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Research Article

Reporting pattern of Adverse drug reactions in a newly set up Tertiary Care Hospital – A preliminary study

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ABSTRACT

Background: The routine preclinical and clinical trials do not guarantee safety of a new drug as these trials usually cover only few thousands of volunteers, but millions of people take these drugs after it is allowed to be marketed. When a new drug is released into the market, its real test begins as various co-morbidities throw up important challenges to this new molecule.
Adverse drug reactions (ADRs) have a major impact on public health. Pharmacovigilance has become a very important tool to analyse these ADRs. Identification of ADRs and their reporting pattern can provide useful information for their prevention. Hence this study was done to see the pattern of ADRs at the newly set up ADR monitoring centre (AMC) of AIIMS Patna for 24 months.
Materials and Methods: It was a prospective and observational study carried out between May 2016 to April 2018. Both outpatients and inpatients were included in the study. The ADRs in the form of Individual Case Safety Reports (ICSRs) were sent to IPC Ghaziabad through Vigiflow (Indian database of ADRs reporting).
Results: The occurrence of ADRs was more common in females (52%) compared to males. Patients in the age group of 41-60 years (37%) were most commonly involved. Parenteral route (53%) was the most frequent route causing ADRs. Oncology department (29%) reported the maximum percentage of ADRs. Skin and subcutaneous tissue were the most common organ system involved. Majority of the patients with ADRs were inpatients (55%). Maximum (61%) ADRs were of Type A. Health care professionals (HCPs) reported the maximum no (79%) of ADRs. Among HCPs junior residents reported the highest no of ADRs. Antimicrobials (40%) were the most common class of drugs causing ADRs. Most of the patients either recovered or were recovering (71%).In causality assessment probable cases (54%) had a higher incidence. A higher percentage of Moderate cases (49%) was seen upon severity assessment. Preventability assessment showed that majority cases (45%) were probably preventable. In 80% of the cases, the suspected drugs causing ADRs were withdrawn. Our AMC shared 0.20% to the total ICSR database which is quite low when compared to JSS Mysore, PGI Chandigarh, GMC Bhavnagar and AIIMS Delhi.
Conclusion: In the last 2 decades, market has been flooded with many new molecules, as a result of which large number of ADRs are happening and sadly many remain unreported which potentially causes high mortality and morbidity. So having good functioning AMCs is important. There has to be an integrated approach among clinicians, pharmacologists and Patient Safety Pharmacovigilance Associates (PSPvA) in establishing, maintaining and constantly improving the ADR monitoring and reporting. Conducting regular training programmes and constantly encouraging HCPs is an important aspect of ADR reporting.

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INTRODUCTION:

Modern medicines have remarkably changed the way in which diseases are managed, reducing morbidity and enhancing the life expectancy associated with a number of diseases. However, despite these benefits, ADRs are common, often hampering the quality of life of patients and being an economic burden to the patients and society. Both desirable clinical effects and undesirable adverse effects now appear to be like two sides of the same coin. The burden of ADRs in the global scenario is high and accounts for considerable morbidity, mortality, and extra-cost to the patients.[1,2] In England, 0.9% of the total hospital admissions were due to ADRs during the year 1999–2008.[3] ADRs are common in the Australian healthcare system also and they contribute to 1% of hospital admissions.[4] In the United States of America, ADRs contribute to 3.4%–7% of hospital admissions.[5] The percentage of hospital admissions due to ADRs in certain countries is even 10% or more.[6]An adverse drug reaction has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'. This definition excludes trivial or expected side effects and poisonings or overdose.[7] An adverse drug event (ADE) is defined as any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with the treatment.[7] Clinical trial conducted prior to drug approval cannot uncover every aspect of health hazards or benefits of the approved drug.[8] For example, teratogenic effects of Thalidomide and more recently of Isotretinoin were identified through observational methods but not through experimental methods. So prescribing the right drug to the right patient at the right dose for the right duration of time becomes very important. Therefore, post marketing surveillance and pharmacovigilance practices are an absolutely must for implementing rational use of drugs.

WHO defines Pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems" [9, 10] The Uppsala Monitoring center (UMC, WHO), Sweden is maintaining an international database of ADR reports from several national centers of different countries.

At the present moment, 131 countries are members of the WHO program for International Drug Monitoring, and 29 associate member countries, in the early stages of establishing their pharmacovigilance systems, are preparing themselves for full membership. [11]

Although, India is a full time member since 1998 [11] in the WHO Programme for International drug monitoring, its contribution to the UMC database is very little. This is mainly due to either absence or poor functioning of an AMC along with a lack of knowledge among the HCPs. [12] In a country like India, with a large population and vast diversity, it is more so necessary to introduce a standard pharmacovigilance program. [13]

However in last two decades significant efforts have been made to improve ADR reporting from different parts of the country. The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Indian Pharmacopeia commission, Ghaziabad is initiating a nation-wide pharmacovigilance programme for protecting the health of the patients by assuring drug safety. The programme is being coordinated by the Indian Pharmacopeia commission, Ghaziabad.[14] The success of any pharmacovigilance program depends upon active involvement of HCPs like doctors, pharmacists, dentists, nurses and even medical students.[15,16] Therefore, every HCP has an immense responsibility towards reporting of ADRs to strengthen the pharmacovigilance program and ultimately provide better patient care. ADR studies are the need of the hour, which can be accomplished through Pharmacovigilance and Post Marketing Surveillance of Drug Safety profiles.

Moreover, pharmaceutical contact, genetics, ethnic diversity all impacts the appearance of ADRs making Pharmacovigilance practices all the more vital to providing optimum patient care.

AIMS AND OBJECTIVES:

Primary Objective:

1. The main objective was to assess the frequency of ADRs in various clinical departments of AIIMS Patna.

Secondary Objective:

1. To find out the drugs commonly causing ADRs along with their outcome and different routes of the suspected drug.
2. To determine the causality, severity and preventability of ADRs.
3. To assess the effectiveness of the AMC at our institution

MATERIALS AND METHODS:

This was a prospective and observational study, which was carried out for a period of 24 months from May 2016 to April 2018 at AIIMS Patna. All patients of either sex, any age, inpatients, outpatients from all clinical departments with suspected ADRs were included in the study. While those patients taking alternatives system of medicines like Ayurveda, Homeopathy, Unani, Siddha, suspected drug toxicities, over dosage, unconscious and patients unable to respond to verbal questions were all excluded from the study. The AMC of AIIMS Patna is one of the peripheral monitoring centers of the Pharmacovigilance Program of India (PvPI). It is coordinated by the Institute's Department of Pharmacology. The study was started after getting approval from Institutional Ethical Committee. The results were analyzed on the basis of demographic pattern, types of patients (in or out patient), routes of drug administration, types of reactions, systems involved, classes of drugs responsible for causing ADRs, frequency of reporting of ADRs by HCPs, outcome, causality (WHO UMC SCALE), severity (Adapted Hartwig scale) and preventability (Modified Schumock and Thornton scale) of ADRs and the submission of ADRs in the form of ICSRs in vigiflow. It is a web-based ICSR management system that is available for use by national pharmacovigilance centers of the WHO Programme for International Drug Monitoring.

The PSPvA along with junior and senior residents of the Department of Pharmacology visited the OPDs and wards of all departments on a daily basis and collected the suspected ADRs in the ADR Reporting Form as reported by treating consultants, residents, interns and nurses. Inpatients suffering an ADR were visited daily until they were discharged, while for those patients who were detected with an ADR during OPD visits, their phone number was taken to follow up on the status of the ADR after the patient went home. If an ADR was suspected by the patient himself/herself then patients were advised to report it either through national helpline no 18001803024 or directly to AIIMS Patna, Department of Pharmacology dedicated landline helpline no. All these suspected ADRs were reported to NCC Ghaziabad through Vigiflow. Those ADRs which 1) required hospitalization or prolonged hospitalization, 2) Caused permanent disabling, 3) Leading to congenital anomaly, 4) were life threatening, and 5) led to death were labeled as serious ADRs. The causality, severity and preventability assessments were done by using appropriate scales by faculties and residents of the department and the PSPvA.

STATISTICS:

The data was recorded in Microsoft Excel Worksheet 2007 and analyzed using statistical package for social sciences (SPSS) for windows version 16. Descriptive statistics and percentages were applied to analyze data.

RESULTS:

Fig. 1: Total no of cases according to sex distribution

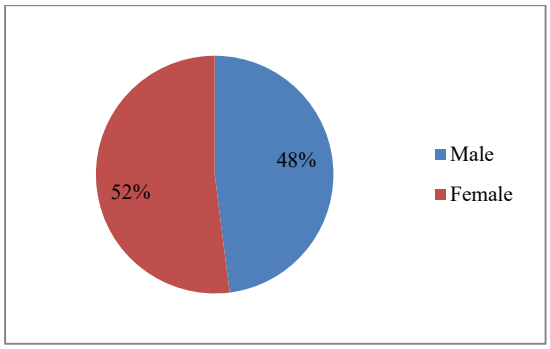

Fig. 2: Age wise distribution of ADRs

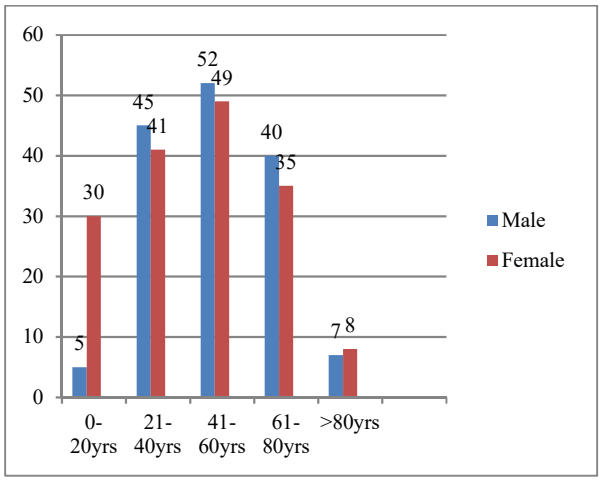

Table 1: Route of drug administration causing ADRs

Routes of drug administration	Number of ADRs (%)
Oral	132 (42%)
Parenteral	165 (53%)
Topical	10 (3%)
Inhalational	5 (2%)
Total	312 (100%)

Fig. 3: Department wise reporting of ADRs (Others include Gynecology, Anesthesia, Surgery, Ophthalmology and Paediatrics)

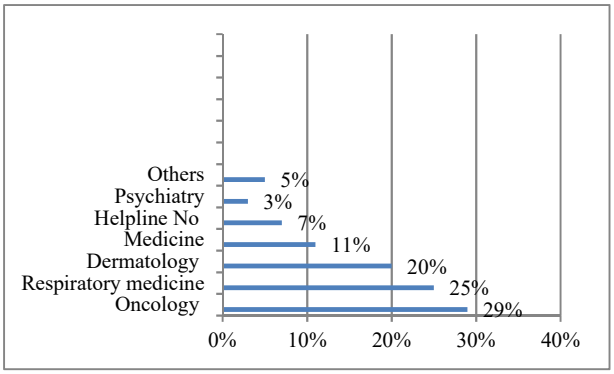

Fig. 4: System wise distribution of ADRs. Total 312 patients complained of 502 ADR

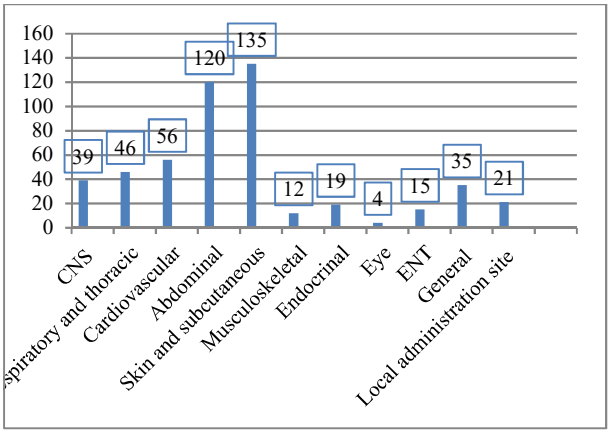

Table 2: Types of patients with ADRs

Types of patients	N (%)
Outpatients	141(45%)
Inpatients	171 (55%)
Total	312 (100%)

Table 3: ADRs according to types of reaction

Types of reaction	N (%)
Type A	191(61%)
Type B	121(39%)
Total	312(100%)

Table 4: Various groups reporting ADRs

Groups reporting ADRs	N (%)
Health care professionals (HCPs)	246 (79%)
Patients	66 (21%)
Total	312(100%)

Fig. 5: Among Health care Professionals reporting from various doctors (Others includes Nursing staff and students)

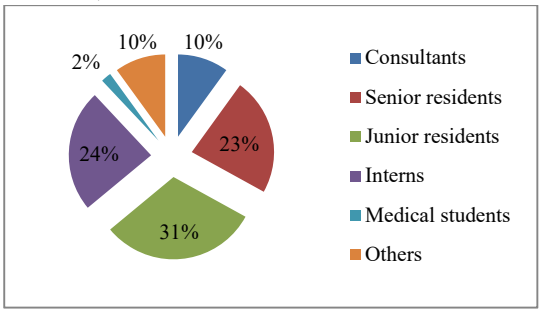

Fig. 6: Different class of drugs causing ADRs. (Others include Oral contraceptive pills, Diuretics, Antiemetics, Hypolipidemic drugs, Anti- ulcer and Iron)

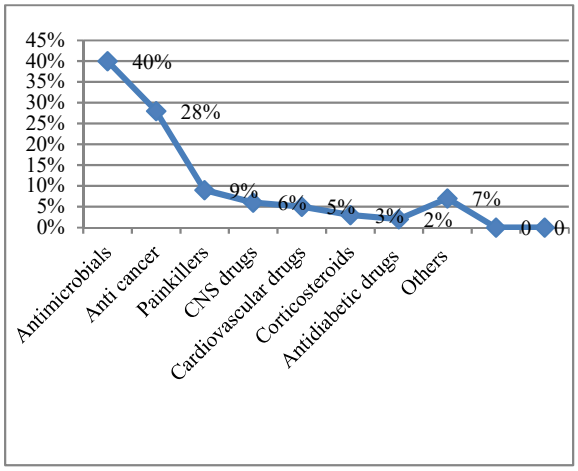

Table 5: Outcome of ADR

Outcome	N (%)
Recovered	151(48%)
Recovering	71 (23%)
Continued	46 (15%)
Loss to follow up	44 (14%)
Total	312 (100%)

Table 6: Causality assessment (WHO UMC SCALE)

Parameters	N (%)
Certain	10 (3%)
Probable	169 (54%)
Possible	133 (43%)
Total	312 (100%)

Table 7: Severity assessment (Adapted Hartwig scale)

Parameters	N (%)
Mild	144 (46%)
Moderate	152 (49%)
Severe	16 (5%)
Total	312 (100%)

Table 8: Preventability criteria (Modified Schumock and Thornton Criteria)

Parameters	N (%)
Definitely preventable	37 (12%)
Probably preventable	141 (45%)
Not preventable	134 (43%)
Total	312 (100%)

Fig.7: Comparing the incidence of our ADR Reporting with some other leading medical institute

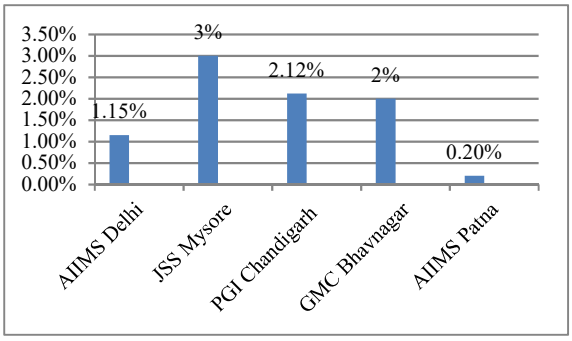

Table 9: Outcome assessment of suspected drug

Outcome	N (%)
Suspected drug stopped	251 (80%)
Suspected drug continued in same dose	37 (12%)
Suspected drug dose reduced	24 (8%)
Total	312 (100%)

DISCUSSION

In the present study a total of 312 ADRs were collected over a period of 24 months. All of them were uploaded on vigiflow and through it submitted to IPC Ghaziabad, the NCC for PvPI.In the present study ADRs occurred slightly more in 163 (52%) females than 149 (48%) in males (Figure-1). This result was in concordance with the results of several previous studies [17].

The patients within the age group between 41-60 were most commonly involved with slight male preponderance (Figure-2); a finding similar to the previous studies [19]. One reason for this is that after the age of ≥35, diseases like hypertension, diabetes, hypercholesterolemia etc. start manifesting necessitating polypharmacy and it's quite understandable that with polypharmacy there is an increased chance of ADRs. The most common route of drug administration in the present study was the parenteral route (n= 165, 53%) (Table-1). Oncology (29%) followed by Respiratory medicine, Dermatology and Medicine were the departments from where most ADRs were collected (Figure-3). There was relatively less reporting from Paediatrics, surgery and anaesthesia departments. The total no. of ADRs were 502 in 312 patients; most likely because many patients had multiple complaints. Skin was the most common system involved (Figure-4). This finding was similar to that seen in several previous studies [21]. Among all the ADRs only one was a newly detected reaction to the association drug (Amisulpiride induced Tinnitus) for which an alert was issued by NCC PvPI Ghaziabad, rest all were well known and documented. Most of the ADRs were collected from patients from the inpatient department. (Table-2). Similar results have been published in earlier studies also. [19] The overall incidence of ADRs was high in hospitalized patients. Total 16 patients were admitted based on seriousness of ADRs. Surprisingly, majority of the ADRs were Type- A (n=191, 61%) (Table-3). This study finding was unlike results given by previously conducted studies. [19]

ADRs were reported in the Department of Pharmacology of AIIMS Patna both by HCPs and by patients (Table-4). As is usual, reporting of ADRs by HCPs was significantly high (n=246, 79%) compared to patient reporting. Among HCPs (Figure-5) maximum reporting was done by junior residents (31%) followed by interns (24%) and senior residents (23%).However reporting from consultants and nursing staffs was on the lower side. The reasons for low reporting from consultants were fear of litigation, don't know what exactly to report, when and how to report an ADR, lack of time, the belief that a single ADR report will make no difference and complacency. One encouraging sign was that young doctors like interns, junior and senior residents were contributing more to ADR reporting; most likely a result of sensitization programs. The classes of drugs most commonly causing ADRs were also assessed. Here majority of the ADRs were caused by antimicrobials (40%) (Figure-6). This finding was similar to findings of numerous previous studies. [20] The reason could have been that antimicrobials are the most common class of drugs to be used in the hospital settings. So the chances of ADRs being reported due to themare also high. We also tried to find out the outcome of the ADRs by aggressive follow up. Majority of the patients had recovered (n=151, 48%) (Table-5) from the ADR at the time of discharge; some were lost to follow up (n=44, 14%).

Causality assessment of ADRs was done according to WHO UMC scale. Upon analysis it was seen that almost half of the ADRs (n=169, 54%) were probable (Table-6). Causality assessment usually yields similar results in most ADR studies. [17, 18, 19] The severity of ADRs was assessed according to Adapted Hartwig scale (Table-7). Most of the ADRs were categorized to be of moderate (n=152, 49%) to mild (n=144, 46%) intensity. This result was in accordance with the results of several such previous studies. [17, 20] The preventability of ADRs was determined by the Modified Schumock and Thornton criteria. Majority of ADRs appeared to be probably preventable (n=141, 46%) followed by not preventable (n= 134, 41%) and definitely preventable (n=37, 13%) (Table-8).

The total no of ICSRs submitted by some medical colleges, hospitals and pharmaceutical industries in the period of 26 months were 153340. We compared the submission rate of ICSRs from our institute with some of the other leading Institutes of the country. Here JSS Mysore led the chart (3%) followed by PGI

Chandigarh (2.12%) and GMC Bhavnagar (2%) (Figure-7). Our AMC contributed a small percentage (0.20%) to the total database of ICSRs from various institutions in Vigiflow. We also tried to find out the outcome of the suspected drug. Here (n=251, 80%) in majority of the patients the suspected drug was withdrawn (Table-9).

Comparison of the present study with some of the past studies in recent times on ADR analysis and monitoring:

Study by	Duration of study	No. of ADRs	Demographic pattern	Most common organ system	Commonest class of drug	Causality assessment
1.Sowmyanaraya. S et al[17]	Sept. 2016 - Aug. 2017	33	F > M 21-30 years	Skin	Antimicrobials	Probable (63.6%)
2. **Chakraborty A et al[18]**	May 2016 – June 2016	44	M > F 12 – 59 years	Gastrointestinal tract	Antimicrobials	Probable (56.81%)
3.Sen M et al[19]	March 2015 - April 2016	60	M > F 41-50 years	Skin	Antimicrobials	Probable (55%)
4. Akalu SD et al[20]	January 2013 - December 2016	228	M > F	Skin	Antimicrobials	Possible (55%)
5.Khot A et al[21]	April 2014-May 2015	120	F > M 61-70 yrs	Skin	Antineoplastic and immunomodulating agents	Possible (75.8%)

LIMITATIONS

The scope of the present study was grossly limited due to lesser no of total ADRs reported; along with poor reporting from consultants and nursing staffs. Also due to various ethical issues, re challenge was hardly, if ever performed; so the majority of the ADRs were under probable and possible causality assessment.

CONCLUSION:

From our study we concluded that females had more ADRs. Skin and subcutaneous tissue was the most common organ system affected. Antimicrobials were the most common class of drugs causing ADRs. Oncology department reported the highest no of ADRs. Majority of the patients with ADRs were inpatients ADR reporting from our institute was low compared to the other leading institutes. One reason of this could be that our AMC is quite new and hopefully ADR reporting from here on will only increase. One crucial and disappointing finding was that ADR reporting by the faculty was lesser than expected. This issue can be addressed with regular and frequent sensitization of HCPs making sure that senior consultants are a part of those sensitization programs along with the other HCPs. Majority of the patients recovered. Most of the ADRs were mild to moderate in severity and under Probable category. Most of the ADRs were probably preventable. ADR reporting is a continuous and evolving process. The current study as well as many such studies concurrently going on as well as being planned will definitely help to reinforce and suggest ways to better ADR reporting.

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ETHICAL APPROVAL:

The study was approved by the Institutional Review Committee of AIIMS Patna.

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