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CUTANEOUS ADVERSE DRUG REACTION: FOCUS ON DEMOGRAPHY, CLINICAL PATTERN, CAUSALITY, SEVERITY AND PREVENTABILITY -A CROSS SECTIONAL STUDY IN A TEACHING HOSPITAL OF RURAL WEST BENGAL

Clinical Pharmacology

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ABSTRACT

BACKGROUND: Cutaneous adverse drug reactions (CADR) are most frequent among all drug induced adverse reactions and encompass maculopapular rash to toxic epidermal necrolysis (TEN) .It is important to explore the CADR in detail to understand it's importance in patient care.
AIM: To document the morphology, demographic pattern, causality, severity and preventability of CADR in the study population as well as to find out the incriminating drugs.
METHODS: In this cross sectional observational study over one year, 118 newly diagnosed patient of CADR at Dermatology OPD were recruited after obtaining written informed consent and requisite ethics approval. Detailed drug history, morphology, evolution and duration of the rash, temporality with drug exposure and the effect of dechallenge were documented in the CRF.
RESULTS : Young adult cases were more reported , Fixed Drug Eruption (FDE) was the commonest CADR followed by urticaria. Antimicrobials (mostly fluoroquinolones) were suspected drugs followed by NSAIDS. Most of the cases 66(55.93%) were mild followed by moderate 34(28.81%) and severe 18(15.25%) ones. Severe ones caused mostly by antiepileptics.The interval between drug intake and CADR ranged from a few minutes to 20 days and total duration of drug reaction was <1 week in majority (73%).Most of the CADR were not preventable(62.7%).
CONCLUSION: Considering the varied presentation and potential severe nature of CADR, both physicians and patients should be vigilant and aware to identify the reactions at the earliest opportunity as majority appeared within one week of drug exposure. A compliance with the national pharmacovigilance programme is very essential to communicate these events for corrective regulatory actions.

KEYWORDS

cutaneous adverse drug reaction, severity, causality, preventability

INTRODUCTION

Drugs are double edged swords; on one hand they can cure or provide relief from various diseases and on the other hand they themselves can cause adverse drug reactions ranging from minor ailments to even death.

Adverse drug reactions(ADR) is defined by WHO as 'any response to a drug which is noxious and unintended and which occurs at doses, normally used for prophylaxis or diagnosis or therapy or disease or for modification of physiological function'. It excludes supra-therapeutic doses, drug abuse and treatment failure and errors, which occur while drug administration[1].

Drugs no matter how safe are full of adverse effects and the most commonly used drugs have adverse reactions more than 1%.[2] Cutaneous ADRs are most common among the various adverse reactions having wide spectrum ranging from maculopapular rashes to toxic epidermal necrolysis (TEN).[3]They occur in up to 8% of global population and in 2-3% of hospitalized patients. The incidence of cutaneous ADRs in developed countries is around 1-3% and comparatively higher in developing countries around 2-5%.[4]ADRs are causes of significant morbidity and mortality in patients and place a considerable economic burden on the society which is estimated to be around 5-9% of all hospital costs.[5]

The incidence and severity of ADRs can be influenced by patient-related factors like age, sex, genetic factors, concurrent ailments, and drug related factors like type of drug, route of drug administration, duration of treatment and dosage. The other important risk factors associated with adverse drug reactions are increased number of medicine exposures, geriatric age, length of hospital stay and function of excreting organs.

Reporting of adverse drug reactions (ADR) is extremely important. It helps to recognize the type of drug reaction and the causative agent in a particular set of population. It also helps in taking steps to reduce the detrimental effects to the patients and substitution of harmful ones with safer alternatives during therapy.ADR reporting in the form of post-marketing surveillance substantiates for continuous scrutiny of new drugs and even withdrawal of already marketed drugs leading to improvement of the public health at large. Many instances of suspected CADRs in different forms are accounted by the physicians. Therefore, both the dermatologists as well as the practicing physicians should be conscious with these conditions to enable early diagnosis and prompt withdrawal of the causative drug to prevent mortality.[6]

Systematic monitoring and surveillance of adverse drug reactions will help in ensuring safer prescription and limit the adverse effects of drugs with their undue consequences and sensitizing awareness among the healthcare professionals to report and follow up the events.[7]

AIMS AND OBJECTIVES

The objective of the study was to document the frequency, morphology, demographic pattern of cutaneous ADRs (CADR) in the study population, to assess causality, severity, preventability, recent trends in clinical variants of CADR and the incriminating drugs.

MATERIALS AND METHODS

This is a hospital based, unicentric, cross sectional observational study carried out for one year from February 2018 to January 2019 in 118 patients at a tertiary care teaching hospital in rural West Bengal. All new patients irrespective of age and sex, having various drug induced cutaneous reactions attending the out patient clinic and referred from other specialities to the dermatology department during the study period were included in the study. The protocol of the study was approved by the Institutional Ethics Committee(MMC/IEC-2017/2698 dated 22/12/2017).

Patients with intentional or accidental poisoning, those who developed ADR during blood or blood product transfusion and those with no definitive history of drug intake during the appearance of dermatological reactions or in recent past preceding the reaction were not included in the study. The diagnosis and line of treatment was given by the physician in charge of the Department of Dermatology. All the requisite tests like hematological, biochemical investigations, HIV (ELISA), venereal disease research laboratory (VDRL) test and histopathological examination were done wherever indicated. Severe cases were hospitalized. Depending on the severity of the reaction the follow up of the patient varied.The written informed consent was taken from all the study participants.

The data was collected and entered in a pre-designed case report form

(CRF). To establish the etiologic agent for a particular type of reaction, attention was paid to the detailed drug history, duration of the rash, morphology of the eruption, temporal association with the drug exposure, approximate latency period, and prognosis of the lesions after withdrawal of the drug, i.e., Dechallenge (wherever possible). Rechallenge of the offending drug was not done. All the information of ADR was recorded in ADR reporting form and reported through Vigiflow to the National Co-ordinating Centre of Pharmacovigilance Programme of India. Causality assessment was done with the help of WHO – UMC scale and Naranjo's scale, Severity and Preventability were assessed by Hartwig and Siegel's severity scale and Schumock and Thornton's preventability scale respectively[8,9,10,11]

Descriptive statistics like mean and percentages were used for analysis and interpretation of results. Statistical analysis was performed using Microsoft Excell and SPSS version 21.

RESULT

In the present study total 118 patients with definite drug intake history were enrolled. Among the study subjects, 53(44.91%) were male and 65(55.08%) were female. The male to female ratio was 0.8:1. The oldest patient in study was of 69 years and the youngest was of 3 years. Majority of cases, i.e., 30 (25.0%) were in the age group of 21-30 years followed by 28 (21.0%) in age group of 31-40 years, 25(21.18%) in 41-50 years and the lowest 6 (5.08%) cases in the age group >61years. Age and Gender distribution of patients in the study is shown in Table 1.

Table 1: Age and Gender distribution of the CADR subjects

GENDER	NUMBER OF PATIENTS	PERCENTAGE %
Male	53	44.91
Female	65	55.08
Age group (years)		
<10	8	6.77
11-20	12	10.16
21-30	30	25.42
31-40	28	23.72
41-50	25	21.18
51-60	9	7.62
>61	6	5.08

Onset of reaction in majority of the patients i.e. 69(58.47%) was between 24 hours and 1 week, followed by <24 h in 32(27.11%) and more than 1 week in 17(14.40%) shown in Table 2. The interval between drug intake and CADR ranged from a few minutes to 20 days. Total duration of reaction was <1 week in 68% and more than 1 week in 32% of the patients.

Table 2 : Categorization of CADR according to onset of the reaction

Onset	Number of patients	Percentage %
< 24 hours	32	27.11
24 hours-1 week	69	58.47
>1 week	17	14.40

Table 3: Clinical pattern of the CADR

Morphological types of drug reactions	Number of patients	Percentage %
Fixed drug eruption(FDE)	47	39..83
Urticaria	26	22.03
Maculopapular eruptions	18	15.25
SJS/TEN	12	10.16
Erythema multiforme(EM)	4	3.38
DHS/DRESS	3	2.54
Angioedema	2	1.69
Miscellaneous	6	5.08

Table 3 shows the distribution of various patterns of CADRs among the study subjects. FDE(fixed drug eruption) was the most frequently observed morphological pattern in 47(39.83%) patients, followed by urticaria 26(22.03%), maculopapular rash 18(15.25%), SJS/TEN 12(10.16%), miscellaneous 6(5.1%), erythema multiforme (EM) 4(3.38%), DRESS/DHS (Drug Rash with Eosinophilia and Systemic Symptoms/ Drug Hypersensitivity Syndrome) 3(2.54%) and lastly angioedema in 2(1.69%) patients. The most common drug groups implicated in cutaneous ADRs included antimicrobials in 66(55.9%) patients followed by NSAIDs in 29(24.6%) patients, antiepileptics in 18(15.3%), and various other drugs in 5(4.2%) patients (Table 4).

Table 4 : Suspected drugs involved in CADR

Drug class	Individual drugs	Number of patients	Percentage(%) out of 118 CADR patients
Antimicrobials		66	55.93
Antibiotics(46)	Amoxycillin	12	10.16
	Amoxycillin+ clavulanic acid	5	4.23
	Ciprofloxacin	7	5.93
	Chloramphenicol	1	0.84
	Cefotaxime	3	2.54
	Cefixime	2	1.69
	Ofloxacin	16	13.55
Anti-mycobacterial (5)	Rifampicin	2	1.69
	Isoniazid	2	1.69
	Dapsone	1	0.84
Antiprotozoal and	Metronidazole	6	5.08
Antihelminthic (13)	Ornidazole	3	2.54
	Secnidazole	3	2.54
	Tinidazole	1	0.84
Antifungal (1)	Fluconazole	1	0.84
Anti retroviral (1)	Zidovudinez+ lamivudine	1	0.84
Other drug class			
NSAIDs (29, 24.57%)	Ibuprofen	11	9.32
	Paracetamol	7	5.93
	Diclofenac	5	4.23
	Nimesulide	3	2.54
	Etoricoxib	3	2.54
Antiepileptics (18, 15.25%)	Carbamazepine	8	6.77
	Phenytoin	6	5.08
	Oxcarbamazepine	4	3.38
Miscellaneous (5, 4.23%)	Methotrexate	3	2.54
	Sulfasalazine	1	0.84
	Erythropoeitin	1	0.84

Among antimicrobials (n=66), the most common incriminating drug class was antibiotics in 46 (55.93%) patients, with maximum number of cutaneous ADRs, from fluoroquinolone group 25(21.18%)(Table 4). The antibiotic most frequently implicated to cause cutaneous ADRs was amoxicillin plus amoxicillin and clavulanic acid in 17(14.40%) patients followed by ofloxacin in 16(13.55%) patients (Table 4). Among NSAIDs(n=29), the majority of cutaneous ADRs were caused by propionic acid derivatives, ibuprofen in 11(9.32%) patients; followed by a para-aminophenol derivate, paracetamol in 7(5.93%), acetic acid derivate, diclofenac in 5(4.23%) patients followed by nimesulide and etoricoxib 3(2.54%) in each group.

Table 5: Categorization of the CADR according to the severity scale

Severity	Number of patients	Percentage %
Mild	66	55.93
Moderate	34	28.81
Severe	18	15.25

Table 6: Categorization of the CADR as per preventability scale

PREVENTABILITY	NUMBER OF PATIENTS	PERCENTAGE %
DEFINITELY PREVENTABLE	36	30.5
PROBABLY PREVENTABLE	8	6.8
NOT PREVENTABLE	74	62.7

The severity of the ADRs was determined by the Modified Hartwig and Siegel's scale. Based on the severity of the reaction, most of the cases 66(55.93%) were mild followed by moderate 34(28.81%) and severe 18(15.25%) (Table 5). The preventability of the ADR was assessed by Schumock and Thornton's preventability scale. Among the 118 ADRs 36(30.5%) were definitely preventable, 8(6.8%) were probably preventable and 74(62.7%) were not preventable (Table 6).

Table 7: Causality assessment of CADR

Causality category	Frequency(%) [WHO-UMC Criteria]	Frequency(%) [NARANJO's Scale]
Certain	11 (9.32)	5 (4.23)
Probable	82 (69.49)	70 (59.32)
Possible	25 (21.18)	43 (36.44)

Causality assessment was done with the help of both WHO-UMC and Naranjo's scale. Most of the study patients were in probable category of the Naranjo's scale, i.e.,70(59.32%) followed by possible in 42(36.44%) and certain in 5(4.23%) of the patients. Results of causality assessment as done by both algorithms in different clinical types of CADR are shown in Table 7.

Among the investigations, a total of 27% of the study patients had hemoglobin of <10 gm/dl and altered liver function tests in 3%, and altered renal function tests in 2.2% . Leukocytosis was seen in 11% of the patients and eosinophilia was noted in 16% of the study subjects suffering from cutaneous adverse drug reaction.

DISCUSSION

In our present study, a total of 118 patients were studied fulfilling the inclusion criteria and different morphological patterns of CADR were observed.

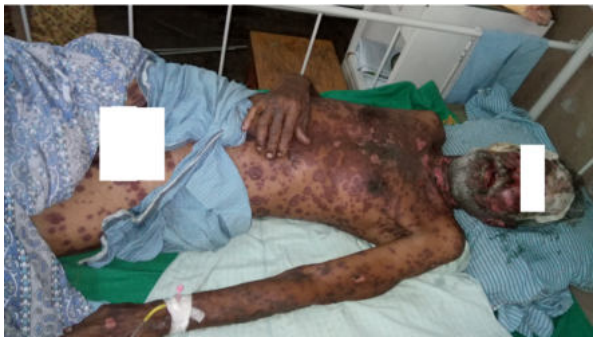
Maximum number of cases, i.e., 30 (25.4%) were in the age group of 21-30 years and minimum number 6(5.1%) in the age group >61years which was in accordance with study by Sharma et al[6] with 30.6% patients in age group 21-30 years and 6.6% in the age group>60 years. However, Mahatme et al[5] showed highest prevalence(40%) in the age group of 51-60 years. The oldest patient in our study was 69 years of age and the youngest was of 3 years. So CADR was mostly reported in case of young and active members of the society.The interval between drug intake and CADR ranged from a few minutes to 20 days while in majority(58.47%) the reactions appeared within one week of drug exposure. Our observations with regard to latency of drug reaction are concurring with similar observations by previous investigators like Sharma et al[6] and Mahatma et al.[5] Total duration of drug reaction was <1 week in majority (73%) of the cases which was comparable to studies by Mahatma et al.[5]The females in our study outnumbered the males. Among the study subjects, 53(44.9%) were male and 65(55.08%) were female. The male to female ratio was 0.8:1 which was in conformity with another study by Sharma et al[6] and Janardan et al.[7]However female preponderance was seen in studies by Mahatme et al[5] and Amrinder et al.[12]

Figure 1: Showing a mild CADR (metronidazole induced FDE)

FDE was the most frequently observed morphological pattern in 47(39.8%) patients (Figure 1), followed by urticaria 26(22%) and maculo-papular rash 18(15.3%), which was comparable to other studies by Sharma et al[6], Brar et al[13], Nivethitha et al[14] and Amrinder et al.[12] However maculo papular eruptions were most frequently observed morphological pattern by Janardan et al [7] and Jagruti et al.[15]The most common drug groups implicated in cutaneous ADRs included antimicrobials in 66(55.9%) patients followed by NSAIDs in 29(24.6%) patients.Nandha *et al*.[16] and Naldi *et al*.[17] also found antimicrobials as the most common offending drug class followed by NSAIDS. However, Brar *et al* showed NSAIDs as the most common offending drug in his study.[13]

Among antimicrobials(n=66), the most common incriminating drug class was of antibiotics in 51 (43.2%) patients, with maximum number of cutaneous ADRs, from fluoroquinolone group 23(19.49%). The antibiotic most frequently implicated to cause cutaneous ADRs was amoxicillin plus amoxicillin and clavulanic acid in 17(14.40%) patients followed by ofloxacin in 16(13.55%) patients.Our findings here are in agreement with an earlier study from Gujarat.[18] However, Pudukadan *et al* and Sharma *et al* found sulfonamides to be the most common drug.[19,20] Among NSAIDs(n=29), the majority of cutaneous ADRs were caused by propionic acid derivate, ibuprofen in 11(%) patients; followed by a para-aminophenol derivate, paracetamol in 7(%), acetic acid derivate, diclofenac in 5(%) patients followed by nimesulide and etoricoxib 3(%) in each group. Among the NSAIDs, paracetamol was the most common drug in an earlier study by Noel *et al*[21].

Figure 2: Showing a severe CADR (phenytoin induced SJS/TEN)



In our study, the implicated drug was found to be the probable cause in 59.3% patients whereas in 36.4% patients it was a possible cause. However similar patterns of causality assessment was seen in studies by Raja *et al*[21] and Nivethitha *et al.*[14] The severity of the ADRs was determined by the Modified Hartwig and Siegel scale. Based on the severity of the reaction, in our study most of the cases 66(55.9%) were mild followed by moderate 34(28.8%) and severe 18(15.3%) similar to studies by Raja et al [22] and Jagruti et al.[15] Severe cases of CADR were mostly SJS/TEN, DRESS/DHS and EM (Figure 2). Suspected medications were antieplileptics (phenytoin, carbamazepine, oxcarbamazepine), chloramphenicol, erythropoietin. However, no mortality was documented among the study subjects and all of the CADR subjects had been recovered fully. The severe cases required a prolonged hospital stay. A few (three in numbers) cases of SJS received outpatient based treatment because of milder and nonprogressive nature of the disease because of early dechallenge of the suspected medications by the patients. Majority (62.7%) of the CADR were non preventable whereas 30.5% definitely preventable which was corroborating with previously published study by Modi *et al*. [22]

Limitation

Though every attempt was undertaken to document each and every case reported to the Dermatology OPD but all cases could not be recorded due to manpower and logistic issues. Naturally, the overall burden of CADR was more than it was reported. This was a limitation of the study.As the study was dependent in spontaneous reporting of the cases, true incidence of CADR could not be ascertained in this study. Underreporting, insufficient information about recently introduced concomitant drugs and single centre study had been other limitations of the present study.

CONCLUSION

The present study revealed that CADR was not so uncommon in day-to-day outpatient setting of a tertiary care hospital in rural West Bengal. As the setting was in rural area, the real disease burden was much more than documented as many of the milder varieties might had remained unreported and unnoticed. Gender difference of CADR was not much documented in the present study whereas more young and active persons were brought to the healthcare facility. FDE and urticarial rash were mostly reported and antimicrobials were suspected as most culprit agents whereas antiepileptics were responsible for most of the severe reactions. As majority of CADR appeared within first week of drug exposure, both physicians and general public should be more vigilant and aware respectively to identify the CADR at the earliest opportunity to prevent further development of a catastrophic event. Proper drug allergy history is a must for every patient and that should be documented clearly and should be communicated in future physician–patient interactions. Public awareness campaign and continued medical education programme should be conducted regularly in different sectors of the society to limit the polypharmacy, unnecessary drug exposure and consequent development of CADR.

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