Research Article

Adverse Drug Reaction Surveillance Study in Patients Visiting a Tertiary Care Hospital in North India

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Abstract

Objectives: The study intended to assess the incidence and types of ADRs reported at a tertiary care hospital in North India. **Methods:** The prospective observational study was carried out by ADR Monitoring Centre, AIIMS, Rishikesh, during an index period of one year from July 2018 to June 2019. It was carried out by a spontaneous reporting method using suspected ADR reporting form of the Pharmacovigilance Program of India (PvPI). The likelihood of a causal relationship between the suspected drug and reported ADRs were analyzed using a standardized WHO-UMC Causality assessment scale. **Results:** During the study, 732, ADRs were collected from various departments. The reported ADRs were categorized and analyzed based on gender, age, clinical manifestations, offending drugs, seriousness criteria and causal relationship. **Conclusions:** In the present study, various types of ADRs were examined, and we identified two new Drug-ADR combinations in the form of potential signals. It was also found that the magnitude of ADRs encountered was not only from the labeled indications of drugs but was also generated from off-labeled prescription practices.

Keywords: Adverse Drug Reaction (ADR), Pharmacovigilance, Causality Assessment.

INTRODUCTION

Patient care has been an integral part of our healthcare system, and drugs play an indispensable role in the treatment and management of diseases. Though, lifesaving drug can itself be the cause of adverse drug reactions ranging from mere inconvenience to permanent disability and death.[1] Thus, pushing the need to establish a system for vigilant capturing of all known/unknown, related/unrelated serious and non-serious ADRs resulting from drug use. Adverse drug reactions are the unintended or unwanted effects of drugs. Various studies in the literature have also reported a wide range of incidences of mortality and morbidity due to the occurrence of adverse drug reactions by the drugs.[2]

The Pharmacovigilance Program of India (PvPI) was started by the Government of

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India and its contribution to the WHO-UMC Pharmacovigilance database is relatively narrow due to the absence of a rigorous monitoring system and lack of awareness regarding ADR reporting among health care providers.[3] Further, the Indian government has not implemented ADRs reporting as mandatory policy unlike some countries such as Spain and Sweden[4] therefore a robust pharmacovigilance system must be established as an obligatory part of drug safety process which provides support not only in terms of collection, surveillance and analysis of the data related to ADRs but also helps in designing strategies for risk minimization and drug utilization approach.

Government hospitals serve as the prime source for generating good ADR database, since a major proportion of India's population prefer government hospitals when they seek health care facilities, hence a hospital-based reporting program can be very helpful in providing valuable information regarding the potential causes and outcomes of drug-related problems.

Thus, the present study was done to monitor and study the incidence of ADRs reported in patients visiting the different departments of AIIMS a tertiary care government hospital in Rishikesh. The data derived from the study outcome will generate a high level of scientific evidence for ensuring safe and rational medication practices and will also add knowledge to the educational database.[5]

MATERIAL & METHODS

Study site/design/duration

The Regional Resource Centre (AIIMS Rishikesh) pioneered to conduct an observational and prospective study for capturing and monitoring of ADRs on patients visiting the AIIMS campus.

The study was done during an index period, from July 2018 to June 2019.

Study population

The ADRs reported and received were from patients attending the outpatient (OPD) and inpatient (IPD) departments of AIIMS hospital in Rishikesh.

Inclusion/Exclusion criteria

There was no specific inclusion and exclusion criterion.

Study method

All healthcare professionals, the clinicians, nurses, pharmacists, and residents were sensitized before the start of the study, to create awareness for ADR reporting. The banners/posters, and leaflets for creating ADR awareness, were displayed in all OPD/IPD sections and nursing counters. The contact information (phone numbers and email ids) of the study authors, were circulated among the clinicians and other healthcare professionals of respective departments to facilitate the reporting of ADRs.[1] The OPD patients were interviewed on routine follow-ups, while the IPD patients were monitored daily throughout their hospital stay for reviewing their records for capturing ADRs.[6] The suspected ADRs are detected from objective findings (i.e.) from biochemical investigation results and subjective markers through the review of clinicians and nurse's notes from patient

record files. The suspected ADRs were carefully analyzed and documented at the ADR Monitoring Centre for further assessment.

The spontaneous reporting method was used with the suspected ADR form of PvPI for recording the data. The patients categorized from having an adverse drug reaction were thoroughly reviewed. All substantial data about the case report was captured on the ADR reporting form to process an ICSR (Individual Case Safety Report).

The reported ADRs were collected and analyzed at ADR Monitoring Centre for completeness and quality check. The ADRs fulfilling the reporting criterion, are further evaluated for assessing various parameters (demographics, clinical manifestations, offending drugs, and seriousness)

The temporal (time) relationship between the administration of the suspected drug and the occurrence of an adverse reaction was assessed using a standardized WHO-UMC Causality assessment scale.[7]

Causality assessment is the method used to establish the extent of the relationship between a drug and a suspected reaction. The assessment of the causal relationship is often highly subjective, based upon an individual clinician's assessment.[8] The causality assessment was done based on seriousness criteria and action taken after the occurrence of a reaction event. Based on the clinician's decision whether to withdraw or continue the drug depending on the severity of the reaction event, the causal relationship was assessed. Descriptive statistics applied for statistical analyses of data and graphical representation of results.

Study Tools

– Suspected ADR reporting form of PvPI 7

– WHO –UMC Causality Assessment Scale 9

RESULTS

Descriptive statistics were used for data analysis and results were expressed as percentages. The various parameters analyzed were represented graphically using figures. A total of 747 ADR cases were received from various sources during the index period out of which only 732 qualifying the reporting criterion were submitted to NCC-PvPI. The results of the study exhibited that 98 % of ADRs were reported from AIIMS and rest 2% from other sources such as consumer reporting and public outreach programs i.e. Adverse Events Following Immunization (AEFI) and National De-worming Day (NDD). (Figure 1) The OPD collection contributed the principal share of ADR reports 86% while the rest 14% were from the IPD. (Figure 2) There was no significant difference in reports received from the male and female gender. However, a higher percentage of ADR occurrence observed in female gender 56% over the male gender 44 %. (Figure 3) The recorded data showed that only 2% of the cases were serious and required immediate hospitalization while the remaining 98% of cases were non-serious. (Figure 4). The spontaneous reporting by clinicians 91% pharmacists 7.5% and nurses 1% contributed significantly to the share of received ADR reports while 0.5% of reports received via consumer reporting. (Figure 5) The majority of ADRs recorded in the middle age group of 41-

50 years followed by other age groups. (Figure 6) The reported ADRs exhibited a wide range of clinical manifestations summarised following System Organ Classes (SOC). The majority of ADRs belonged to the skin and subcutaneous tissue systems (164) due to the use of antibiotics, gastrointestinal systems (128) due to NSAIDs and neurological disorders due to antidepressants (63) followed by the other organ classes. (Figure 7). The reported ADRs were categorized according to various drug classes. The most offending agents belonged to antidepressant drugs (157), anticancer agents (137) ant-diabetics (99), antibiotics (66), NSAIDs (57), and corticosteroids (42) followed by other classes of drugs. (Figure 8) The recorded ADRs were analyzed for possible causal association with the offending agents and it was observed that about 47 % of cases were Probable/likely with moderate severity which required immediate discontinuation

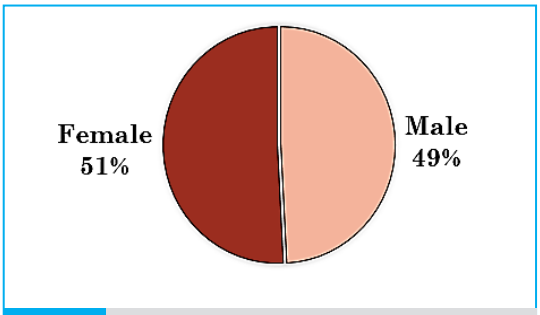

Figure 3 Gender wise distribution of ADRs

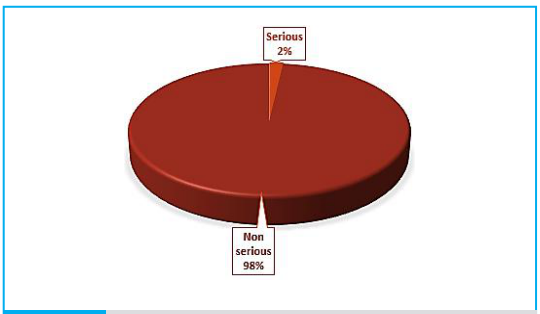

Figure 4 Serious vs Non serious ADRs

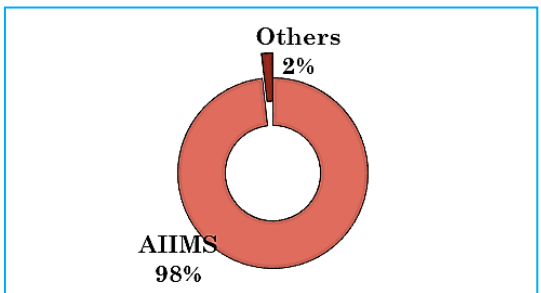

Figure 1 ADRs received from various sources

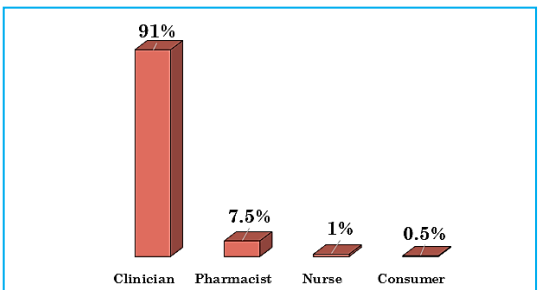

Figure 5 Reporter wise distribution of ADRs

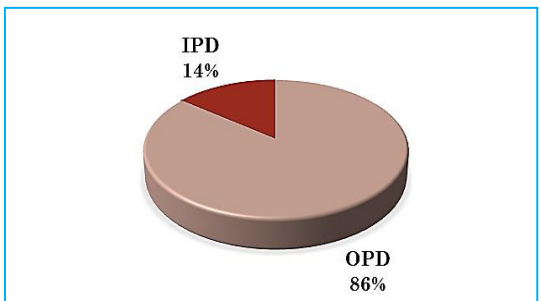

Figure 2 OPD vs IPD wise distribution of ADRs

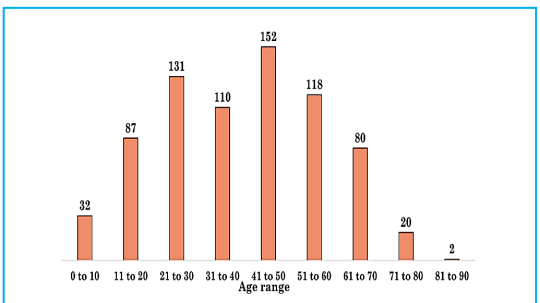

Figure 6 Age wise distribution of ADRs

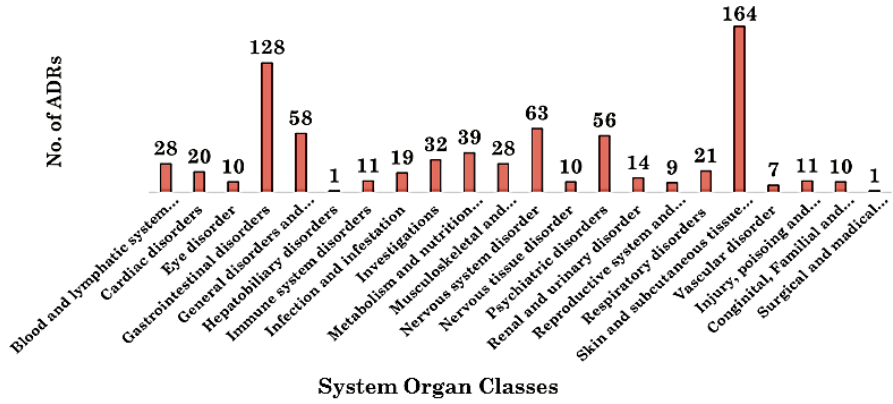

Figure 7 Distribution of ADRs according to System Organ Class (SOC)

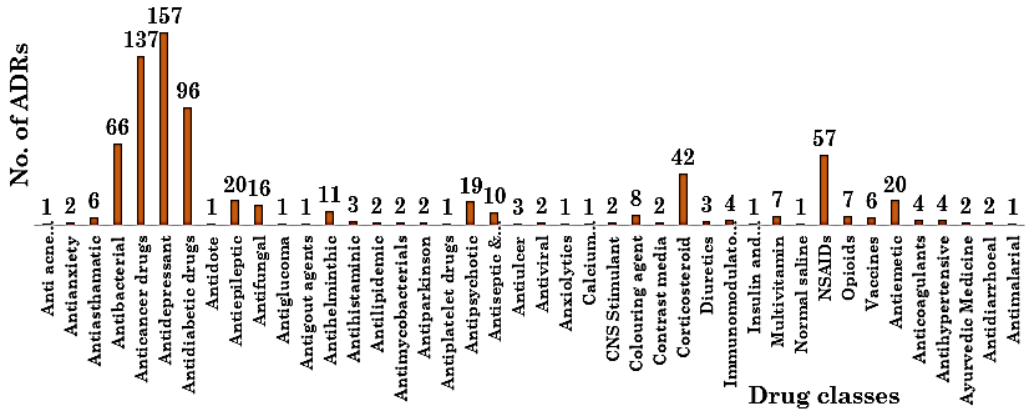

Figure 8 Distribution of ADRs according to Classes of Drugs

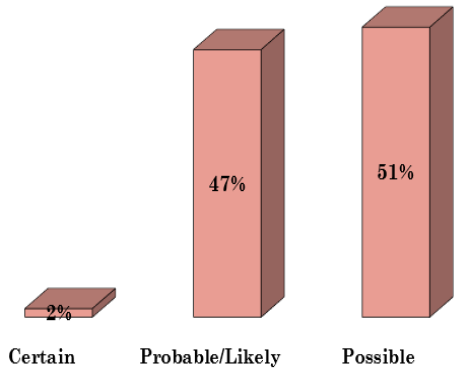

Figure 9 Causality Assessment

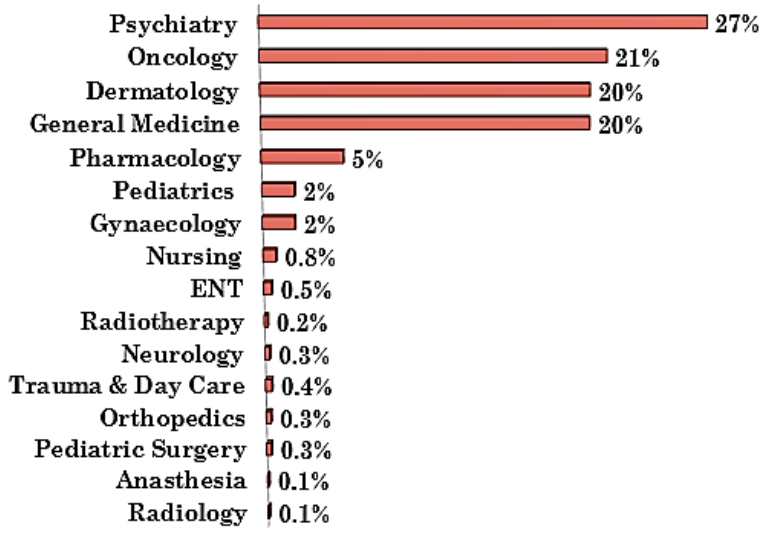

Figure 10 Departments involved in reporting ADRs

or change in drug therapy for abatement of reaction event, 25% cases were Possible with mild to moderate severity where exact nature of suspected drug could not be ascertained while the remaining 2% cases were serious in nature belonging to the Certain category. (Figure 9) The departments that actively contributed to the collection of ADRs were the Department of Psychiatry 27%, Oncology 21%, Dermatology 20%, and General Medicine 20% followed by other departments. (Figure 10)

DISCUSSION

A total of 732 ADRs were reported from various departments. The demographic details of our study are similar to the study published by Mitchell et al which also showed a higher risk ADR occurrence in the female gender as compared with the male gender[10,11] due to various factors such as the higher concentration of adipose tissue in the body, hormonal imbalances, and pharmacokinetic factors such as alteration in levels of cytochrome enzymes (CYP 3A4, CYP2D6, CYP2E1, and CYP1A2 12–16 on the other hand, some studies have reported males predominance over females.[6,17]

In our study, we observed that the drugs commonly prescribed for the treatment of depressive disorders included SSRIs, TCAs, and anti-Anxiety agents. Tardive Dyskinesia, Metabolic Syndrome and Suicidal ideations are some of the commonly reported ADRs.

Moreover, the use is not only restricted to labeled indications but also in an off label manner for various other clinical conditions. Amitriptyline and Gabapentin was the most commonly prescribed drug in an off-label manner for the treatment of myalgia and

neuropathic pain, Clonazepam for insomnia and propranolol for Anxiety.

Some of the ADRs associated with the use of off label prescription of antidepressants included Rebound insomnia and withdrawal symptoms from Amitriptyline and Clonazepam. Studies have shown that off label use of certain anti-depressants over benzodiazepines in anxiety disorders is associated with a higher risk of adverse drug events.[18,19] Similar evidence of the off label use of antipsychotics has been observed in various clinical studies, differing only in certain classes of drugs.[20]

Out of 137 ADRs reported from the Oncology Department, 2% of the patients of chronic myeloid leukemia were resistant to Imatinib drug therapy. We found that there was a genetic predisposition in the patients of CML with a mutation in the BCR-ABL gene. The development of point mutations in the BCR-ABL kinase domain is responsible for the development of Imatinib Resistance in chronic myeloid leukemia.[21] The patients with such genetic disposition do not respond well to the standard Imatinib therapy leading to failure of drug therapy, which is one of the ADR categories that is rarely detected and reported.

During the study, five cases of previously identified signals were strengthened, out of which two cases of Paracetamol induced Stevens-Johnson Syndrome, two cases of Combiflam (Paracetamol/Ibuprofen) induced Stevens-Johnson Syndrome and one case of Combiflam induced Toxic Epidermal Necrolysis were reported from the Department of Dermatology.

Furthermore, 'Methotrexate induced Chronic Plaque Psoriasis' and 'ATT induced Lichenoid Drug Eruption' were identified as newly detected potential signals. Coming to evidence in support of each newly detected signal, both the signals reported more than one case with the same Drug-ADR combination which satisfies the preliminary criteria of two or more than two reports of a given drug-ADR pair with the possible causal association. Other methods of further investigation included extensive search on various online databases and dictionaries such as CIMS, MIMS, EMC, Pubmed, and Vigiaccess tool. Individual drug package insert (US-FDA) was used for reference to ascertain the adverse drug reaction profile of the drug.

CONCLUSION

The present study was an initiative of the ADR Monitoring Centre at AIIMS Rishikesh established under the Pharmacovigilance Program of India run by India Pharmacopoeia Commission. ADR Monitoring Centre at AIIMS Rishikesh has a well-established system of ADR reporting. The extended support from clinicians expedited the process of ADR collection, which enabled us to gather adequate numbers of ADR cases for our study. Department of Psychiatry actively participated in the process of reporting. We also appreciate the cooperation and support of other healthcare professionals, doctors, nursing staff on duty, and technicians who helped us in the successful completion of the study. Though we received favorable support from all healthcare care professionals and supporting staff in data collection, there were some barriers encountered that hindered the predictive course of study. We observed that some of the barriers in reporting of

ADRs included lack of preference and time, ADRs considered non-serious, reluctance to report previously known ADRs, lack of awareness among healthcare professionals about ADR reporting program, and the possibility of legal implications.

Acknowledgment

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