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RESEARCH ARTICLE
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CUTANEOUS ADVERSE DRUG REACTIONS AMONG PATIENTS IN DEPARTMENT OF DERMATOLOGY IN A TERTIARY CARE HOSPITAL

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ABSTRAC

Background

Skin is one of the major organ for adverse reactions. Cutaneous adverse drug reactions (CADRs) are the most common type of adverse drug reaction and the clinical presentation varies (incidence is 2-5%). They are mistaken for signs of underlying disease, resulting in unnecessary investigations and delay in treatment. The treatment of ADRs increases the costs of patient care. [1-5] So awareness about them was found to be essential for early detection and prevention. This study aimed to find the proportion of CADRs, causality, severity, preventability and drugs producing it in a tertiary care hospital.

Methods

A cross-sectional study was conducted among 160 patients attended in the outpatient department, who had a history of drug intake within a period of 1 week, in the department of Dermatology in a tertiary care hospital Kerala India. Only 40 (25%) patients had cutaneous ADRs. All the relevant information was recorded in the CDSCO[3] suspected adverse drug reaction reporting form by the Dermatologist was collected and analysed. Causality was assessed using Naranjo Algorithm.[6] Severity was assessed by Modified Hartwig and Siegel Scale.[7] The preventability was assessed using Modified Schumock and Thornton scale.[8] Data were analysed using descriptive statistics.

Results

In the present study, out of 40 patients with cutaneous ADR, the highest incidence of cutaneous ADRs was in the age group of 41 -50 years (23%), and more frequently in male patients (52.5 %). Antimicrobials were the most commonly implicated drugs (55%) followed by Non-Steroidal Anti-inflammatory drugs (NSAIDs) (28%) and anti-epileptics (5%). The most commonly observed morphological pattern was maculopapular rash (22.5%) followed by fixed drug eruptions (12.5%) and 5% had Steven Johnson Syndrome. 32.5% cases had concomitant medicines. Causality assessment was certain, probable and possible for 0%, 25% and 75% of the reactions respectively.

One case was of level 5 severity, 37 cases of mild (level 2) severities and two cases of moderate (level 4) severity. 97.5 % cases were not preventable and 2.5% cases was probably preventable.

Conclusion

Antimicrobials were the culprit drugs for most of the cutaneous adverse reactions followed by NSAIDs**.** Identification and timely reporting of cutaneous adverse drug reactions reduces their future occurrences and encourages rational prescribing and reduces the cost of healthcare.

Keywords: CADRs (Cutaneous ADRs), Causality, Preventability, Severity-Assessment, Fixed Drug Eruption (FDE)

INTRODUCTION

Adverse drug reaction is any noxious change which is suspected to be due to drug, occurs at doses normally used in humans for prophylaxis, diagnosis, treatment of disease or for modification of physiological function (WHO definition).[1-5] Adverse drug reactions cause death in 0.1% of medical and 0.01 % of surgical patients and adversely affect the quality of life. They are mistaken for signs of underlying disease, resulting in unnecessary investigations and delay in treatment. Moreover treatment of ADRs increases the costs of patient care. Cutaneous drug eruptions are the most common type of adverse reactions to drug therapy, with an incidence rate of 2–6%**.**[4,9] Cutaneous Adverse Drug Reaction (CADR) is defined as any undesirable change in the structure or function of the skin, its appendages, or mucous membranes, and it encompasses all adverse events related to the drugs, regardless of the etiology.[5] The clinical presentation of drug related cutaneous reactions ranges from mild rash to severe rash besides causing life-threatening reactions. Cutaneous drug reaction is suspected in any patient who is currently taking any medicine or recently been exposed to any medicine including the prescribed and over-the-counter medicines, herbal or homoeopathic preparations, vaccines or contrast media. In some patients non-drug components of a medicine, i.e. the pharmaceutical excipients may also cause hypersensitivity reactions like cutaneous drug eruptions. Incidence of CADRs in developed countries ranges from 1 to 3% among in-patients.[10] In developing countries such as India, it is 2–5% among in-patients and 2.6% in the out-patient setting.[11-13] The healthcare system can promote the spontaneous reporting of dermatological ADR to Pharmacovigilance centre's for ensuring safe drug use and patient care.

Different studies show variation in the data based on presentation of cutaneous drug reaction, its distribution amongst both sexes, the offending drug and causality assessment. This study was done to find the proportion of cutaneous adverse drug reactions in patients attending the department of Dermatology and describe the cutaneous ADR profile of different groups of drugs, causality of drug induced skin reactions by using Naranjo's algorithm.[6] describe the severity and preventability of adverse drug reactions by using Modified Hartwig and Seigel scale [7] and Modified Schumock and Thornton scale.[8]

MATERIALS AND METHODS

This was a cross-sectional study conducted among 160 patients in the outpatient department of Dermatology, in a tertiary care hospital Kerala. Details of all the patients of either sex, had a history of drug intake within a period of 1week, were included in the study. The study was conducted over a period of 6 months.

Exclusion Criteria

Incomplete ADR forms

Study Procedure

After obtaining IRC and IEC approval for the study, CDSCO-ADR reporting form filled and reported by the Dermatologist was collected and analyzed. All the details regarding patient's basic data like age, gender, present illness, past medical history, co-morbidities, concomitant medications, lab data, details of the drugs suspected to be causing ADR and the details of cutaneous reactions etc.

were recorded in the *ADR reporting form by the Dermatologist*. Re-challenge was not attempted due to associated risks and ethical concerns. The collected data were analysed for demographic details, drug details, causality, preventability, and severity of adverse effects. Causality was assessed by using Naranjo's Algorithm,[6] preventability by Schumock and Thornton scale[8] and severity by modified Hartwig scale.[7]

Ethical policy and Institutional Review board statement

The study was conducted in the department of Dermatology government medical college Kollam after getting IRC clearance (No.004/2018 GMCKLM dated 28/05/2018) and IEC CLEARANCE (IEC No.006/2018/GMCKLM Dated 07/06/2018)

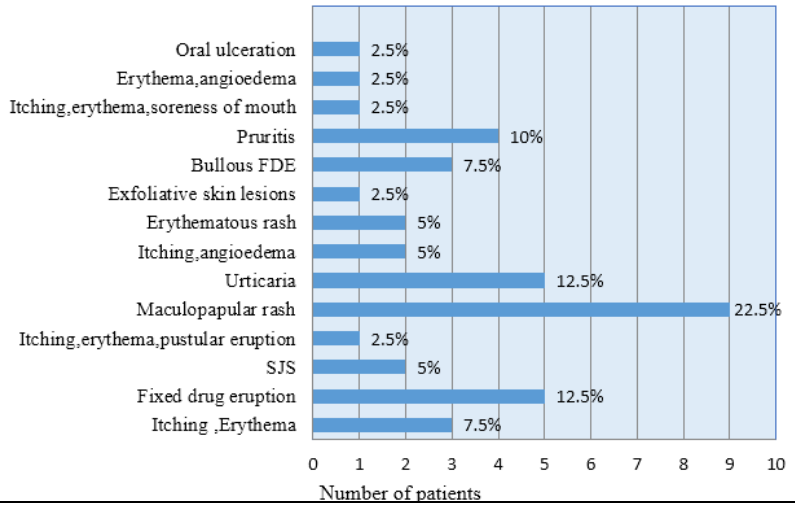
Statistical Analysis

The data were sorted, coded, and entered into Statistical Package for the Social Science (SPSS) and subsequently analysed. Variables like gender, type of CADR, causative drugs, causality, severity, preventability, and final outcome were expressed as frequency and percentage.

RESULTS

A total of 160 patients with a recent history of drug intake were enrolled in the present study. Only 40 (25%) patients had cutaneous ADRs. Majority of cases, i.e., 9 (23%) were in the age group of 41 -50 years followed by 8(20 %) in age group of 51 to 60 & 61 to 70 years and the lowest number of one case was in the age group 80years & above. In the present study, males (52.5%) were more frequently affected than females (47.5%). Out of 40 patients with cutaneous ADRs, only 3 (7.5%) patients had a positive history of previous cutaneous adverse drug reactions. Maculopapular rash was the most frequently observed morphological pattern in (22.5%) patients, followed by urticaria similar to the findings in the study.[4,5,10,13] and FDE in 5 (12.5%) patients, pruritus 4 (10%), SJS in two (5%) and were referred to higher centre.

Figure 1--Spectrum of CADRs



The common groups of drugs associated with CADRs include antimicrobials followed by NSAIDs, Antiepileptics, similar to the studies[4,5,10,13] anti-rheumatoid, anti-hypertensives and topical agents.

Drug Class	Drugs	n (%)
Antimicrobials	Amoxicillin clavulanic acid (6), Azithromycin (3), Ciprofloxacin(2),Fluconazole(2),Cloxacillin (2) , Levofloxacin(1) Ampicillin- cloxacillin(1), Doxycycline(1) Metronidazole(1) HRZE (1) Amoxicillin(1), Terbinafine (1)	22(55)
NSAIDs	Paracetamol(5),Diclofenac (4) Naproxen (1), Etoricoxib (1)	11(27.5)
Anticonvulsants	Phenytoin(1),Valproic acid(1)	2(5)
Antirheumatiod	HCQ+Sufasalazine(1)	1(2.5)
Antihypertensive	Enalapril(1)	1(2.5)
Immunomodulator	Lenalidomide(1)	1(2.5)
Topical agents	Azelaic acid+Tretinoin cream(1)glycerine magsulf(1)	2(5)
Table 1: Top drug classes causing CADRS with drugs –		

CADRs	Top Drugs	n (%)
Maculopapular rash	Azithromycin(2), Amoxicillin(2), Paracetamol(2), Levofloxacin(1)	11(22.5)
Urticaria	Amoxicillin clavulanic acid(2),Diclofenac (2)	5(12.5%)
Fixed drug eruptions	Fluconazole(2),Amoxicillin clavulanic acid (1), Doxycycline (1) , Diclofenac (1)	5(12.5%)
Pruritus	Ciprofloxacin(1),Azithromycin(1)	4(10)
SJS	Levofloxacin(1),Amoxicillin(1)	2(5)
Table 2: CADRs with drugs		

The maximum cutaneous ADRs, i.e., 32 (80%) occurred in the lag period of 2-7 days followed by 8 (20%) in less than 2 days. After the causality assessment of cutaneous ADRs as per Naranjo Algorithm, majority of cases, i.e., ten (25%) cases as probable and 30 (75%) were categorized as possible. As per Hartwig severity scale, One case was of level 5 severity, 37 cases of mild (level 2)severity and two cases of moderate (level 4) severity. The preventability was assessed using Modified Schumock and Thornton scale. 97.5 % cases were not preventable and 2.5% cases was probably preventable.

Causality	n (%)
Certain	0
Probable	10 (25)
Possible	30 (75)
Severity	
Mild	37 (92.5)
Moderate	2 (5)
Severe	1 (2.5)
Preventability	
Definitely preventable	0
Probably preventable	1 (2.5)
Not preventable	39 (97.5)
Table 3: Causality , severity and preventability	

Outcome	n (%)
Lost to follow up	2
Continuing	0
Recovering	0
Recovered	38
Table 4: Outcome	

DISCUSSION

This study included 40 patients with cutaneous ADRs, were the maximum number of patients from the age group of 41-50 years. The males in our study outnumbered the females. Most of the male patients had concomitant medicines than females. Only 3(7.5%) patients had a previous history of cutaneous ADRs to drugs. The most common cutaneous ADRs recorded were maculopapular rash followed by urticaria & fixed drug eruptions, followed by pruritus, bullous FDE, erythematous rash and Steven Johnson syndrome. The most common incriminating drug class was of antimicrobials (55%) and NSAIDs (28%).[4,5] The maximum numbers of cutaneous ADRs were induced by amoxicillin clavulanic acid (maculopapular rash, angioedema, urticaria, rash, FDE) similar to findings in studies.[9,12,14-16] Most of the cases were managed symptomatically by stopping the drugs. After Causality assessment, the implicated drug was found to be a probable cause in 25% of patients, possible in 75 % of patients. The assessment might vary with the type of scales used for the assessment of ADRs in different regions. Out of total 40 cases of cutaneous ADRs, maximum cases, i.e., 37 were of mild severities, 2 cases of moderate (level 4) and one case of severe (level 5) severities.

Limitation

This study was conducted in a single centre. Patients who developed ADRs in the hospital may not be truly reflective of the whole population. Most of the non-serious cutaneous ADRs were managed in the casualty itself. Causality assessment had some uncertainty in patients with multiple drugs, especially rechallenge was not attempted due to ethical reasons. Long-term follow-up and monitoring of the patients could not be done. There is also the problem of underreporting of mild and self-limiting cases.

CONCLUSION

CADR are common among ADRs with a reporting rate of 25%. Antibiotics contributed more to the ADRs followed by Non-steroidal anti-inflammatory drugs (NSAIDs). Most of the reactions were of mild to moderate severity and were managed symptomatically. Pharmacovigilance awareness programs should be conducted among various levels of health-care professionals to enhance the impact of understanding and timely reporting of ADRs. A careful history taking and rational prescription of drugs can prevent most of the reactions.

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