A Clinico-Etiological Study of Cutaneous Adverse Drug Reactions at Tertiary Care Centre.

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Abstract:
Background: Adverse drug reactions are important cause of morbidity, hospitalization, increased health expenditure and even death. Adverse drugs are unavoidable consequences of drug therapy and can occur with any class of drugs. CADRs are the most frequent ADRs. Aim of this study is to recognize different clinical manifestations of CADRs and to find out the cause and identify the common offending drugs. Materials and Methods: A cross sectional study was done over a period of 9 months from March 2019 to November 2019 after institutional ethics committee approval. All patients presenting to the dermatology OPD and IPD with cutaneous manifestations after drug consumptions and those referred from other departments are included in our study. Patients having incomplete history of drug intake were excluded from the study. Results: A total of 136 CADRs are reported during the study period. Among 136 cases, 74 were females and 62 males. Patients presented with Maculopapular rashes 53 (38.97%), Drug induced urticaria 26 (19.12%), FDE 21 (15.44%), Acneiform eruptions 14 (10.29%), Erythema multiforme 8 (5.88%), Exfoliative dermatitis 7 (5.15%), SJS-TEN 6 (4.41%), DRESS 1 (0.74%). Conclusion: Knowledge of pattern and offending drugs help in better management, reducing complications and preventing recurrences in these patients.

Keywords: Adverse drugs, Cutaneous adverse drug reactions, maculopapular rash, drug induced urticaria, FDE, erythema multiforme, SJS TEN, exfoliative dermatitis, DRESS.

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I. Introduction

Adverse reactions to drugs are an unpredictable and unfortunate event associated with modern medicine. The World Health Organisation (WHO) defines Adverse Drug Reactions as a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological functions.¹ Cutaneous adverse drug reactions (CADRs) are probably the most frequent of all manifestations of drug sensitivity. They comprise 10-20% of the reported ADRs with an overall incidence rate of 2-3% in hospitalised patients.² CADRs related hospitalisations have consistently increased which has caused significant economic burden to a developing country like India.

Cutaneous adverse drug reactions (CADRs) is defined as any undesirable change in the structure or functions of the skin, its appendages or mucous membranes, and it encompasses all adverse events related to drug eruption, regardless of its etiology.³ The common CADRs are skin rash, urticaria, fixed drug eruptions (FDE), angioedema etc. Severe CADRs endangering patients life are Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS) and Acute generalised exanthematous pustulosis (AGEP).⁴ Causality assessment is the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event. In most cases these events are diagnosed clinically with help of detailed history. Recognition of the offending drug enables early withdrawal and improved outcomes.

Atopy, genetic variation in drug metabolism, HLA variation, co morbidities, active viral infection, immune status of the patient and concomitant intake of other drugs can alter the rate, presentation, course and outcome of CADRs.⁵ Continuous discovery of new molecule and their introduction into the market, increasing habit of self medication, practice of poly pharmacy, availability of over the counter medications all predict a future rise in incidence of CADRs. Only about half of drug reactions can be detected in the premarketing trials.⁶
The present study was conducted to assess the pattern of CADRs with respect to age and sex, evaluate the clinical spectrum and outcome of CADRs and identify the offending drugs in patients attending our tertiary care centre. The aim is to get an idea about the pattern of CADRs in the local population. Through our study we also tried to raise awareness in the study population through counselling to prevent recurrences in the future.

II. Materials And Methods

This was a cross sectional hospital based study done over a period of 9 months from March 2019 to November 2019 in the Department of Dermatology of a tertiary care centre. All patients, irrespective of age and sex, presenting to the Dermatology OPD and IPD with cutaneous manifestations after drug intake and also those referred from other department who were considered to be having adverse drug reaction were screened. All cases of cutaneous adverse drug reactions with a causal relationship of ‘definitive’, ‘probable’ and ‘possible’ according to Naranjo scale and willing to participate were included in our study. Patients with unclear drug history, doubtful causality, reactions to topical application of drugs and indigenous medications were excluded. Informed written consent was taken from the patients. The study was approved by Institutional Ethics Committee.

Patients age and sex, underlying co-morbidities, detailed drug history, illness prompting drug intake, time sequence of events, clinical manifestations were recorded. Detailed cutaneous examinations of lesions were performed to assess the morphology and pattern. Improvement of mucocutaneous lesions after withdrawal of offending drug was also assessed. Rechallenge was not attempted due to associated risks and ethical concerns.

Pie chart, Bar diagrams and percentage calculation was done using Microsoft Excel.

III. Results

A total of 136 cases of CADRs were included in our study, selected from patients attending both OPD, IPD and also those referred from other departments. Out of these majority were females 74 (54.41%) while 62 cases were males (45.6%). Male to female ratio was 0.83:1.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number(n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>74</td>
<td>54.41%</td>
</tr>
<tr>
<td>Female</td>
<td>62</td>
<td>45.6%</td>
</tr>
</tbody>
</table>

Table 1- Sex distribution among study population.

The study revealed that majority of patients belonged to 30-45 yrs age group - 49 (36.03%). 17.65% of the study population were less than 18 yrs.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-18</td>
<td>24</td>
<td>17.65%</td>
</tr>
<tr>
<td>18-30</td>
<td>31</td>
<td>22.79%</td>
</tr>
<tr>
<td>30-45</td>
<td>49</td>
<td>36.03%</td>
</tr>
<tr>
<td>45-65</td>
<td>19</td>
<td>13.97%</td>
</tr>
<tr>
<td>&gt;65</td>
<td>13</td>
<td>09.56%</td>
</tr>
</tbody>
</table>

Table 2- Age distribution.

In majority of cases around 70 (51.47%), Antimicrobials were the offending drugs followed by NSAIDs which were the second most common cause seen in 34 cases (25%). Antiepileptic were also found to be the culprit in 13.23% of the cases. Among antimicrobials, Cephalosporins were most common followed by Fluoroquinolones.
62 patients (45.58%) had no history of consumption of same drug or drug of same family in the past, whereas 30 patients (22.06%) had taken same or similar drug previously. Remaining 44 patients (32.36%) could not recall if they had taken these drugs previously.

The most common CADRs encountered was maculopapular rash seen in about 53 patients (38.97%). Drug induced urticaria was found in 26 patients (19.12%) and FDE in 21 patients (15.44%).

Bar diagram 1- Pattern of presentation among cases of CADRs.
Image 1- Drug induced urticarial rash, over anterior chest in a patient.
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Image 2a&b- Images show a female developing maculopapular rash after self medicating with antimicrobial of cephalosporin group.

Image 3- A female who had taken NSAIDs for headache developing typical iris lesions of erythema multiforme

Image 4- A male with a lesion of FDE following Fluoroquinolone intake for diarrhoea.
In our study around 14 patients had Severe Cutaneous Adverse Drug Reactions (10.29% of total cases). Among these majority had Exfoliative Dermatitis-7 cases followed by SJS TEN - 6 cases and one case of DRESS syndrome.

Image 5- A patient of Steven Johnson Syndrome.

Image 6- Image shows a patient who developed diffuse exfoliation, 2 months after starting MDT-MB adult for Hansen’s disease.

The most common drug responsible for maculopapular rash was Cephalosporins followed by Anti Epileptics. Drug induced urticaria was the second most common finding in our study population. Cephalosporins were the most common offending agent in these cases followed by Non Steroidal Anti Inflammatory Drugs(NSAIDs). Most common drug causing FDE was NSAIDs followed by Fluoroquinolones. Majority of reactions appeared within 1-7 days of drug intake 72 cases (52.94%) whereas in 39 cases (28.68%) it appeared within 24 hours of drug intake.

<table>
<thead>
<tr>
<th>Onset</th>
<th>Number (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 hrs</td>
<td>39</td>
<td>28.68%</td>
</tr>
<tr>
<td>1-7 days</td>
<td>72</td>
<td>52.94%</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>25</td>
<td>18.38%</td>
</tr>
</tbody>
</table>

Table 3- Onset of drug reaction.

Majority of patients were treated on OPD basis and they responded well to treatment. 12.5% (17 cases) of patients required hospitalisations. Among hospitalised patient 14 (82.35% of hospitalised cases) recovered completely while fatality was seen in 3 cases (17.65% of hospitalised cases).

Based on Naranjoscale, causality was established. 108 cases (79.41%) were found to be probable and 6 (4.41%) were definitive. 22 cases (16.18%) fell under possible category.
IV. Discussion

The study revealed that most of the cases were females 74 compared to 62 males. The finding were similar to that of Pudukadan et al and Nandha et al. In contrast a study by Patel and Margatia showed male predominance in cases.

Antimicrobials (51.47%) were the most common offending drug in our study. This was supported by similar findings of Choon et al, Padukadan et al and Nandha et al. Al-Raie et al found NSAIDs to be the most common causative drug which was second most common in our study. According to Noel et al, Anti-Epileptics were the most common offending drug. The variations in various studies can be attributed to different pattern of drug usage in different populations.

The most common presentation seen in the study was maculopapular rash (38.97%) which was similar to finding of Saha et al, Choon et al, Nandha et al, Sharma et al, Noen et al. Al-Raie et al found drug induced urticaria whereas Padukadan et al found FDE to be the most common finding. Drug induced urticaria and FDE was second and third most common finding respectively in our study. This could be due to difference in the pattern of drug use and the different pharmacogenetic traits of the population under study.

In our study Cephalosporin was the most common drug group responsible for Maculopapular Rash followed by anti-epileptics. Whereas, Amrinder et al found Ampicillin to be the most common causative drug for Maculopapular Rash and Saha et al, Noel et al found Anti-epileptics to be the most common cause. Sever Cutaneous Adverse Drug Reactions (SCADRs) formed only 10.29% of total study population. The finding was lower than those reported by Saha et al (32.04%) and Sasidharanpillai et al (13.20%).

Exfoliative dermatitis was found the most common SCADR whereas SJS-TEN was second most common in our study. A study by Choon et al and Patel et al revealed SJS-TEN to be the most common SCADR.

LIMITATIONS

The study was a single institution based study with limited study population. The findings of the study may not be true reflection of the whole population.

Rechallenge was not done in our study due to ethical concerns. Long term follow up was not done so pattern of recurrences could not be reported.

V. Conclusion

Cases of CADRs differ from each other in manifestations and time between drug intake and onset of reactions. There is no gold standard investigation for establishing causality in cases of CADR, however there are certain guidelines like WHO-UMC and Naranjo scale available. In addition to these proper history, response to withdrawal of drug, rechallenge test (not done in our study) can be employed.

Early identification and prompt management can significantly reduce morbidity and mortality in patients of CADRs. Also, awareness regarding self medication and re-administration of recognised offending drug can prevent recurrences.
CADRs are difficult to predict and variable in acuteness, therefore knowledge of pattern of offending drugs, early reporting, detection and management can help us achieve a favourable prognosis in these cases.

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Conflict of Interest- There are no conflict of interests.

References