ADVERSE DRUG REACTIONS, Pharmacovigilance, WHO-UMC, Naranjo's causality scale.

Study revealed that the reporting rate was low. Only cutaneous reactions were reported. More awareness needs to be created to address

Keywords: Adverse drug reactions, Pharmacovigilance, WHO-UMC, Naranjo's causality scale.

INTRODUCTION

Adverse drug reaction (ADR) is defined by the World Health Organisation (WHO) as “any noxious, unintended or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions” [1]. ADRs are the fourth leading cause of death ahead of diabetes, pulmonary disease, AIDS, road traffic accidents [2]. Serious ADRs account for 6.7% of all hospital admissions and account for 5% of all hospital admissions and occur in 10-20% of hospitalized patients [3-4]. They place a substantial burden on healthcare resources.

Pharmacovigilance aims to identify the rare and serious drug reactions of marketed products through rigorous monitoring and reporting [5]. This helps the regulatory authorities to permit safe medicines in the market benefitting the patients.

In 2010, Central Drugs Standard Control Organization (CDSCO) under the aegis of Govt. of India, Ministry of Health and Family welfare and Pharmacovigilance Programme of India (PoP) has established adverse drug monitoring centres in various tertiary care hospitals all over India with the objective to improve the reporting rate of ADRs in India [6].

In spite of the above measures, under reporting is still a matter of concern. Therefore, there is a need to enhance physicians’ awareness about detection, management, prevention and reporting of ADRs [7]. More importance should be given to voluntary reporting as it contributes significantly to successful pharmacovigilance [8].

With this background the present study was conducted with the aim of improving the clinicians’ awareness about monitoring and reporting ADRs which would ultimately benefit the health of the patients. The study was also intended to identify areas which should be addressed to improve the reporting rate.

The primary objectives of the present study were to:

- Characterize the nature, severity, seriousness and predictability of the ADRs
- Estimate the incidence of ADRs
- Identify the drug most commonly involved in ADRs.
Evaluation of the reports
The reports which had complete information of the essential elements were selected for analysis. The reactions were analyzed based on the following categories.

1. Type of reaction - (based on Rawlins and Thompson criteria) [10]
   - Type A: Augmented pharmacologic effects - dose dependent and predictable
   - Type B: Idiosyncratic effects - dose independent and unpredictable
   - Type C: Chronic effects
   - Type D: Delayed effects
   - Type E: End of treatment effects
   - Type F: Failure of therapy
   - Type G: Genetic reaction.

2. Severity
   The severity of a reaction was determined based on the classification systems of WHO and system of Hartwig et al. [11]. The severity of a reaction was classified as mild, moderate, severe or serious.

   - In mild reactions (ADRs) the reaction was self remitting. Over a period of time with or without an antidote and did not extend the stay of the patient in the hospital.
   - Moderate ADRs were those reactions which required therapy and hospital admission for 1 day.
   - Severe ADRs were those which required life threatening measures or required prolonged hospital stay usually in the intensive care unit.

3. Seriousness of a reaction based on the following: (WHO criteria) [1]
   - Death
   - Disability (significant, persistent/permanent congenital anomaly)
   - Life threatening
   - Required intervention to prevent further impairment or damage.

4. The causality of the drug to reaction established by Naranjo scale [12] and WHO scale [5].

5. The predictability of ADR based on criteria modified from the Council of International Organization for Medical Sciences [13] considering the incidence of the reactions as reported in the literature and past history of reactions to the suspect drug.

6. Groups of suspected drugs associated with ADR. The suspect drugs were grouped on their pharmacological class to know most common group causing the reactions.

Results
The results were analyzed using descriptive statistics and a feedback was sent to the clinical departments on the common drugs that caused the reactions. A feedback was sent to all the clinical departments to be given to patients who present with ADR due to suspect drugs which would help during follow-up and further management.

Results
54 ADR forms were received by the pharmacovigilance unit from various clinical departments. Forty five out of the 54 forms were selected for analysis since they satisfied the criteria laid down by the PvPI, the rest were rejected as they were incomplete in terms of the essential elements as shown in Table 1.

Evaluation of quality of the reports
Therefore 45 reactions were analysed for the type, severity, seriousness, causality and predictability of the ADR.

Demographic characteristics of patients with suspect ADR
Out of the 45 patients 31 (69%) were between 20 and 60 years and 14 (31%) were <20 years of age. Almost equal gender distribution was found with slight male preponderance. 24 (53%) males and 21 (47%) females.

Type and severity of suspect ADRs
44 (98%) were of Type B (idiosyncratic) and only 1 (2%) was Type A as per Rawlins and Thompsons criteria. 24 (53%) were mild, 20 (45%) were moderate and 1 (2%) were severe in nature.

Seriousness of reactions
There were, 4 (9%) serious reactions, categorized as serious as they required hospitalization as shown in Fig. 1. Table 2 shows the reactions observed. There was no death reported due to the ADRs.

Causality of drugs implicated in suspect ADRs
The causality was assessed for 66 drugs from 45 reactions using Naranjo scale as shown in Fig. 2.

Predictability of the reactions
The predictability of an ADR was assessed for 30 of the 45 reports where single drug or fixed dose combination were prescribed. Among the 30 reports, 27 (90%) were predictable (reference in product literature is available). Three out of the 27 reactions had previous history of ADR to the same suspect drug. 3 (10%) were not predictable reactions as literature showed <1% incidence of ADR to that particular drug.

Major classes of drugs implicated in suspect ADRs
Antibiotics were implicated as most common groups of drugs associated with ADRs followed by non-steroidal anti-inflammatory drugs (NSAIDS) shown in Table 3. Among the antibiotics, ciprofloxacin had contributed to majority of reactions. Diclofenac and paracetamol were the majorly involved NSAIDs. Most of the reactions that occurred were cutaneous in nature.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Missing data elements</th>
<th>Number of reports</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Date of starting and stopping drug</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Drug name</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Date of reaction</td>
<td>3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Reaction</th>
<th>Suspect drug/drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stevens-Johnson syndrome</td>
<td>Carbamazepine, sodium valproate, erythromycin</td>
</tr>
<tr>
<td>2</td>
<td>Bullous fixed drug reaction</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>3</td>
<td>Multiple erythematous wheals</td>
<td>Nimesulide, Chlomphenicol, Caffeine</td>
</tr>
<tr>
<td>4</td>
<td>Fixed drug eruption</td>
<td>Levofloxacin</td>
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</table>

<table>
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<tr>
<th>Class of drugs</th>
<th>ADRs (n)</th>
<th>ADRs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterials</td>
<td>16</td>
<td>32.67</td>
</tr>
<tr>
<td>Antifungal</td>
<td>3</td>
<td>6.12</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>6</td>
<td>12.25</td>
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<tr>
<td>Analgesics</td>
<td>12</td>
<td>24.49</td>
</tr>
<tr>
<td>Others</td>
<td>12</td>
<td>24.49</td>
</tr>
</tbody>
</table>

ADR: Adverse drug reaction
Most of the reactions were predictable, predictability being assessed by literature search and history of similar reaction. Such reactions could have been prevented by careful history taking and/or carrying out the patch test [17] to identify causality of reaction. Giving alert cards have shown to reduce further incidence of drug reactions [18]. Hence we also followed the same and distributed the cards.

Causality assessment showed that most of them were in the possible category. This could probably due to the fact that multiple drugs were prescribed at the same time and there was insufficient data.

CONCLUSION

The study showed that the reactions were mild in nature, mainly of Type 1 and hypersensitivity cutaneous reactions, possibly related to the suspect drugs. The systemic reactions were underreported. The overall reporting rate was low. There is a need to improve awareness among the clinicians to emphasise their role in voluntary reporting of ADRs, on generating quality reports, critically monitor the ADRs so as to prevent them further.

REFERENCES