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Original Research Article

Clinical profile and causality of cutaneous adverse drug reactions among patients attending tertiary care teaching hospital in South India

Archana Mavoori[1]*, Sudha Bala[2], Sneha Pamar[1], Karunasree Podila[3], Deepthi Sriram[1]

[1]Department of Dermatology, [2]Department of Community Medicine, [3]Department of Pharmacology, ESIC Medical College, Hyderabad, Telangana, India

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***Correspondence:**
Dr. Archana Mavoori,
E-mail: archana.mavoori@gmail.com

ABSTRACT

Background: Any undesirable change in the structure or function of the skin and its appendages related to drug eruption regardless of the aetiology is called the cutaneous adverse drug reaction (CADR). Manifestations are varied with diverse morphological pattern ranging from trivial urticarial to severe form of vasculitis which are fatal. Identifying the culprit drug in this new era with advanced development of multi drugs is a challenging task and can help in prevention of further complications and provide safer drugs. Objective of the study was to assess the clinical profile and causality of CADR among patients in a tertiary care hospital of Hyderabad.
Methods: An observational hospital-based study was undertaken over a 6 months period among patients attending dermatology OPD of medical college and hospital located at Hyderabad. Patients presenting with suspected drug-related cutaneous lesions were included where the drug responsible was ascertained. Drug history was recorded in a format specified in Indian National Pharmacovigilance Programme and causality assessment carried out as per world health organization-uppsala monitoring centre criteria.
Results: The study population consisted of females (52.4%) and males (47.6%). Majority of them were in the age group of 51-60 years. Most common pattern of CADR noted were urticaria (19.05%) followed by erythema multiforme (17.46%) and morbilliform rash (17.46%). The common drugs categorised for these reactions comprised of antibiotics (39%), nonsteroidal anti-inflammatory drugs (26%) followed by anti tubercular treatment (18%).
Conclusions: CADR contribute to significant morbidity among industrial workers and role of pharmacovigilance should be further emphasized to reduce such reactions.

Keywords: Cutaneous adverse drug reaction, Causality assessment, Common drugs, Pharmacovigilance, Morphological patterns

INTRODUCTION

Improved science and technology have brought improved treatment outcomes, extended treatment courses, longer survival, thereby increasing the frequency and duration of drugs. Therefore, the prevalence of drug sensitization is rising with subsequent increase of adverse drug reaction (ADR). Of all other organs affected by ADR, the skin is most frequently involved leading to cutaneous adverse drug reaction (CADR). Thereby posing a medical emergency.

CADR was observed in 0.1-1% of patients during pre-marketing drug trials, and several post-marketing

analyses reveal that their incidence can be as high as 1-8 % for certain types of drugs (nonsteroidal anti-inflammatory drugs (NSAIDS), antibiotics, anti-epileptics).[1]

The incidence of these reactions amongst hospitalized patients ranges from 1 to 3 %. Most cutaneous adverse drug eruptions are benign in nature, mostly occurring as maculo papular eruptions or urticarial affecting quality of life; but few are fatal causing death.[2] These include various forms such as angioedema, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Careful history taking of the lag period after drug intake and presenting symptoms, followed by detailed examination of the skin lesions, mucosa and various systems help in early diagnosis of these reactions and treatment by withdrawal of causative drug.

Thus, safety monitoring of medicines has emerged as an integral part of clinical practice in India and the ministry of health and family welfare (MOHFW), government of India, in the year 2010, launched the national pharmacovigilance programme of India to inspire confidence and trust among patients and healthcare professionals with respect to medicines safety.[3] Under this multiple adverse drug reaction monitoring centres were established with main functions of collection of adverse events as per the standard protocol, following up to the completeness of the adverse drug reaction reports and uploading of reports. This consists of four sections i.e., details of patients, suspected adverse reaction, suspected medications and reporter's information. Causality assessment has become the common routine procedure in this program. world health organization-uppsala monitoring centre (WHO-UMC) has developed structured and harmonised assessment of causality.[4]

These adverse reactions are amenable for secondary prevention strategies. Therefore, an attempt has been made to take up this hospital based descriptive study among patients attending tertiary care hospital of Hyderabad with an objective to assess the clinical profile and causality of cutaneous adverse drug reactions.

METHODS

A hospital based descriptive study was undertaken among patients who were attending dermatology outpatient along with referrals from other departments of ESIC Medical College and Hospital located at Sanathnagar, Hyderabad. This was undertaken over a period of six months from April 2018 to September 2018.

All the patients presenting with CADR as per definition who had documented evidence of having taken the suspected drug, patients of both the sexes and of all age groups with visible skin lesions were included in this study. Cases due to reactions to vaccines, cutaneous adverse drug reactions due to over dosages of the drugs, those who could not recall the names of the drugs, those lesions related to acute conditions such as fever, communicable infections or collagen vascular diseases and patients on alternative systems of medicine such as homeopathy, herbal, ayurveda, etc., were excluded as their formulae was unknown.

The data was collected from each patient's medical records and interview schedule where questionnaire was used to extract information on age, gender, date of admission, drug history, the type of skin lesions for which patients were admitted and the final diagnosis of CADR, reasons for drug administration, time interval between the use of drug and the onset of CADR was recorded. Prior institutional ethical committee clearance was obtained from our institute and written informed consent was also taken from the participants after explaining the study.

Drug history was recorded in a format that is mentioned in Indian national pharmacovigilance programme and causality assessment carried out as per WHO-UMC criteria.

The WHO-UMC system that has been developed in consultation with the national centres participating in the programme for international drug monitoring and is meant as a practical tool for the assessment of case reports. It is a combined assessment which includes the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. The case was considered to be certain/definite when the event is with plausible time relationship to drug intake, those which cannot be explained by disease or other medications, the response to drug withdrawal is plausible (pharmacologically, pathologically), event is definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) and rechallenge, if necessary, is satisfactory. Probable or likely: event with reasonable time relationship to drug intake, those which are unlikely to be attributed to other drugs or disease, the response to drug withdrawal is clinically reasonable, and where re challenge is not required. Possible was any event with reasonable time relationship to intake of drug, those events which could also be explained by disease or other drugs and those where information on drug withdrawal may be lacking or unclear.

Results were analysed with descriptive statistical methods using the statistical package for the social sciences (SPSS 20.0) software.

RESULTS

Out of total 63 cases over a period of six months 33 (52.4%) were females and 30 (47.6%) were males. Mean age was found to be 36.52±15.4 years. The most common age group to be affected is 51-60 years and is detailed in Table 1.

Table 1: Age wise distribution of study subjects.

Age group (in years)	Number	Percentage (%)
0-10	5	18.5
11-20	2	7.4
21-30	2	7.4
31-40	4	14.6
41-50	5	18.5
51-60	8	29.6
61-70	0	0
71-80	1	4
81-90	0	0
Total	27	100

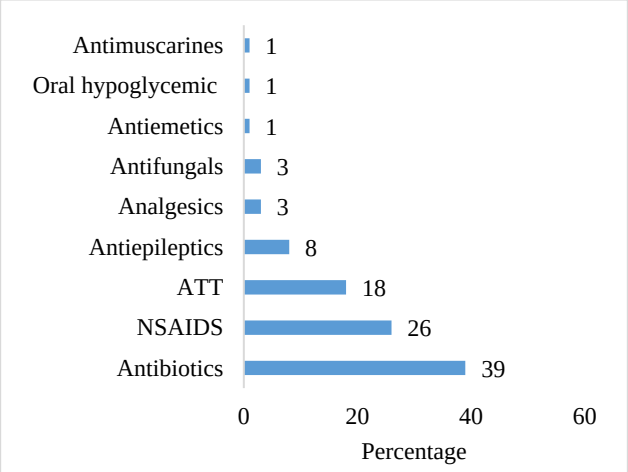

Figure 1: Common group of drugs causing CADR.

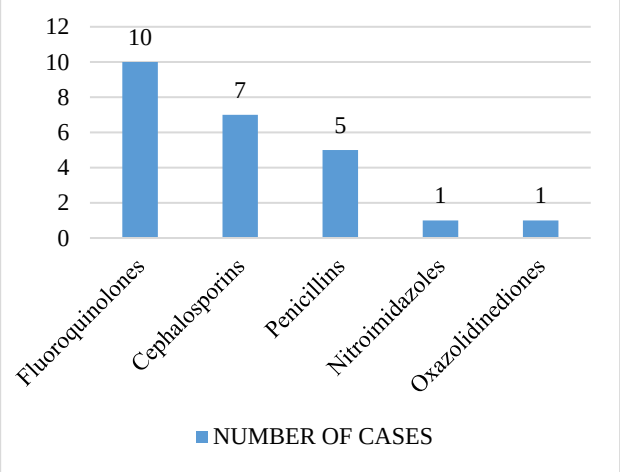

Figure 2: Most common class of antibiotics causing CADR.

The most common group of drugs causing CADRs are the antibiotics 24 (39%) followed by NSAIDs 16 (26%), anti tubercular treatment (ATT) 11 (18%), anti-epileptics 5 (8%), analgesics 2 (3%), anti fungals 2 (3%) and other drugs accounting for rest of the cases (Figure 1). Among antibiotics, most cases belonged to fluoroquinolone group (10 cases) followed by cephalosporin group (7 cases), penicillin group (5 cases), nitroimidazoles (1 case) and oxazolidinediones (1 case) (Figure 2).

Reasons for which they have taken the medications were mainly diarrhoeal diseases, fever, myalgia, seizures and diabetes. Mode of administration was mainly orally 61 (96.83%) and rest 2 (3.17%) through intravenous administration.

Table 2: Common type of CADR noted.

Type of reaction	Count of type of reaction	Percentage (%)
Urticaria	12	19.05
EMF	11	17.46
Morbilliform rash	11	17.46
SJS	10	15.88
Angioedema	7	11.11
Bullous FDE	5	7.94
Drug induced vasculitis	2	3.17
TEN	2	3.1
AGEP	2	3.17
Erythroderma	1	1.59

The most common reaction pattern is urticaria 12 (19.05%) followed by erythema multiforme (EMF) 11 (17.46%), morbilliform rash 11 (17.46%) SJS 10 (15.88%), angioedema 7 (11.11%), bullous fixed drug eruption (FDE) 5 (7.94%), drug induced vasculitis 2 (3.17%), acute generalised exanthematous pustulosis (AGEP) 2 (3.17%), toxic epidermal necrolysis (TEN) 2 (3.17%), erythroderma 1 (1.59%) (Table 2).

According to WHO-UMC causality grading 32 (50.79%) CADRs were classified as definite, 18 (28.57%) CADRs as possible and 13 (20.64%) reactions as a probable cause.

DISCUSSION

Cutaneous adverse drug reactions are distressing to both the patient and treating physician. Mortality can occur in severe reactions such as drug induced angioedema, TEN, erythroderma. The quality of life may be significantly diminished due to increased morbidity hospitalization and prolongation of hospital stay.

Drug reactions are a common reason for litigation. Every physician should warn a patient about potential adverse effects, prescribing a drug to a patient who is previously sensitized and prescribing a related medication with cross-reactivity are common medico legal pitfalls and therefore should not be taken lightly. In a cases of multiple drug therapy, reaction time is helpful in suggesting the offending medication, which can prevent withdrawal of an innocent medication.

Socio demographic variables

Our study found 52.4% females and 47.6% males developing ACDR. Mean age was found to be 36.52±15.4 years. The most common age group to be affected is 51-60 years.

Fatemeh Mokhtari in their study in a referral university at Iran found 60.8% females in their study and the mean age of occurrence of the CADR was at the age of 29.48±21.18 years which is lesser than our study.[5] Similar to our study manivannan in their study in south India at madhurai also found the occurrence of CADR more among females 66% and the mean age of 36.20 years.[6]

Contrast to our study Mahatme et al in their study conducted at Malaysia found males and females were equally affected and the mean age for the study population was 47.0±17.5 years.[7] These differences could be due to different settings and varying ethnicity.

Common group of drugs

The most common group of drugs causing CADRs are the antibiotics (39%), nonsteroidal anti-inflammatory drugs (NSAIDs) 26% followed by ATT 18%, anti-epileptics 8%, analgesics and antifungals 3% each and antiemetics, antimuscarinics and oral hypoglycaemics contributing to 1% each. And of these drugs 96.83% were administered orally for diarrhoeal diseases, fever and body pains majorly. Similar to our study Mahatme et al found Antimicrobial agents (AMAs) (48%) were responsible for majority of the detected CADRs, this is followed by nonsteroidal anti-inflammatory drugs (24%), anti-hypertensives (8%), and antiepileptics (4%) in their study found at secunderabad railway hospital.[7]

Pudukadan et al in their study from tertiary care hospital in south India reported that antimicrobials formed the major group (58.88%), followed by anti-epileptics and NSAIDs (15.55% each).[8] Sharma et al in their study at Jammu found the most common classes of drugs implicated as antimicrobials in (40%) patients followed by nonsteroidal anti-inflammatory drugs in (35.3%), steroids (22%), anticonvulsants (8%).[9]

Common reaction patterns

The most common reaction pattern is urticaria 19.05%, erythema multiforme, morbilliform rash accounting for 17.46% each, Stevens Johnson syndrome 15.88%, angioedema 11.11%, bullous fixed drug eruption 7.94%, drug induced vasculitis, AGEP, TEN 3.17% each, erythroderma 1.59%.

Pang et al in their study among south east Asians found exanthema (68.3%), urticarial (14.5%), FDE (5.3%), AGEP (4.0%), fixed drug eruption, DRESS (4.0%), SJS (4.0%), TEN (1.3%), SJS or TEN overlap (1.3%), generalised exfolative dermatitis (1.0%) and drug induced vasculitis (1.3%). The three most common presentations in this study were: drug exanthem, urticaria and FDE. Drug exanthema accounted for close to half of all CADR in the study while urticaria accounted for 14.5%. Scar accounted for 11 patients making up 15.0% of all CADR.[10]

Saha et al observed among population of Eastern India a variety of patterns such as morbilliform eruption (30.18%), fixed drug eruption (24.52%), and SJS-TEN and overlap of these two (24.50%) comprised bulk of the CADRs. Other types of CADRs seen were erythroderma (7.54%), urticaria (5.6%), phototoxic drug reaction (3.8%), pityriasis rosea-like rash (1.89%), and severe mucositis (1.80%). Of these, cases of SJS-TEN or overlap of SJS-TEN and exfoliative dermatitis were life threatening and represented the severe variants of CADR (32.04%).[11]

In our study as per WHO-UMC causality grading found 50.79% CADRs classified as definite, 28.57% CADRs as possible and 20.64% reactions as a probable cause.

Contrast to our study Jayanthi etal in their study found as per the WHO-UMC causality assessment found the majority of the CADRs had a probable causal relationship with the implicated drug. And also indicated 80.4% as probable and 19.6% as possible causes.[12] Study done by Chavda et al in Gujarat also found majority as probable causal 77%, definite (8%) and possible as 15% using WHO-UMC criteria.[13] These variations could be due to the reaction to the common drugs used in different areas having different distribution of diseases.

CONCLUSION

It is an utmost necessity for a dermatologist to have a comprehensive understanding of the clinical types of CADRs, knowledge of the medications which are frequently incriminated in such adverse reactions. This would help in minimizing the extent of iatrogenic morbidity and mortality.

Major bulk of CADR result from physician prescribed drugs rather than over-the-counter drugs. Hence, awareness on part of the dermatologist can help in timely detection of cutaneous reactions, thereby reducing damage from them.

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