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Adverse Drug Reactions at a Tertiary Care Hospital in South India- A Prospective analysis

Authors
M.Malathi[1], Dr M.Shanthi[2], Thirumalai Nambi[3]
[1]Assistant Professor, Institute of Pharmacology, Madurai Medical College, Madurai
Email: *poojamuthudch@yahoo.co.in*
[2]Professor, Institute of Pharmacology, Madurai Medical College Madurai
[3]Pharmacovigilance Associate, Institute of Pharmacology, Madurai Medical College Madurai
Email: *nambina@gmail.com*
Corresponding Author
Dr M.Shanthi
Professor, Institute of Pharmacology, Madurai Medical College Madurai
Email: *shanthi babu24@gmail.com*

Abstract

Aim: *Adverse drug reactions are the recognized hazards of any treatment at any point of time. The aim of this study is to analyze the ADRs during one year period in various department of Government Rajaji Hospital, Madurai, Tamilnadu, the relationship between each reaction and the drug and preventability of the ADR.*

Materials and Methods: *The study involved total sum of 500 Individual case safety reports (ICSRs) collected from the period of January 2016 to December 2016. The WHO causality assessment scale was used to assess the relationship between the adverse drug reaction and the suspected drug. ADR preventability was assessed using Modified Shumock and Thornton scale.*

Results: *Out of total of 500 ICSR's 62% were reported in the age group above 40 years, 31% were between 16 to 40 years; 6% between 3 to 16 years and just 1% reported below the age of 3 years. Anti cancer drugs tops the list with 55 % of ADR , 14 % for Anti-retroviral drugs, 13 % for Antibacterial agents, 8 % for Anti tuberculosis drugs, 3 % reported for Anti epileptic drugs; 2% for NSAID'S and 7% miscellaneous drugs. According to the WHO causality assessment scale 22 % of ICSRs were possible cases, 65 % were probable and 13% were certain. Among 500 ADRs 15% was preventable 30% probably preventable 55% were not preventable.*

Conclusion: *The study reveals how monitoring helps to quantify the burden of ADR and focus the preventable ADR, find out unknown reactions and to reduce the physical, psychological and economic burden to the patient.*

Keywords: *Individual case safety reports, adverse drug reactions, WHO causality assessment scale, preventability.*

INTRODUCTION

Drugs are double edged weapon. They are the most common medical intervention and are primarily used to relieve suffering. But drugs themselves can do unintended harm. It affects not only affects patient recovery but also acts as an economic burden to the patient and the society Adverse drug reactions are unintended, and occurs at doses normally used in human for the prophylaxis, diagnosis, treatment 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, genetics, availability of spurious drugs, poly pharmacy are some of the causes of ADR.[1] The availability of fixed dose combination of drugs, for various diseases like Tuberculosis, HIV infection and diabetes, may also cause ADRs. A study in USA reveals that 3 patients die due to adverse drug reaction for every 1000 hospitalized patients.(2) Indian Pharmacopoeia commission functioning as National Coordination centre (NCC-PvPI) for receiving reports from Adverse drug reaction monitoring centers under Pharmacovigilance Programme of India. The Uppsala WHO International drug monitoring centre, Sweden provides the technical support.(3) The reporting of adverse drug reactions helps in establishing the prevalence of adverse drug reactions , complete the clinical trial data by finding out the unknown adverse drug reaction, and helps NCC-PvPI to suggest regulatory actions to the Central Drugs Standard Control Organization (CDSCO).

MATERIALS AND METHODS

This study is a prospective observational study involving data analysis of ADRs in 500 patients reported by various departments of Government Hospital to the ADR Monitoring center (AMC), from the period January 2016 to December 2016. The Suspected Adverse Drug Reaction Reporting forms of Pharmacovigilance Programme of India, were distributed to all the departments of the hospital and the reports were collected daily.

These forms carries detailed information such as Patient initial, age at onset of reaction, gender, reaction terms, date of onset of reaction, date of commencement of therapy, suspected medications, indication, dose, nature ,severity and outcome of reaction, de-challenge and re-challenge details, reporter's information and date of report.

The clinical parameters were collected from the case file of each patient and also the patients were enquired and detailed history was taken to justify the relationship between the drug and the adverse 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 carried out by Causality assessment committee by using WHO Causality assessment scale and reported as 'Certain', 'Probable' and 'Possible' cases. Preventability was assessed using Modified Shumock and Thornton scale. Criteria for preventability correspond directly to the questions published by Schumock and Thornton (Table 1). Any answer of "yes" to any question suggests that the ADR might have been preventable. Patient and drug therapy were evaluated to identify various predisposing factors responsible for an ADR.

The seriousness of reactions were categorized as fatal, life threatening, hospitalization, disability and congenital anomaly and the outcome of reactions were reported as recovered, recovering, continuing, fatal and unknown cases as per Guidance document for spontaneous adverse drug reaction reporting, Indian Pharmacopoeia Commission-2014.

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RESULTS

As per gender distribution, 250 female patients and 250 male patients were reported with adverse drug reaction (Figure 1), which contributes to 50% each gender.

Among these reports age below three years was 1% of total report, 3-16 years was 6% , 16-40 years was 31% and 62% of adverse reactions were reported above 40 years (figure 2).

As expected anti cancer drugs had the maximum number of ADRs with 276 reports, anti retroviral drugs – 67, antibacterial- 63; anti tuberculosis drugs- 39; anti epileptics-16; NSAID- 11; anti-snake venom- 6; Intravenous fluids- 5; and others like anti diabetic, anti hyperlipdemia, antihypert-ensive, antiulcer, anti psychiatrics, vaccines and immunosuppressant contributed to 17 ADRs (figure 3).

As far as the seriousness of the ADR's is concerned 120 patients were serious reactions and 380 patients were non-serious cases (Table 1).

The outcome of adverse reactions were analyzed and it was observed that 49.2% patients belonged to the category of 'recovering' (246/500 patients); 19% (95/500) of 'unknown' ; 18 % (88/500) of 'recovered'; 13.8% (69/500) of 'continuing'; 0.4 % (2/500) of fatal cases were reported. (figure 5)

As per WHO-UMC causality assessment scale (figure 5) the cases were reported under certain, probable and possible category.

17 % were preventable ADRs, 32% were probably preventable and 51% were not preventable.

Preventability criteria according to Schumock and Thornton scale

Definitely Preventable 1. Was there a history of allergy or previous reactions to the drug?

2. Was the drug involved inappropriate for the patient's clinical condition?

3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?

4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?

5. Was there a known treatment for the Adverse Drug Reaction?

Probably Preventable

6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?

7. Was a drug interaction involved in the ADR?

8. Was poor compliance involved in the ADR?

9. Were preventative measures not prescribed or administered to the patient? Not preventable: If all above criteria not fulfilled

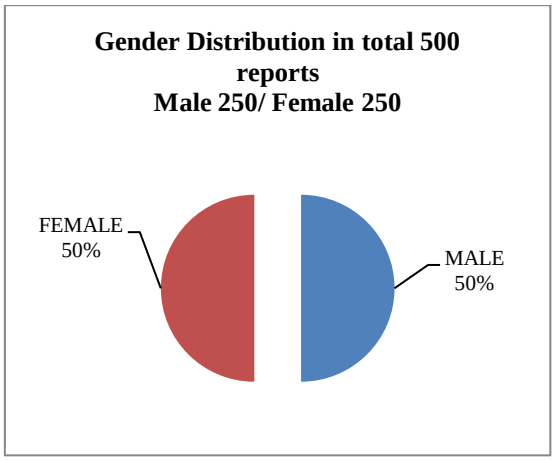

Figure 1: Percentage of gender distribution of ADR's

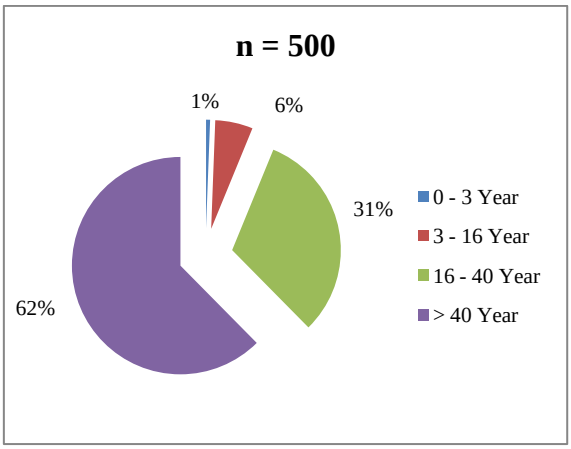

Figure 2: Percentage of age wise distribution of ADR's

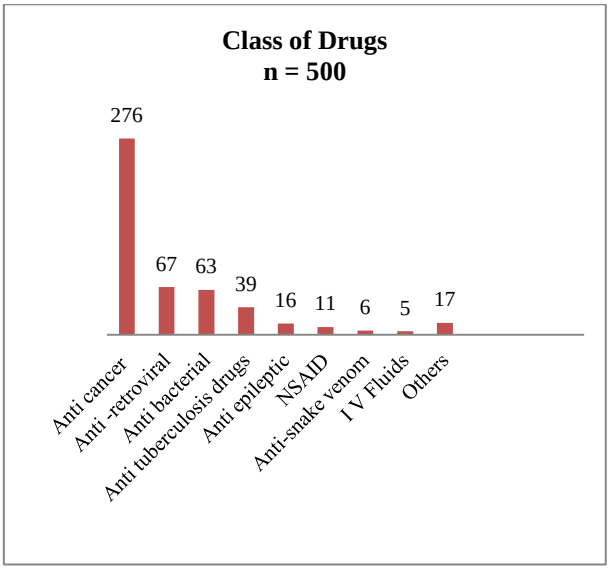

Figure 3: Class of Suspected drugs reported ADR's

Table 1: Severity Level

S:NO	Seriousness of ADR	Number of cases
1	Serious	24%
2	Non serious	76%

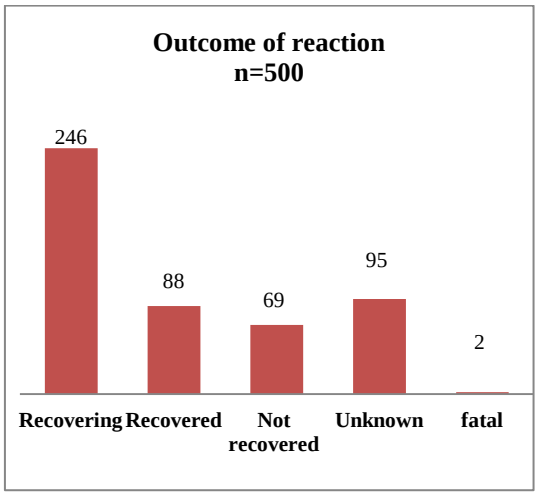

Figure 4: Outcome of ADR's (Guidance document IPC)

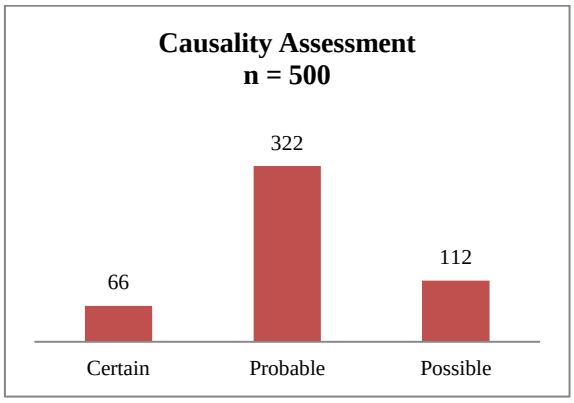

Figure 5: Causality Assessment (WHO Scale)

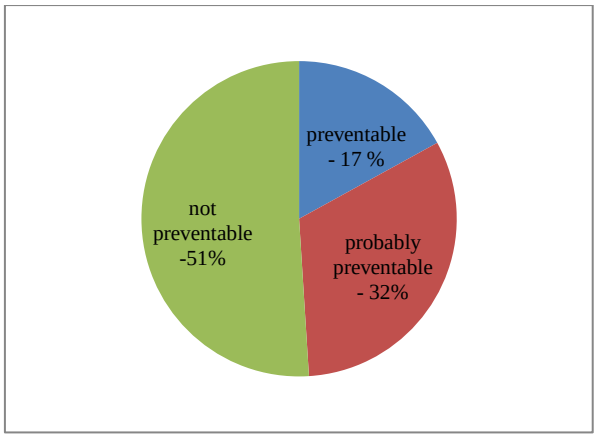

Figure 6: Preventability of ADR

DISCUSSION

In total number of 500 adverse drug reaction cases, majority were reported for adult group when compare to child and infant groups.[4] The number of drugs for various illness was more for elderly patients which resulted in more ADR's. Adverse drug reactions for anti cancer drugs was predominantly more, than any other class of drugs, as they known to cause more ADRs.[5&6] The next class of drugs were antibiotics in particular cotrimoxazole, ciprofloxacin, doxycycline, cefopodoxime, cefadroxil, Amoxicillin/ Clavulanic acid and ofloxacin were reported for cutaneous adverse drug reactions.[7,8] The antiepiletic like carbamazepine caused serious cutaneous adverse drug reactions like stevens-johnsosn syndrome and Toxic epidermal necrolysis.[8] The fixed dose combination of anti retroviral and anti tuberculosis drug caused cutaneous adverse drug reactions, altered liver enzymes, jaundice and anaemia.[9] The anti retroviral Efavirenz caused Toxic epidermal necrolysis, when it was consumed along with alcohol and fatty meal (Pork meat). [10]

As per the Guidance document of Indian Pharmacopeia commission the majority of reaction outcome was recovering and recovered cases. [4]The maximum of continuing adverse drug reactions reported for anti cancer drugs as the patient undergoes cyclic treatment, the adverse reactions were part and parcel of the therapy.[5,6] Two ADR's were reported as fatal cases, one was Efavienz with fatty meal and alcohol leads to serious cutaneous reaction of TEN. [10] The another one was Injection ondansetron and dicyclomine induced drug eruption all over the body. [11,] The efavirenz induced Gynaecomastia [12] The DRESS Syndrome was reported for Carbamazepine. [13]

Linezolid induced Peripheral neuropathy [14] The HCQS (Hydroxychloroquine sulphate) induced AGEP (Acute generalized exanthematous pustulosis[15] was reported as very rare ADR's. INH induced generalized seizures were reported for Categort I ATT regimen, Anaphylactic shock

induced by Oral cefadroxil tablets were all very rare cases of ADR reported in our study. Methotrexate induced Pancytopenia was reported as an Uncommon ADR's.[16,] Ototoxicity was reported for Kanamycin and Oxaliplatin.) Many cases of Palmar-Plantar erythrodysthesia are reported for Sorafenib.

CONCLUSION

The increase in number of reports emphasizes the importance of monitoring and reporting of adverse drug reactions to the ADR monitoring centers is vital to ensure the safety use of drugs. The fatal case of Toxic epidermal necrolysis induced by Efavirenz with alcohol and fatty meal indicates the necessity of drug counseling for anti-retroviral drugs under National public health Programme. In addition, Pharmacovigilance is the need of hour to monitor the ADR in Public health programmes like RNTCP, DOT and ART centers drugs, where the use of fixed dose combinations are more. Elderly patients have many comorbid condition and should be monitored for ADR's as they have co morbid conditions.. Death due to, drug reaction is unacceptable. Although many of the drugs implicated have proven benefit measures need to be put into action to reduce burden of ADR and therefore improve the benefit harm ratio of drugs. To conclude, the monitoring and reporting of ADR's at every health care level is very imperative for the safety use of drugs and to safeguard the patients. The balance between benefit and risk of a specific medicinal product also varies between individual patients. So
any conclusion with regard to benefits and risks of a specific medicinal product always requires detailed evaluation and scientific assessment of all available data.

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