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Original Research Article

A prospective study of clinical spectrum of cutaneous adverse drug reactions and their incidence in Indian population

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ABSTRACT

Background: Making the diagnosis of a drug-induced reaction requires familiarity with the clinical patterns as the current understanding of the disease processes is not enough to explain about apparently similar pathological mechanisms generating different clinical patterns. Therefore, it remains useful and relevant to overlay a pathological understanding with a clinical classification. This study concentrated on observing and documenting the clinical presentation of cutaneous adverse drug reactions (CADR) encountered in patients. The purpose of the study was to evaluate causality, severity and preventability of Dermatological ADRs.

Objective: To study morphological types of CADR and their incidence in Indian population Method: A prospective, observational study was carried out over a period of one year at Out Patient Department of Dermatology, Government Medical College, Amritsar with diagnosed CADRs. The suspected ADRs were evaluated for causality by Naranjo's Probability scale and severity by Hartwig and Siegel scale.

Result: Total 54 patients were enrolled. The incidence of CADR was 0.09%. Most commonly manifested ADR was fixed drug eruption (FDE) i.e. 35.2%. Maximum incidence of dermatological ADRs were observed with antimicrobial agents (39%) followed by non-steroidal anti-inflammatory drugs (NSAIDS) (24%). Naranjo's Probabilty scale showed most cases of probable (68.5%) ADRs were of moderate severity (90.7%).

Conclusion: Awareness about CADR is essential for early detection, management of patients and drug safety. The healthcare system can promote the spontaneous reporting of dermatological ADR to Pharmacovigilance centers for ensuring safe drug usage and patient care.

1. Introduction

The definition of adverse drug reactions (ADR) as given by WHO is "any response to a drug which is noxious and unintended and which occurs at doses, normally used for prophylaxis, diagnosis or therapy of disease or for modification of physiological function". It excludes supra-therapeutic doses, drug abuse, treatment failure and errors, which occur with drug administration.[1] Cutaneous adverse drug reactions (CADR) are the commonest ADR (30-45%) and responsible for about 2% of hospital admissions.[2–5] They may range from mild (two-thirds) to severe or life threatening (one-third) in a hospital setting.[4] Approximately 2-7% CADR are severe.[6] In India, CADR account for 2-5% of all inpatients, while it affects 2-6% of outpatients.[7]

Risk factors, such as female gender, older age, viral infections (notably HIV), iatrogenic immunosuppression, underlying immune-mediated diseases and cancer, have been related to more severe CADR.[8,9]

The common CADRs are skin rash, urticaria, fixed drug eruption (FDE), angioedema, and contact dermatitis. Serious CADRs i.e. severe cutaneous adverse reactions (SCARs) are Stevens-Johnson syndrome (SJS), toxic

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epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP).[10,11]

Because of the ready visibility of signs in skin, cutaneous manifestations are frequently the earliest sign of systemic drug allergy and can therefore prove critical in providing information on the severity and prognosis of the allergic reaction. Making the diagnosis of a CADR requires familiarity with the clinical patterns. This study concentrated on observing and documenting the various clinical patterns of CADR and their respective incidence in Indian patients so as to add information into the pool of scientific knowledge. This information can help pharmacovigilance centres for ensuring safe drug use and to improve quality of patient care.

2. Results

Out of 58701 new patients, who attended the OPD during the study period of 12 months, a total of 54 patients were diagnosed with CADR. The overall incidence of CADR during this period in this study was found to be 0.09%. Mean age of our study was 33.24 ±15.324, the youngest of our patient being 3 year old and eldest being 65 years old. Based upon age (in years), our study patients were divided into 3 groups: Group A 0-20, Group B 21-40, Group C 41-60 and above. Group B and C had 20 (37%) patients each and group A had 14 (25.9%) patients (Graph 1).

Male to female ratio of 1.7 was observed in our study. 28(51.9%) cases belonged to rural residence and 26(48.1%) cases had urban residence.12 (22.2%) cases of CADR were housewives and 11(20.4%) cases were students, the remaining being the labourer, government employees, businessman etc.

Most common initial site involved in CADR patients was upper limb in 15(27.7%) cases followed by lower limb in 10(18.5%) cases, face in 7(12.9%) cases, 5(9.2%) cases each over back and lips and 3(5.55%) cases each over chest, abdomen and genitals.

Only 6(11.1%) cases presented with constitutional symptoms in the form of fever/arthralgia. 44(81.48%) patients complained of itching and 10(11.9%) patients had no itching complaints. 11(13.09%) patients were having itching of mild intensity, in 27 (50%) patients, it was moderate in intensity while 6(11.11%) patients had severe itching complaint. History of atopy was present in only 2(3.7%) cases. 5(9.3%) cases of the total enrolled patients in our study were chronic smokers and 12(22.2%) cases gave history of alcohol consumption. The incubation period ranged from 5 hours to 69 days with a mean of 5.53 days ± 11.17 days. 37% cases reported incubation period within 1 day, 67% cases within 3 days and 89% within 7 days.

No patient had history of previous episode of drug allergy to the same or similar drug. None of the cases had any history of family members with CADRs.

All of the patients had taken drugs in one form or other for a duration ranging from 1 day to 68 days. The duration of drug intake before appearance of CADR has been shown in Table 1.

The mean AEC count was 339 ± 73.189 on the day of presentation to hospital. Mean of mild, moderate, severe cases (based upon HS score) was 260, 341.82, 330.25 with p value of 0.535 signifying no significant difference among groups as shown in Table 2.

The mean Naranjo Probability (NP) Score was 4.78±1.475. Depending upon NP Score, cases were categorized as follows: 37 (68.5%) cases of probable CADR, 16(29.6%) cases of possible CADR and 1 (1.9%) case of definite CADR (Graph 2).

Distribution of causative agents in CADR patients: The most common causative agents found in our study were antimicrobial drugs, responsible in 21 (39%) cases, NSAIDS were responsible for 13 (24 %) case, 9(16.6%) cases were reported due to anti-epileptic drugs, ranitidine and allopurinol were responsible in 2(3.7%) cases each, while 1(1.9%) case each was found to be due to ACE inhibitor, PPI and montelukast (Graph 3).

As per Hartwig Siegel (HS) scoring system, the patients were placed according to severity of symptoms in 3 groups i.e. mild, moderate and severe groups. Patients with moderate severity were most common with 49(90.7%) cases followed by 4 (7.4 %) cases in severe and only 1(1.9%) case in mild severity group (1.9%).

Morphological pattern of drug reactions in our study cases revealed FDE to be the most common presentation of CADR in 19 (35.2%)cases, out of which 3 (5.7%) were of bullous FDE. Maculopapular rash was the next common pattern present in 12 (22.2%) cases. Beside these, the following distribution was observed in our study: urticarial drug rash in 5(9.3%) cases, lichenoid drug rash in 4(7.4%) cases, exanthematous drug rash in 3(5.6%) cases, TEN in 2(3.7%)cases, purpuric drug rash in 2(3.7%) cases and 1(1.9%) case each of AGEP, erythroderma, drug induced acneiform eruptions, SJS, SDRIFE, psoriasiform drug rash and vasculitis.Graph 4

Table 1: Distribution of therapy days among CADR patients

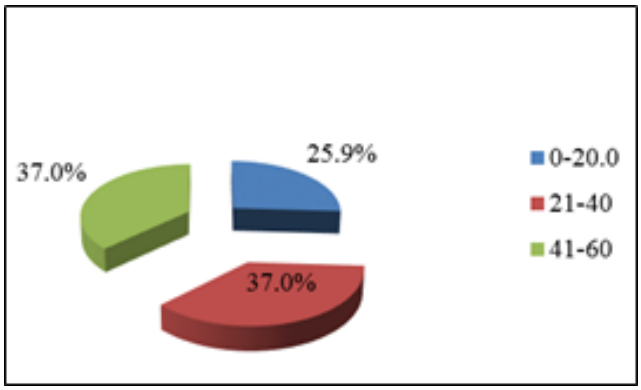
Therapy days	No. of cases	Percentage
< 2	17	31.5%
3-6.0	25	46.3%
>6	12	22.2%

3. Discussion

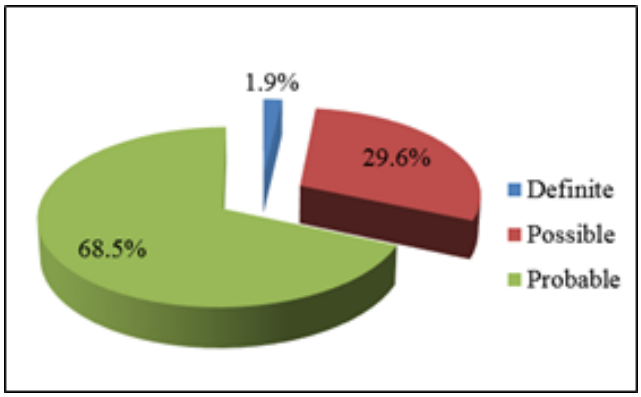
Adverse drug reactions (ADRs) place a considerable economic burden on the society. Therefore, prior to the administration of any drug, risk and benefit factors should be seriously evaluated.

Table 2: Absolute eosinophil count (AEC) distribution in CADR patients (per μL)

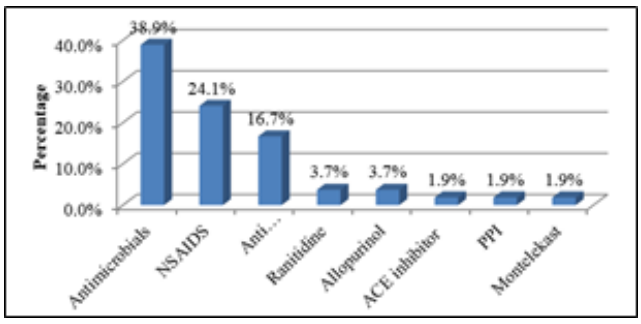
Severity of cases	No. of cases	Mean AEC	Standard Deviation	Standard Error	95% Confidence Interval for Mean		Minimum AEC	Maximum AEC	p-value
					Lower Bound	Upper Bound			
Mild	1	260.00	.	.	.	.	260.00	260.00	
Moderate	49	341.82	68.66	9.81	322.10	361.54	150.00	540.00	0.533
Severe c	4	330.25	130.03	65.01	123.35	537.15	190.00	491.00	



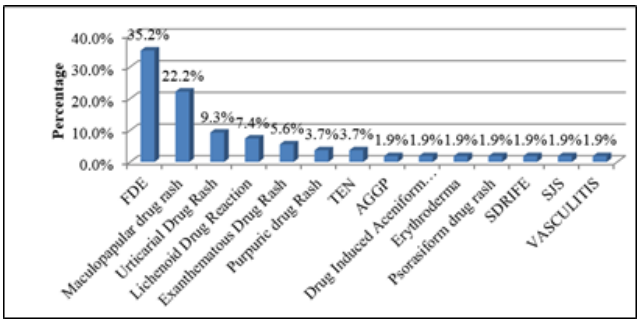
Graph 1: Age distribution of CADR patients (in years)



Graph 2: Probable causality among CADR patients based upon NP score



Graph 3: Distribution of causative agents in CADR patients



Graph 4: Distribution of morphological patterns of CADR case

The mean age of our patients in our study has been found to be comparable to findings of studies by Gohel et al[12] (38 ± 19.73 years), Saha et al[13] (33.8±17.19 years) and Puddukadan et al[14] (37.06 ± 18.17 years).

Based upon age groups, 37% each was found in age group of 21-40 and 41-60 and above while 0-20 years age group had 25.9% of cases. The study by Raksha et al[15] reported 19% patients in age group of 0-20, 41 percent in age group of 21-40 and 40% patients in 40 years above. In a study done by Puddukadan et al[14] 0-20 group included 25% patients, 21-40 had 50 % patients while 40 and above group had 25 % patients.

Male preponderance in the form of male to female ratio of 1.7 has been found in our study. Sharma et al observed male preponderance (M: F = 1.47:1)[16] with male to female ratio of 1.79:1 as noted in study by Hiware et al.[17] Contrary to our findings, female preponderance in CADR has been reported by Puddukadan et al[14] and Saha et al.[13] This difference may be due to less literacy rate among our study group females.

History of atopy was present in 2 cases (3.7%) only which has been reported to be 1.44% in a study by Patel et al.[18] This difference in our studies could be attributed to a small group of 54 patients only as compared to 8337 patients as well as smaller duration of our study i.e. 1 year as compared to 10 years of study by Patel et al.[18]

History of previous drug allergy was reported in 16(29.6%) cases which was present in 22% cases in a study by Anjaneyan et aland 18.92% patients in a study by Patel et al.[18] Morphological patterns of drug reaction in our study revealed fixed drug eruption to be the most

common CADR i.e. 19 (35.2%) cases, out of which 3 cases were of bullous FDE. Maculopapular drug rash was present in 12(22.2%) cases being the second most common CADR in our study. The third most common lesion was urticarial drug rash in 5 (9.3%) cases and fourth being lichenoid drug rash in 4(7.4%) cases. Similar pattern has been reported in Puddukadan et al study.[19]

In the study by Raksha et al[15] and Sharma et al[17] the commonest pattern was FDE (30.5%), followed by urticaria (18.5%) and morbilliform rash (18%). An incidence of 0.09% CADR has been established in our study as compared to 0.3% reported in Anjaneyan et al,[20] 3.78 % in Gohel et al,[12] Low literacy rate and per capita income in our study group may be the potential cause of under reporting of cases, which may be the reason of low incidence in our study.

Pruritus has been the major complaint of our patients with 80% of CADR cases exhibiting pruritus as compared to 37% as reported in a study by Anjaneyan et al.[20] Most common site involved in our patients was the upper limbs which has similarly been reported by Anjaneyan et al.[20] The second most common site was lower limbs and third most common site was face, in contrast to the study by Anjaneyan et al,[20] where face was second most common site followed by the lower limb.

50% of our cases had incubation period within 1 to 7 days which was also reported in a study by Hotchandani et al[21] also. 67% of our cases had developed CADR within 3 days which has also been reported similarly in a study by Anjaneyan et al[20](69%). In our study, 37% of patients developed CADR within 24 hours while Anjaneyan et al reported it to be 55%.[20]

Depending upon Naranjo Probability score, cases were distributed as follows: 37(68.5%) Probable, 16(29.6%) Possible and 1(1.9%) Definite case of CADR, which were almost comparable to study by Gohel et al[12] and Lihite et al.[22]

The causative agents traced in our study have reported antimicrobial drugs to be the commonest causative agent responsible in 21 (38.9%) cases. NSAIDS were the second most common agents responsible for 13(24.1%) cases followed by 9(16.7%) cases due to anti-epileptic drugs. Ranitidine and allopurinol were responsible for 2(3.7%) cases each while ACE inhibitor, PPI and montelukast were culprit drugs in 1(1.9%) case each. Similar findings have been reported by Gohel et al[12] who found Antimicrobial agents as the commonest causative drugs (43.30%) followed by non-steroidal anti-inflammatory drugs (26.80%) and antiepleptics (18%) being the third most common drugs while Patel et al[18] observed antimicrobials in 45.46% cases, NSAIDs in 20.87%cases, anti-epileptics in 14.57% cases. Sushma et al[23] reported antibiotics in 45% cases, antiepileptics in 19% cases ,NSAIDs in 19% cases. Contrary to these reports, some studies have reported anti-epileptic to be the second most common causative drug and NSAIDS as the third most common cause like studies by Sharma et al,[16] (antimicrobials in 42.6% cases, anticonvulsants in 22.2% cases and NSAIDs in 18% cases), Pudukadan et al[19] (antimicrobials in 58.88% cases , anti-epileptics in 15.55%, NSAIDs in 15.50%) and Saha et al[13] (antimicrobials in 50% cases ,analgesics in 11.30% cases, antiepileptics in 11.20% cases and allopurinol in 7.50% cases) .

In our study, based upon the severity by HS score, patients with moderate severity were most common with 49 (90.7%) cases followed by 4 (7.4 %) severe cases and 1(1.9%) case in mild severity group which had been reported similarly in a study by Gohel et al.[12]

Mean Absolute Eosinophil Count (AEC) reported in our study was 339.44 as compared to 356.83 seen in a study by Anjaneyan et al.[20] In our study eosinophilia (AEC > 500 cells/mm^3) was seen in 1.9% case as compared to 20% cases in the study by Anjaneyan et al[20] and 42.2% of patients in the study by Pudukadan et al.[14]

The p value was not significantly different for AEC among mild, moderate and severe groups of CADR which is the same finding as that in study by Anjaneyan et al.[20] Our study shows that the AEC is not significantly associated with severity of drug reactions which has been stated by Puddukadan et al too.[19]

Since most of the patients attending the OPD of this hospital belong to relatively poor socio-economic status, the pattern of drug usage amongst them is mostly restricted to drugs that are supplied free of cost from the hospital. As a consequence, the suspect drugs were mostly from the hospital OPD supply list. This was an important limitation of this study as the suspected drug data generated from this study may not be truly reflective of the pattern in other tertiary care centres which are catering to patients of higher socio-economic status.

Duration of our study was only one year due to time constraints of research work and there was lack of long term follow up due to time bound study.

4. Conclusion

Awareness about CADR is essential for early detection and prevention. FDE and maculopapular rash are the most common CADR. Classification based upon clinical patterns of CADR can prove to be a vital cog in management because the exact pathological mechanisms behind the different CADR are yet to be ascertained. The healthcare system can promote the spontaneous reporting of dermatological ADR to Pharmacovigilance centres for ensuring safe drug use and patient care.

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6. Conflicts of Interest

There are no conflicts of interest.

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