACDRs and constitute 47 (47%) cases. This was similar to the study done by Nandha et al (48.3%). The common drugs implicated are amoxicillin / clavulanic acid (5), cotrimoxazole (5) and ofloxacin (5).

Amongst the anti tuberculous medications (12 cases), the commonest morphological pattern was acneiform eruptions (5 cases).

Non-steroidal anti-inflammatory drugs (26 cases) are the second most common group in our study with 26% of cases similar to the study done by Nandha et al (21.90).

Antiepileptics constitute 13 (13%) cases, and the most common clinical pattern was maculopapular rash (4 cases) followed by DRESS in 3 cases. Other reactions include urticaria, FDE, SJS to TEN spectrum. Our study correlated with Nandha et al (13.20%). Among antiepileptics phenytoin was the culprit drug in 7% of cases similar to the study done by Patel et al (6.46%).

CONCLUSION

In our study, the commonest ACDR was maculopapular rash followed by urticaria, FDE and acneiform eruption. Severe cutaneous drug reactions were observed, along with certain rare drug reactions like drug reaction with eosinophilia and systemic symptoms (DRESS). Antimicrobials as a group were the most common offending agents. However, when individual drugs were taken into considerations then diclofenac (13%) followed by isoniazid (11%), efavirenz (9) and prednisolone (8%) in the order were the offending drugs. Reaction time ranged from 1 to 60 days, with shortest time for urticaria (15 minutes) and longest for DRESS syndrome (60 days). In our study, it was commonly seen to be within 24 hours.

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institutional ethics committee

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