Journal of Pakistan Association of Dermatologists. 2022;**32(1)**:22-26.

Original Article

Study of cutaneous adverse reactions to drugs

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Abstract

Background Due to the casual and wide use of the drugs, the incidence of harmful effects have increased dramatically. These effects may present as toxic effect, side effect or adverse effects. The study is conducted to assess the frequency, pattern of CADRs and culprit drugs.

Methods This study was carried out for one year in Rohilkhand Medical College and Hospital, Bareilly, U.P. It included 114 patients showing clinical manifestations of CADR.

Results FDE was the most common CADR, in 46 (40.35%) patients followed by 22 (19.30%) patients with maculopapular rash. Out of114 patients enrolled, 19 (16.67%) were found to have SCADR. Most common severe cutaneous adverse reactions was erythroderma (31.58%), followed by SJS (26.32%). Most common culprit class of drugs were antibiotic (30.70%) followed by nonsteroidal anti-inflammatory drugs (22.81%), antifungal (12.28%). As per WHO-UMC causality assessment, in the study, certain, probable and possible categories were 7.89%, 38.60% and 31.58% respectively.

Conclusion It was found that fixed drug eruption was the most common type of morphological pattern of CADRs and antibiotics was the most common culprit class of drugs.

Key words
Cutaneous adverse drug reactions, SJS, TEN, FDE, Antibiotics.

Introduction

Drugs have played an important role in the development of medical science. The WHO has defined a drug as "a substance or a product that is used or intended to be used to modify or explore physiological systems or pathological states of the recipient".[1] These drug being therapeutically effective in certain conditions, may even have potential to cause harmful effects. Due to the casual and wide use of these drugs, the incidence of harmful effects have increased dramatically. These effects may present as toxic effect, side effect or adverse effects. Adverse drug reactions (ADRs) are described as "A response to a medicine in humans or animals which is noxious and unintended and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine".[1] Cutaneous adverse drug reactions (CADR) are one of the common cause of hospitalization. It's prevalence is approximately 2% to 3 % in hospitalized patients.[2] It is also a common cause of hospitalization in children. In outpatient studies of CADRs, 2.5% of children treated with drug, and up to 12% of children treated with an antibiotic may encounter CADR.[3] ADRs are more likely to occur in females than males.[4] The two factors on which latent period, that is the time interval between drug intake and onset of symptoms, depends upon are the type of reaction pattern and the culprit drug. This may vary from

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< 1 hour to 172 days.[5] Different drugs cause different patterns and the frequency of each pattern varies. Common clinical patterns of drug reaction are exanthematous, fixed drug eruption (FDE), urticaria, angioedema, acneiform, etc. Fortunately, most of the reactions are not severe and do not cause significant complications and abnormalities. But few reactions such as Stevens- Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug induced hypersensitivity syndrome, erythroderma (ERY), drug reaction with eosinophilia and systemic symptoms (DRESS) and vasculitis may have serious consequences, complications and sequelae.

Many studies have been done to know the different clinical patterns to different drugs in different parts of the world and to establish the causality of the reaction. This type of study has not been done recently in Rohilkhand region of western U.P. and hence this study was done to find out the prevalence of cutaneous adverse reactions to drugs in this population.

Methods

It is a hospital based observational cross sectional study. The study was carried out for a period of one Year (November 2018 to October 2019) in Outpatient and Inpatient Department of Dermatology, Venereology and Leprosy, Rohilkhand Medical College and Hospital, a tertiary care hospital in Rohilkhand region, Bareilly, U.P.

114 patients were studied according to the sample size formula for finite population for cross sectional study i.e. $N=4pq/l^2$. Patients showing clinical manifestations of CADR due to systemically administered drugs, those who were willing for the study, and mentally stable, oriented and coherent patients were included in the study whereas those patients who did not give consent or was mentally unstable, disoriented or was a drug abuser were excluded.

An informed consent was obtained from patient/ guardian. Detailed history regarding date of administration of drug, date of onset of lesions, formulations, dosage was noted. Tabulation of multiple drugs if taken (where more than one drug was suspected to be the cause), nature of the reaction (acute/ delayed) and severity, previous history of drugs, previous sensitizing exposure if any, and any associated medical/ surgical illness was also recorded. Clinical examination was done, including general, systemic and local examinations. Laboratory investigations where ever needed was done. Determining a culprit drug is often difficult when the patient is taking multiple drugs. In such patients, most probable culprit drug was considered according to the previous studies and data available. Based on who-umc.org guidelines, the causality assessment was done and the cases were categorised into certain, probable, possible, unlikely, conditional or unclassifiable. Deliberate re-challenge was avoided due to ethical reasons but accidental re-challenge whenever occurred was noted. All the patients were educated regarding avoiding self-medication.

Results

114 patients were enrolled, out of which male and female ratio was almost equal (male 60, female 54). Maximum number of people were in the age group of 21- 30 years. Most of the cases were students (25.44%) **(Table 1)**.

Most common pattern among different morphological types of adverse drug reactions found was FDE, in 46 (40.35%) patients. This was followed by 22 cases of (19.30%) maculopapular rash (MP) and 20 cases of (17.54%) urticaria (U) which may be present

Table 1 Demographic data**.**

Parameters	*Number*	*Percentage (%)*
Age group		
≤ 20	31	27.19
21-30	38	33.33
31-40	16	14.04
41-50	15	13.16
51-60	6	5.26
>60	8	7.02
Gender		
Male	60	52.63
Female	54	47.37
Occupation		
Business	9	7.89
Driver	1	0.88
Farmer	7	6.14
House wife	24	21.05
Job	26	22.81
Nothing	4	3.51
Retired	6	5.26
Shopkeeper	5	4.39
Student	29	25.44
Worker	3	2.63

Table 2 Different clinical patterns of drug reaction**.**

Clinical pattern	*Number*	*Percentage (%)*
AGEP	2	1.75
DRESS	3	2.63
EMF	4	3.51
ERY	6	5.26
FDE	46	40.35
MP	22	19.30
SJS	5	4.39
TEN	3	2.63
U(+/- AO)	20	17.54
UV	3	2.63
Total	114	100.00

along with angioedema (U+/-AO). Less commonly seen morphological patterns were erythroderma, in 6 (5.26%) patients, SJS in 5 (4.39%) patients, erythema multiforme (EMF) in 4 (3.51%) patients whereas TEN, urticarial vasculitis (UV) and DRESS each was found in 3 (2.63%) patients. Least common pattern found was acute generalized exanthematous pustules (AGEP), in 2 (1.75%) patients only **(Table 2)**.

Among 114 patients who got enrolled, 19 patients (16.67%) were found to have SCADR **(Table 3)**. Most common severe cutaneous adverse drug reaction found was erythroderma which was seen in 6 cases (31.58%), followed by 5 cases of SJS (26.32%), 3 cases of TEN (15.79%), 3 cases of DRESS (15.79%) and 2 cases of AGEP (10.53%).

Table 3 Frequency of severe cutaneous adverse drug reactions**.**

Clinical pattern	*Frequency*	*Percentage (%)*
AGEP	2	10.53
DRESS	3	15.79
ERY	6	31.58
SJS	5	26.32
TEN	3	15.79
Total	19	100.0

Table 4 Frequency of each class of drug causing reaction**.**

Class of drug	*Number*	*Percentage (%)*
NSAIDs	26	22.81%
Antibiotic	35	30.70%
Antiepileptic	9	7.89%
Antifungal	14	12.28%
Anthelmintic	1	0.88%
Antiamoebic	1	0.88%
Antispasmodic	1	0.88%
H2-blocker	1	0.88%

Most common culprit class of drug found to cause these adverse reactions was antibiotics, in 35 patients (30.70%) followed by NSAIDs (26 patients; 22.81%), antifungals (14 patients; 12.28%) and epileptics (9 patients; 7.89%). Many drugs remained unknown (in 25 patients; 21.93%). Less commonly found group of drugs were antiamoebic (0.88%) antispasmodic (0.88%), anthelmintic (0.88%), H2-blocker (0.88%) and PDE inhibitors (0.88%) **(Table 4)**.

According to the causality assessment as per WHO-UMC assessment criteria, out of 114 patients, maximum number of cases 44 (38.60%) were found in probable group which was followed by 36 (31.58%) cases in possible and 9 cases (7.89%) in certain category. In 25 cases (21.93%) the exact nature of drug was not known hence kept in unclassified category. **(Figure 1)**.

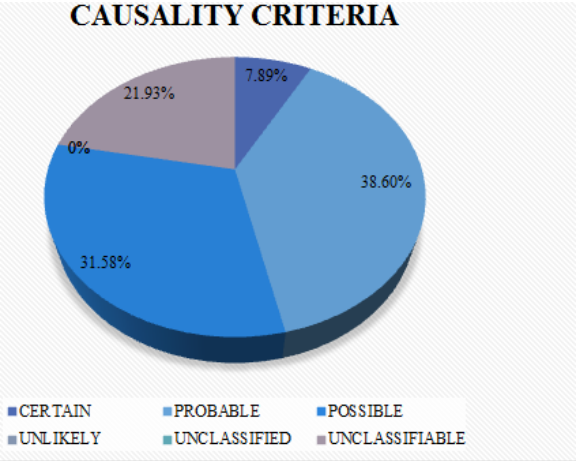

Figure 1

Discussion

Common morphological patterns: In this study, it was found that FDE was the most common CADR, in 46 (40.35%) patients followed by 22 (19.30%) patients with maculopapular rash and 20 patients (17.54%) with urticaria which may be present along with angioedema. This was similar to the study conducted by Agrawal A et al who found out that in the total study population, most common clinical patterns were fixed drug reaction, in 28.75%, followed by maculopapular drug rash in 26.3%, and urticarial rash in 20.6%. Few less commonly noticed CADRs were a lichenoid eruption, acneiform eruption, and baboon syndrome, generalized pruritus, pityriasis rosea, and vasculitis.[6] It was slightly different from the study conducted by Acharya T et al who found that acneiform eruption (25%) followed by fixed drug eruption (22.92%) were the most common clinical patterns.[7]

Severe cutaneous patterns: In this study, 114 patients were enrolled, out of which 19 (16.67%) were found to have SCADR. Most common severe cutaneous adverse reactions was erythroderma (6 cases, 31.58%), followed by 5 cases of SJS (26.32%), 3 cases of TEN (15.79%), 3 cases of DRESS (15.79%) and 2 cases of AGEP (10.53%). This was similar to the study conducted by Jha N et al. where they found severe cutaneous adverse drug reactions (SCADRs) to have occurred in 12 patients, out of which Stevens–Johnson syndrome - Toxic epidermal necrolysis was the most common.[8] It was contradictory to study conducted by Grando LR et al in 2014 on SCADRs who found that the most common form was DRESS (45.6%) followed by 16 cases of TEN (28%), 13 cases of SJS (22.8%) and two cases of AGEP (3.5%).[9]

Common causative agents: In this study, most common culprit class of drugs were antibiotic (30.70%) followed by nonsteroidal anti-inflammatory drugs (22.81%), antifungal (12.28%) and anti-epileptics (7.89%). It was similar to the study conducted in 2018 by Agrawal A et who concluded that the most common culprit drugs were antimicrobials (37.5%) followed by nonsteroidal anti-inflammatory drugs 25%, anti-epileptics 12.5%, and antifungal 6.25%.[6] and to the study conducted by Sharma R et al in 2015 in Jammu who found that the most common class of drug responsible for reaction were antimicrobials (40%) followed by nonsteroidal anti-inflammatory drugs (in 35.3%).[10] It was contradictory to the study done in 2014 by Grando LR et al where they found anticonvulsants (40.4%) to be the commonest of all.[9]

Individual causative suspected drug: In this study, it was found that amongst antibiotics, amoxycillin, cephalosporins and ofloxacin were the most common culprit drugs and amongst NSAIDS, nimesulide was the most common drug causing reactions. Amongst antiepileptics, phenytoin and amongst antifungals, itraconazole and griseofulvin were the most common drugs involved. It was similar to the study done by Nandha et al in 2011 who found that co-trimoxazole, amoxicillin, fluoroquinolones, ibuprofen, nimesulide and phenytoin were the common drugs to cause reaction.[11] It was also

seen by Thakkar S et al that antimicrobial commonly causing drug reaction were fluoroquinolones and penicillins and nonsteroidal anti-inflammatory drug causing drug reactions were mainly diclofenac and ibuprofen in outdoor patients while diclofenac and indomethacin in indoor patients.[12]

Causality assessment: As per WHO-UMC causality assessment, in the study, certain, probable and possible categories were 7.89%, 38.60% and 31.58% respectively which was comparable to the studies conducted by SP Shah et al in 2011 where the cases in each group were 2%, 23% and 46% respectively and Sejal Thakkar et al where it was 2.92%, 35.08% and 38.01% respectively. In this study the number of patients in the unclassifiable group were 25 (21.93%) which was similar to the studies done by SP Shah et al (29%) and Sejal Thakkar et al (24.56%).[12,13]

Conclusion

Knowing about the common patterns and culprit drugs is important for the timely diagnosis and treatment as well as for the avoidance in future.

The major limitations of the study were inability to measure drug levels in blood and perform re-challenge which caused hinderance in determining the exact causal association in multiple drug users. Thus the preventability of further episodes could not be assured. In future, similar studies can be done using other causality assessment scores like Naranjo's algorithm as they are more clinically acceptable, simplified and their results will have less subjective variations though they are more time consuming.

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