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An Observational Study of Clinical Pattern of Adverse Cutaneous Drug Reactions and Causative Agents in Tertiary Health Care Center.

KEYWORDS: Adverse cutaneous drug reactions, causative agents.

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ABSTRACT *Adverse cutaneous drug reactions (ACDRs) are caused by a wide variety of agents. The pattern of cutaneous ADR and the drugs responsible for them is changing every year.*

Aims: Our objective was to evaluate the clinical pattern of ACDRs and the causative drugs in the tertiary health care center.

Methods: fifty five patients with adverse cutaneous drug reactions were recruited for this study during 2013-2014.

Results: The Most of ACDRs belonged to the age group of 21-30 years (27.27%). The male to female ratio was1.75:1. The most common eruptions observed were maculopapular rash (41.81%) followed by fixed drug eruption (20%), Erythema multiforme and SJS/TEN (10.90%), and the most common causes were NSAIDs followed by antimicrobial agents.

Conclusion: The pattern of ACDRs And the drugs causing them is remarkably different in our population. Knowledge of these drug eruptions, the causative drugs and the prognostic indicators is essential for the clinician.

INTRODUCTION

The Cutaneous Drug Reactions (CDRs) are the most frequent adverse events in patients who receive drug therapy. The incidence of adverse cutaneous drug reactions (ACDR) in developed countries range from 1- 3% among in-patients[1,2] whereas in developing countries like India is 2- 5% among in-patients[3,4,5,6,7]. As innovation in medicine occurs and new drugs continue to be developed there is potential for the occurrence of an increasing number of cutaneous drug reactions. There is a wide spectrum of cutaneous ADR ranging from a transient maculopapular rash to fatal toxic epidermal necrolysis (TEN).[8]

The pattern of ACDRs and the drugs responsible for them is changing every year, however the true incidence of drug eruptions is difficult to determine largely because many mild and transitory reactions are not recorded. On the other hand skin changes due to other aetiology (e.g., viral exanthem misdiagnosed as morbilliform eruption and herpes labialis as bullous fixed drug reaction) are sometimes incorrectly attributed to drugs. This study was therefore designed to evaluate the clinical pattern of all cutaneous ADRs and to establish the causal link between the suspected drug and the reaction by using the WHO causality definitions.[9]

MATERIAL AND METHODS

The study was a prospective hospital based observational study. After getting approval from the institutional ethical committee, the study was jointly conducted in the Department of Pharmacology and Department of dermatology, NSCB medical college, Jabalpur over a period of one year (October 2013 to September 2014).

The patients attending dermatology OPD with suspected ACDRs and the in- patients referred from other department with suspected ACDRs were enrolled. The participants had given the informed written consent before they were enrolled in the study. The diagnosis of the ACDRs was based on detail drug history and a thorough clinical examination done by consultant dermatologist. The patient who consume medicines other than allopathic medications(like Ayurvedic/Homeopathic etc) and who are not able to recall the name of suspected medicine consumed(improper drug history) were excluded from the study. Detailed history of the patient including present illness and past or concurrent systemic illness were also taken. The criteria for the diagnosis of ACDRs were as follows: [3]

1. The time interval between the introduction of the drug and the onset of a reaction should be within a specific time (Maculopapular rash: <7 days, Urticaria: 7- 21 days, Steven Johnson Syndrome/Toxic Epidermal Necrosis (SJS/TEN), Erythema multiforme: 1- 3 weeks, Drug hypersensitivity syndrome: 2- 6 weeks, Photodermatitis: up to 1 year, Exfoliative dermatitis: 1- 6 weeks, Fixed drug eruption: 30 min- 16 h).

The reaction was not considered as drug induced if the drug was administered after the onset of reaction.

2. Improvement in the condition of the patient after dechallenge/withdrawal of the suspected drug.

3. Drug rechallenge producing similar reaction again.

The clinical pattern of ACDRs was assessed on local examination by consultant dermatologist on the basis of its site, nature, extent, colour & distribution of lesion, and pattern was recorded in form of maculopapular rash, urticaria, angioedema, fixed drug reaction, purpura, photosensitivity etc.

To establish the etiologic agents for ACDRs, attention was paid to the drug history, temporal correlation with the drug, duration of the rash, pattern of lesion, improvement of lesion on withdrawal of drug & recurrence of lesion on rechallenge if possible. Rechallenge was not undertaken in any of our cases because of the possible associated risks.

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If more than one drug was thought to be responsible, the most likely offending agent was noted and the impression was confirmed by subsidence of the reaction with time or on withdrawing the drug. Finally data was recorded in CDSCO form.[10]and was compiled and analysed.

Based on the WHO causality definitions,[11] ADRs were categorized as certain, probable, possible and unlikely.

RESULTS AND DISCUSSION

A total of 58 cases of adverse drug reactions were identified. Out of these 3 cases had to be excluded from the final because they failed to state the names of the offending drugs or the data was insufficient to make reliable analysis. The remaining 55 cases of ACDRs were analyzed further.

ACDRs were found relatively common in males than in females (ratio 1.75:1) Our study results are similar to the other Indian studies where male preponderance was observed.[12,13]

Majority of the patients with ACDRs belonged to the age group of 21-30 years followed by 41-50 and >50 yrs with male predominance. The ACDRs were more common in adult patients (80%) as compare to the children (20%).

Of the various types of ACDRs the most common pattern observed was maculopapular rash (41.81%) followed by fixed drug eruption (20%), Erythema multiforme and SJS/TEN (10.90%), Other types of ACDRs that were observed in our study included 3.63% each of Exfoliative dermatitis, urticaria, Vasculitis and photosensitivity and 1.81% of Serum sickness. A recent study conducted in southern India has reported that the most common observed reactions were fixed drug eruptions (31.1%) and maculopapular rashes (12.2%).[7]

Analysis of the data shows that NSAIDs were the most common drugs followed by antimicrobial agents. Most of the patients had taken the medication for pain, fever and infection. This may be the reason for NSAIDs followed by antimicrobial were the most common agents causing ACDRs in our study population. But many different studies carried out elsewhere in India[7,14,15] have reported antimicrobial agents as the major group of drugs causing ACDRs followed by NSAIDs. Some studies also have reported antiepileptics as the major culprit of ACDRs.[3]

Table-1 Clinical Pattern of ACDRs

Type of reaction	Present study (n=55) Frequency	Drugs involved
Maculopapular rash	23(41.81%)	NSAIDs (15cases) Antimicrobials (3cases) Antiepileptics (2 cases) INH,Chloroquine,Thaizide(1case each)
Fixed drug eruption	11(20%)	NSAIDs (5 cases) Antimicrobials (6 cases)
Erythema multiforme	06(10.90%)	NSAIDs (5 cases) Antimicrobial agents (1 cases)
Steven Johnson Syndrome/ Toxic Epidermal Necrosis	06(10.90%)	NSAIDs (6cases) Antimicrobial agents (3 cases)
Exfoliative dermatitis	02(3.63%)	INH and Phenytoin (each group)
Urticaria	02(3.63%)	Combiflam and Metrogyl
Vasculitis	02(3.63%)	Tramadol and Ibuprofen(each case)
Photosensitivity	02(3.63%)	NSAIDs and Isotretonoin(each group)
Serum sickness	01(1.81%)	Penicillin groups
Total	55	

Considering individual drugs, Ibuprofen & PCM followed by sulphonamide and penicillin were the most common causative agents observed in this study. While Sulfonamides followed by ibuprofen were the most common causative agents observed in other studies.[7,13,15]

NSAIDs (65.21%) were the most common drug group causing maculopapular rashes followed by antimicrobials (13.04%) and antiepileptics (10.90%) while Antimicrobials (54.54%) were most common drug causing fixed drug eruption followed by NSAIDs(45.45%) in our study. NSAIDs and Cotrimoxazole were the most common cause of FDE in earlier studies carried out else where in India.[13,15]

Among antimicrobials Doxycycline and Ciplox-TZ (combination of Ciprofloxacin and Tinidazole) and among NSAIDs, Combiflam (combination of PCM and Ibuprofen) were the frequently reported agents causing FDE. Apart from these, 6 cases of erythema multiforme and SJS/TEN were recorded which account for 10.09% each of total reactions. NSAIDs were the

Table-2 causality assessment of ACDRs using WHO-UMC criteria

Type of reaction	Present study (n=55) WHO-UMC criteria		Noel et al. (n=56) Naranjo's scale	Ghosh et al. (n=53) WHO-UMC criteria
Certain	04	7.27%	2%	5%
Probable	40	72.72%	80%	55%
Possible	11	20%	18%	40%
Total	55	100	100	100

most common causative agents followed by antimicrobials in our study. In our study only 2 cases (3.63%) of urticaria (due to combiflam and metrogyl) were found. Each 2 cases (3.63%) vasculitis (due to tramadol and ibuprofen), photosensitivity (due to NSAIDs and isotretonoin) and exfoliative dermatitis (due to INH & phenytoin) and one case of serum sickness (due to penicillin groups) were also reported in this study (Table-1).

In causality assessment rechallenge was not attempted due to ethical issues and hence maximum numbers of ACDRs were labelled as probable cases. Dechallenge was done in all the cases and it was positive in 44 cases, of which 40 cases (72.72%) were probable where as 11 cases (20%) were considered possible because dechallenge data was either negative or doubtful and the reaction could be attributed to existing clinical conditions. But 4 cases (7.27%) were classified under the category of certain, as rechallenge data was available in these patients who were administered the same drug unknowingly (Table-2). Most of the reaction were mild to moderate in nature and could be managed by supportive treatment and withdrawal of culprit drug. Only 12.72% reaction was of severe grade that required hospitalization.

To conclude, the pattern of ACDRs and the drugs causing them are slightly different in our population. Variation in type of reaction and drugs involved in this study and other different studies could be due to different ethnic group characteristics and different patterns of drug usage in different part of our country. A sound knowledge of these drug eruptions may help the clinician to better manage their cases.

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