IMPORTANCE OF REPORTING ADVERSE DRUG REACTIONS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

AIM: To study the importance of reporting adverse drug reactions (ADRs) caused by different group of drugs in various departments of Government Rajaji Hospital, Madurai, Tamilnadu and assessing the relationship between the reactions and the drugs by using WHO Causality assessment scale (WCAS).

Materials and Methods: The study involved total of 434 Individual Case Safety Reports (ICSRs) from January 2015 to November 2015, at the Department of Dermatology, Medical Oncology, General Medicine, Pediatrics, Obstetrics &Gynecology and ART centre of the hospital and were assessed by WCAS. All the ADRs were supported with relevant clinical biochemical data.

Results: A total of 434 ADRs were reported in our study. Age wise analysis showed that 91% were above 16 years, 8% were between 3 to 16 years and 1% was below 3 years. Analysis of causative agents revealed that 52% of cases were reported for anti-cancer drugs; 19% for antibiotics; 5% cases for antiepileptics; 5% cases for anti-retro viral drugs; 3% for ATT drugs and the remaining 14% for miscellaneous drugs. According to the WCAS, 51% of ICSRs were possible cases and 49% were probable ICSRs. On analysis of outcome of the reactions, 274 cases were recovering; 43 cases were recovered; 104 cases were not recovering; 3 cases
were fatal and 10 cases were reported as unknown cases. **Conclusion:** The study emphasizes the creating the culture of reporting the ADRs from all the department of hospital so as to confirm the existing ADRs and also to find out the unlisted reactions for regulatory actions.

**KEYWORDS:** Adverse drug Reactions, Individual case safety reports, WHO causality assessment scale, unlisted reactions.

**INTRODUCTION**

Adverse drug reactions (ADRs) are unintended reactions which occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972).[1] Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.[1] The drug – drug interactions, polypharmacy, over the counter drugs (OTC) and availability of spurious drugs may cause adverse drug reactions.[1] It has been suggested that adverse drug reactions may cause 5700 death per year in UK.[2] ADRs were the 4th commonest cause of death in USA.[3] The availability of fixed dose combination of drugs, for various diseases like tuberculosis, HIV infection and hypertension, may cause ADRs. A study in USA reveals that 3 patients die due to ADR for every 1000 hospitalized patients.[4] Indian Pharmacopoeia commission functioning as National Coordination centre receives ADRs from Adverse drug reaction monitoring centers under the Pharmacovigilance Programme of India (PvPI). PvPI is in technical collaboration with Uppsala WHO International drug monitoring centre, Sweden.[5] The reporting of ADRs confirms the existing ADRs and also helps to complete the clinical trial data by finding out the unlisted adverse drug reactions.

The ADRs reported by Government Rajaji Hospital to the adverse drug reaction Monitoring center, Madurai Medical College emphasizes the importance of reporting ADRs to PvPI. This information will be useful for regulatory actions and thereby human sufferings from adverse drug reactions can be avoided.

**MATERIALS AND METHODS**

The study involved analysis of ADRs of 434 patients reported by various departments of Government Rajaji Hospital to the adverse drug reaction Monitoring center (AMC), Madurai Medical College from the period January 2015 to November 2015. The Suspected ADR Reporting forms (SADRRF) given by Pharmacovigilance Programme of India were
distributed to all the departments of the hospital and the reports were collected by the Pharmacovigilance technical associate on a daily visit to the respective wards in the hospital. These forms carry information such as patient initial, age at onset of reaction, gender, reaction terms, date of onset of reaction, suspected medications, dose, date of therapy started, indication of use, seriousness of reaction, outcome of reaction, de-challenge and re-challenge details, reporter’s information and date of report.

The clinical parameters were also collected from the case file of each patient and the patients were interviewed to support the relationship between the drug and the suspected reaction. The severity of reaction and the outcome of reaction were assessed by the Guidance document for spontaneous adverse drug reaction reporting, Indian Pharmacopoeia Commission-2014. The causality assessment was carried out by causality assessment committee (CAC) using WHO Causality assessment scale and reported as ‘Probable’ and ‘Possible cases’. No case was reported as certain or unlikely.

Majority of the reports were received from Department of Medical Oncology and Dermatology. Reports were also received from General Medicine, ART centre, Pediatrics and Obstetric & Gynecology department.

The seriousness of reactions were categorized as fatal, life threatening, hospitalization, disability and congenital anomaly as per Guidance document for spontaneous adverse drug reaction reporting, Indian Pharmacopoeia Commission-2014.

The outcome of reactions were reported as recovered, recovering, continuing, fatal and unknown as per Guidance document for spontaneous adverse drug reaction reporting, Indian Pharmacopoeia Commission-2014.

**RESULTS**

As per gender distribution, 242 female patients and 192 male patients were reported with adverse drug reaction (Table 1), which contributes 56% of female and 44% of male patients (figure 1). The age of the subjects ranges from 0-3 years; 3-16 years; above 16 years in which below three years of age carries 1% of the total reports, 3-16 years carries 8% of reports and 91% adverse reactions were reported above 16 years of age (figure 2).

The group of suspected drugs reported was anti cancer drugs - 225; antibiotics - 82; anti epileptics - 21; anti retroviral drugs - 22; anti tuberculosis drugs - 14; NSAID - 14; steroids
and anti diabetics 4 each; IV fluids - 22 and others 27 which includes anti-hypertensive, hypolipidemic drugs, antifungal, antileprotic, diuretics and anti-psychotic drugs (figure 3).

Out of 434 ADRs, 124 patients were reported as serious cases and 310 patients were reported as non-serious cases (Table 2).

When the outcome of adverse reactions reported were analyzed, it was noted that 63% patient belonged to the category of ‘recovering’ (274/474 patients); 10% (43/474) to ‘recovered’; 24% (104/474) to ‘continuing’; 2.3% to unknown (10 /474) and 0.7% (3/474) to fatal category (Figure 5 & Table 3).

According to causality assessment, the cases were reported as either probable or possible and no case was reported as certain as per WHO-UMC causality assessment scale (figure 5).

**Table 1: Sex wise distribution of ADR’S**

<table>
<thead>
<tr>
<th>S.N</th>
<th>Gender</th>
<th>Number of ADR’s n= 434</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Female</td>
<td>242</td>
</tr>
<tr>
<td>2.</td>
<td>Male</td>
<td>192</td>
</tr>
</tbody>
</table>

![Figure 1: Percentage of gender distribution of ADR’s](image1)

![Figure 2: Percentage of age wise distribution of ADR’s](image2)
Figure 3: Class of Suspected drugs reported ADR’s

Table 2: Severity Level (Guidance document IPC) N = 434

<table>
<thead>
<tr>
<th>Level of severity</th>
<th>Number of ADR’s</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td>124</td>
<td>28%</td>
</tr>
<tr>
<td>Non serious</td>
<td>310</td>
<td>72%</td>
</tr>
</tbody>
</table>

Figure 4: Outcome of ADR’s (Guidance document IPC)

Table 3: Percentage of Outcome of ADR’s

<table>
<thead>
<tr>
<th>S.N</th>
<th>Outcome of reaction</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Recovering</td>
<td>63%</td>
</tr>
<tr>
<td>2.</td>
<td>Recovered</td>
<td>24%</td>
</tr>
<tr>
<td>3.</td>
<td>Continuing</td>
<td>10%</td>
</tr>
<tr>
<td>4.</td>
<td>Unknown</td>
<td>2.3%</td>
</tr>
<tr>
<td>5.</td>
<td>Fatal</td>
<td>0.69%</td>
</tr>
</tbody>
</table>
DISCUSSION

In total number of 434 ADRs reported, majority were reported for adult group when compared to child and infant groups. As elderly patients were taking multi drugs for various illnesses, the chances of occurrence of ADRs in that age group is likely high. In our study, it was noted that the incidence of ADRs were high in the females when compared to the males. Adverse drug reactions due to anti cancer drugs were predominantly reported as they are known to cause more ADRs. The next class of drugs were antibiotics and in particular cotrimoxazole, ciprofloxacin, doxycycline, cefixime and ofloxacin are notorious to cause cutaneous adverse drug reactions. The antiepileptics like carbamazepine, phenytoin and sodium valproate were reported for more serious cutaneous adverse drug reactions like Stevens-Johnson syndrome. The fixed dose combination of anti retroviral and anti tuberculosis drug were reported for cutaneous adverse drug reactions, altered liver enzymes, jaundice and anemia.

As per the Guidance document of Indian Pharmacopeia commission, the majority of reaction outcome was ‘recovering’ and ‘recovered’ cases. The maximum of ‘continuing’ ADR outcome were reported for anti-cancer drugs as the patient undergoes cyclic treatment and all the patients receiving cytotoxic drugs suffer one or more ADR’s. Three patients were reported as fatal cases; one with methotrexate induced bone marrow suppression, one with anti tuberculosis drugs induced hepatic encephalopathy and one with serious cutaneous adverse reaction by immunosuppressant leflunomide. In the case of methotrexate and leflunomide, the patients consumed the drug as OTC (over the counter). It shows that the sale of these drugs over the counter would cost the life of the patients.
CONCLUSION
The total number of reports emphasizes that the stringent adverse reaction monitoring and reporting them to Pharmacovigilance Programme of India are very imperative. Some fatal cases due to OTC availability of immunosuppressant like Methotrexate and leflunomide makes clear that the ADR monitoring is essential in Pharmacy level also. Similarly Pharmacovigilance is the need of hour to monitor the fixed dose combination drugs in case of anti retroviral and anti tuberculosis treatment. Moreover drug usage by the elderly patients with co-morbid conditions should be monitored as this age group reported more adverse drug reactions. ADR monitoring and reporting to Pharmacovigilance is much needed now to prevent the adverse drug reactions and safeguard the patients. In conclusion, Pharmacovigilance is needed for the prevention of drug induced human sufferings and to avoid financial risks associated with unexpected adverse effect. Safe use of drugs to safeguard the patients is the ultimate goal of Pharmacovigilance Programme of India and it should be implemented at every health care level.

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