Original Article

Strengthen the Monitoring and Reporting of Adverse Drug Reaction at a Tertiary Teaching Hospital

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Abstract

Adverse Drug Reaction (ADR) is under-reported in India despite being the top producer of generic drugs in the world due to limited knowledge of the importance of reporting and monitoring ADR among the people of India; including the healthcare professionals. This perspective and observational study were designed to strengthen ADR monitoring over a period of six months based on medical records data analysis and personal interviews of patients. Data from various parameters were included in the evaluation like patient demographic characteristics, drug_profile, and drug reaction outcomes. The severity of drug reaction and predisposing factors were also assessed. The overall incidence rate of serious ADRs in the patient population as per reports was 0.24% and gender was not significant risk factor. The highest ADR rate was 59.61% in 19-64 years and the moderate ADR rate was 19.23% in the age group of 65 years and above in general medicine wards. The most common ADR was urticaria with rashes, with an antibiotic class of drugs (42.3%). The majority of ADR (Type A reaction) had moderate severity, thus most of them require intervention, out of which 48.07% of the patients received symptomatic treatment. The most common disposing factor was poly-pharmacy (82.69%). The results obtained will contribute to the design of a new program for the Pharmacovigilance services i.e., ADR monitoring and reporting in every hospital throughout the nation. The quality and quantity of ADR reporting by clinical pharmacists will be strengthened and improved, which ensure the safer use of drugs in hospitals.

Keywords: ADR monitoring, Pharmacovigilance, Drug safety, Naranjo's causality assessment scale

Introduction

India is also known as 'the pharmacy of the world' because of its massive production of generic drugs, therefore, an excellent healthcare system is a must-have, where every healthcare professional knows all possible risks and benefits of a drug, and are well-informed about the importance of monitoring and reporting ADRs to regulate and provide better quality drugs to ensure the safety of every patient [1]. Yet, a study shows that India's contribution to the global safety database (WHO) is only up to 3%, with a competence score of 0.93 out of 1. The percentage of total admission to hospital due to ADR was 0.7% out of which there is 1.8% death, whereas, in England, 0.9% of total hospital admissions were due to ADR, 1% in Austria, and 3.4-7% in Australia. This report shows that ADR is highly under-reported in India considering its population and status of drug production [2]. However, due to India being a developing country, the importance of implementing Pharmacovigilance services is not well understood by the majority of the people, including healthcare professionals. Despite its frequent occurrence, ADRs are greatly underreported due to the lack of official culture in its monitoring [3, 4].

Most of the ADRs occur due to medication error, drug interactions, polypharmacy, patient compliance, and sometimes, due to the use of counterfeit or substandard drugs. Unwanted reactions that occur due to deliberate excessive or accidental dosage and maladministration can be considered as adverse events [5, 6]. ADR adversely affects the patient's quality of life and is believed to occur almost every day in healthcare institutions throughout the country. ADR is one of the leading roots of morbidity, mortality, hospitalization, and increased healthcare costs in many countries [7]. This can be attributed to the lack of a proper Pharmacovigilance system in India. Therefore, robust and pro-active Pharmacovigilance (PV) services are the need of the hour [8].

A formal ADR monitoring was introduced and initiated back in 1986 under the observation of the Drug Controller

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General of India (DCGI) [3]. They brought a spotlight on the possible adverse impact of prescription medicines and stressed the need for rational prescribing. Thus, after much struggle, the National Programme of Pharmacovigilance (NPP) was established in 2005 which was then changed to the Pharmacovigilance Programme of India (PvPI) in 2010. Currently, there are 250 PvPI established ADR monitoring centers across the country [3, 7]. PvPI aims to protect the health of the Indian people by making sure that the advantages of medicines balance the risks of using them. PV works hard to establish a relationship of trust between the physician and the patients. It not only improves patient safety, but also boosts public confidence in the country's healthcare system and helps discover inferior drugs as well as prescribing, dispensing, and administration problems [9, 10]. However, all of these can be possible only if ADR reporting and monitoring are taken seriously by all; including the healthcare professionals [11, 12]. The information acquired from the research may be valuable in recognizing and reducing unnecessary ADRs, as well as improving healthcare personnel's abilities to control ADRs more effectively in general [13]. Over 20 million Individual Case Safety Reports (ICSRs) have been created and given to WHO-vigibase too far [5]. When we consider that India is home to around 15% of the world's population, this enormous number represents barely 1-2 percent when seen in a global context [7, 8].

The main goal of this study is to strengthen the Pharmacovigilance services in hospitals by undertaking ADR reporting and monitoring by regular passive surveillance of ADR which will create awareness among the healthcare professional of the institution and sensitize them to the importance of ADR detection and monitoring. This will, hopefully, lead to an increase in their engagement and will result not just in the quantification, but also, in an improvement in the ability for precise identification of ADR. The triggered alerts can then be evaluated to guide the kind of clinical interventions required to prevent the emergence of ADR and mitigation of actual ADR.

Materials and Methods

Not many reports on incidence of ADRs are available in North Indian hospitals. An Adverse Event Reporting System (AERS) has existed in this tertiary care hospital since 2014 under the supervision of clinical pharmacology department of teaching hospital. The ADR reporting unit of this hospital is one of the state's ADR monitoring centers (AMC) among 11 centers in the state. This study was conducted for a period of six months from September 2019 to February 2020 at the tertiary care hospital of Haryana state. This is an observational study, based on ADR collected from all the in-patients with suspected adverse drug reactions/side effects from various departments. The study protocol was approved by the Institutional Ethics Committee (IEC) of University with reference no. MMIMSR/IEC/2019 /1561.

Study Design and Patient Criteria

All the patients with suspected and reported ADR or side effects in general medicine, pediatrics, psychiatry, gynecology & obstetrics, and surgery departments were included in the study. Patients treated on an outpatient basis and admitted to intensive care units were not included in the research. All the relevant and necessary data was gathered by patients' case notes, treatment charts, laboratory reports, interviewing the patient or patient's caretaker(s), or any other relevant source.

Data Analysis

The reported ADRs were defined and categorized as per the operational guidelines framed by National Pharmacovigilance Programme of India (PvPI). The severity of reaction, onset time, predisposing factors, predictability, preventability, and outcome of the reaction were recorded for every suspected ADR. The identified ADRs were assessed by using Naranjo's Causality Assessment Scale, which categorizes ADRs into four different categories based on their respective scores *i.e*, doubtful (score=0), possible (score 1-4), probable (score 5-8), definite (score ≥9), [14].

The severity of the ADRs was also determined through the Modified Hartwig Scale, which classified them as extreme, moderate, or mild [15]. The ADRs' preventability was determined using Schumock and Thornton's criteria, and the ADRs were divided into three categories: possibly avoidable, definitely preventable, and preventable [16]. Each ADR was classed into Type A (augmented) or Type B (standard) according to Rawlins and Thompson's classification (bizarre) [17].

Statistical Analysis

Since the study is qualitative, only the mean and standard deviations are implicated for analyzing the data obtained. The methods that were used to present the information gathered were the use of the number, average ± standard error mean, and percentages.

Results and Discussion

We analyzed more than 250 patients during a period study period in different wards of a tertiary care hospital. Out of which a total of 52 ADRs were noticed, put down, and reported. People between 19 to 60 years of age (60%) are the majority of ADR patients, followed by 0 to 18years (21%) and the age group above 60 with the least (19%) numbers of ADRs reported. The study revealed that more male patients (64%) were affected compared with females (36%). However, gender was not found to be a predisposing factor for the reactions **(Table 1)**.

Table 1. Patient's demographic details

Data	(n=52)	Percentage
Gender		
Male	33	64%
Female	19	36%

Age Distribution		
0-18 yrs	11	21%
19-60 yrs	31	60%
Above 60 yrs	10	19%

The analysis showed that the general medicine department reported the highest number of ADRs (55.76%), followed by the respiratory department (21.15%), and the pediatrics department (15.38%). The departments of obstetrics & gynecology, psychiatry, dermatology, and surgery showed the least report which is less than 2% **(Table 2)**.

Table 2. Department wise ADR report

Departments	No. of ADR	Percentage
General Medicine	29	55.76%
Respiratory	11	21.15%
Paediatrics	8	15.38%
Surgery	1	1.92%
Dermatology	1	1.92%
Psychiatry	1	1.92%
Gynaecology	1	1.92%

According to an analysis of the system involved, the skin was the most affected (38.46%), followed by the gastrointestinal system (23.07%). The involvement of the nervous system was less than 20% (19.23%), followed by the endocrine system (9.61%), and respiratory system (5.76%). Muscular system and miscellaneous was found to be the least involved system with less than 2% each **(Table 3)**.

Table 3. System wise ADR reports

Systems	No. of Patients	Percentage
Integumentary system	20	38.46%
Gastrointestinal system	12	23.07%
Nervous system	10	19.23%
Endocrine system	5	9.61%
Respiratory system	3	5.76%
Muscular system	1	1.92%
Miscellaneous	1	1.92%

One day of hospitalization was the least amount of time before ADR development, the median time being 51.63 days, and the maximum time was seven years (delayed reaction due to chronic use of the drug). The reactions that were perceived within two weeks of hospitalization constituted 38.46% of total number of adverse reactions identified in this study. In this study, ATT shows the largest number of ADR (9.61%), followed by ceftriaxone and a combination of piperacillin & tazobactam with a percentage of 7.69%, then vancomycin, acetaminophen, phenytoin, and pantoprazole with 3.84% of ADR. The majority of the drugs which cause ADR were found to be from antibiotics (36.53%), followed by analgesic (9.61%), then antihypertensive drugs with less than 4%. All drugs were prescribed by oral route only **(Table 4)**.

Table 4. Drug-wise ADR

Drug Class	Name of Drug	Frequency of ADR	ADR reported
Antitubercular drugs	Streptomycin	1	Hepatitis,
	Isoniazid	1	Hepatitis
	ATT[1]	5	Gastritis, LFT[2] dysfunction, Mild Itching, discoloration of body secretion
Antibacterial drugs	Doxycycline	1	Severe diarrhea
	Gentamycin	1	Mild headache
	Cloxacillin	1	Chills & rigors
	Ceftriaxone	4	Rashes & red patches on face, urticaria, headache, dizziness
	Piperacillin+Tazobactam	2	Urticaria, vomiting, hemetemeis
	Amoxicillin+Clavulanic acid	1	Tingling sensation, mouth ulcers
	Meropenem	1	Skin lesions
	Moxifloxacin	1	Restlessness and urticaria
	Vancomycin	2	Urticaria, shivering, sweating, restlessness
	Amoxicillin+Dicloxicillin	1	Stomachache
	Metronidazole	1	Vomiting, abdominal pain
	Ofloxacin + Ornidazole	2	GI[3] distress, nausea, SJS[4]
	Cefotaxin	1	Urticaria
	Clarithromycin	1	Cough, breathlessness
	Piperacillin	1	Rashes,
	Cefotaxime	1	LFT[2] dysfunction
Antihypertensive drugs	Amlodipine+Atenolol	1	Bulloid pemphizoid, multiple erythemmatous plagues of various shapes, multiple lesions filled with fluid
	Ramipril	1	Severe dry cough

Analgesic	Naproxen	1	Constipation
	Baclofen	1	Hemiparesis
	Etodolac	1	Diarrhea
	Acetaminophen	1	Anaphylaxis(itching all over the body), erythema, lesions
	Tramadol	1	Seizure
Anti-depressant	Escitalopram	1	Gastritis
Antimalarial drug	Chloroquine	1	Headache
Antiviral drugs	Acyclovir	1	Rashes + Pruritis + Ataxia
Anticancer drugs	Imatinib	1	Pleural effusion
Anti-diabetic drugs	Tenepride	1	Urticarial rashes
Anti-epileptic drugs	Phenytoin	1	Pruritis, anxiety
Alpha-adrenergic blockers	Silidosin	1	Erythema, tingling sensation
Corticosteroids	Methylprednisolone	1	Itching, rashes
Miscellaneous	Omnipaque	1	Rashes, tingling sensation
	Iron capsule	1	Constipation

*[1]Antituberculer treatment, [2]Liver function test, [3]Gastrointestina, [4]Stevens-Johnson syndrome

The occurrence of ADR with respect to the organ system in this study was found to be highest in the skin with a total of 20 ADR reports (38.46%), followed by GIT with 12 ADR reports (23.07%), CNS with 10 ADRs (19.23%), endocrine with 5 ADRs (9.61%), respiratory with 3 ADRs (5.76%), muscular with 1 ADR (1.92%), and miscellaneous with 1 ADR (1.92%) **(Table 5)**.

Table 5. ADRs related to Organ System

SYSTEM	ADR	DRUG	No. of patients	Percentage
Skin	Urticarial rashes	Ceftriaxone, Methylprednisolone, Tenepride, Acetaminophen	5	38.46%
	Urticaria	Piperacillin + Tazobactam, ATT[1], Moxifloxacin, Vancomycin, Cefotaxin, Piperacillin, Pantoprazole	7	
	Rashes	Ceftriaxone, Silidosin, Acyclovir, Omnipague	4	
	SJS[2]	Ofloxacin + Ornidazole	1	
	Skin lesions	Meropenem, Acetaminophen	2	
	Sweating	Vancomycin	1	
GIT[3]	Diarrhea	Doxycycline	1	23.07%
	Gastritis	Escitalopram, ATT[1], Etodolac & Acetaminophen	3	
	Nausea and Vomiting	Pantoprazole, Piperacillin & Tazobactam, Metronidazole, Ofloxacin & Ornidazole	4	
	Constipation	Naproxen, iron capsules	2	
	Stomachache	Amoxicillin & Dicloxacillin	1	
	Hemetemesis	Tazobactam & Piperacillin	1	
CNS[4]	Dizziness	Phenytoin, Ceftriaxone	1	19.23%
	Seizure	Tramadol	1	
	Headache	Ceftiaxone, Chloroquine, Gentamycin	3	
	Restlessness (anxiety)	Moxifloxacin	1	
	Tingling sensation	Amoxicillin & Clavulanic acid, Omnipague	2	
	Chills & rigors	Cloxacillin	1	
	Drowsiness	Ompague	1	
Endocrine	Hepatitis	Streptomycin, ATT[1], Isoniazid	3	9.61%
	LFT[5] dysfunction	ATT[1], Cefotaxime	2	
Respiratory	Cough	Clarithromycin, Ramipril	2	5.76%
	Pleural effusion	Imatinib	1	
Muscular	Hemiparesis	Baclofen	1	1.92%
Misc[6]	Discolouration of body secretion	ATT[1]	1	1.92%

[1]Antitubercular treatment; [2]Stevens-Johnson syndrome; [3]Gastrointestinal tract, [4]Central nervous system, [5]Liver function test, [6]Miscellanous

According to Naranjo's Causality Assessment scale, the number of ADR reported as 'Probable' were 61.53%, 'Possible' with 34.61%, 'Definite' constituted 1.92%, and 'Unlikely' accounts only for 1.92%. Out of the total 52, ADRs reported, 29 were of Type A and 23 of Type B. Hypersensitivity reactions like, skin rashes are the most common way of spotting Type B reaction. No reactions could be attributed to categories C, D, E or F. Percentage calculations showed 55.76% and 44.23% occurrence for Category A and B respectively **(Figure 1)**. In this study, Type A reactions were considered as predictable, therefore the overall predictability of ADRs reported during the period of study period was 55.76%.

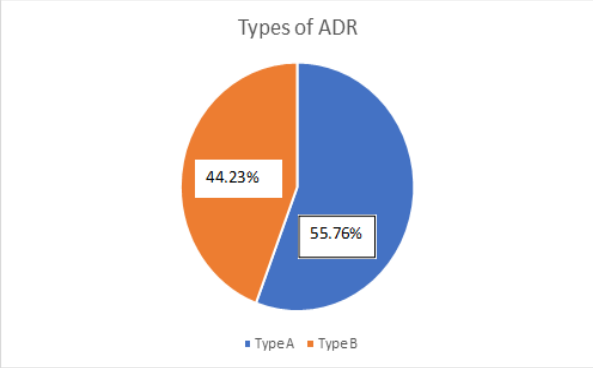

Figure 1. Graphical representation of types of ADR found in the study (Based on Rawlin & Thompson Classification of ADRs)

The Schumock and Thornton scale was used to determine preventability. ADRs were divided into three categories: those that were certainly preventable, those that were probably preventable, and those that were not preventable. The overall preventability rate was discovered to be 55.76 %. Assessment of severity showed 71.15% moderate, 26.92% mild, and 1.92% severe grades. The study's findings have the potential to raise awareness among healthcare practitioners about the effects of ADRs on therapy. The severity was determined using the modified Hartwig and Siegel scale. The majority of the reactions (34.61 %) were classified as Level 3. Level 4A responses accounted for 17 (32.69%) of all reactions. The total amount of reactions from other levels were 8(15.38%), 6 (11.55%), 1 (1.92%), and 1 (1.92%) belonging to Level 2, 1, 4B, and Level 5 grades respectively. No deadly reactions were witnessed with 75% of the patients attaining complete recovery and 25% of the patient's improvement were unknown **(Figure 2)**.

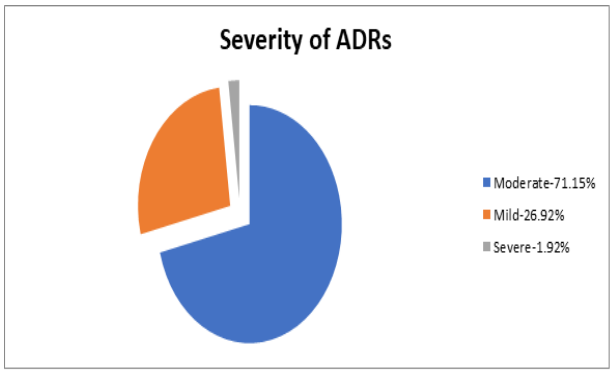

Figure 2. Graphical representation of different types of the severity of ADRs reported (According to Schumock and Thornton's severity assessment scale)

There are several predisposing factors among which polypharmacy constituted the highest percentage (82.69%) of ADR was seen, followed by age, intercurrent disease, chronic use, and genetic with 3.84% of total reports and use of contrast with 1.92%. Pharmacovigilance centers' primary function is to collect and process data on adverse drug reactions (ADRs) and to assist hospitals in identifying these events [12, 18]. The Centers' efforts are aimed at lowering medication-related risks, improving patient quality of life preventing iatrogenic disorders, and lowering healthcare costs. This study shows that at least 29 ADRs could have been avoided, which could help save healthcare system resources and reduce the harm brought to patients by the use of medication.

A total of 52 ADRs were reported to the Hospital's AMC within 6 months of the study period. There were a total of 20866 patients admitted to the hospital in six months of the study; 6128 in general medicine, 1671 in the orthopedics department, 214 in psychiatry, 3630 in obstetrics and gynecology, 3099 in the pediatric department, 1063 in the skin department, 3785 in general surgery, and 1276 in the respiratory department. The number of ADR reports submitted constitutes 0.24% of the total number of patients admitted in the hospital from departments of general medicine, gynecology and obstetrics, psychiatry, pediatrics, and surgery. Also, the total 136 ADRs reported constitutes only up to 0.65% of the total number of patients admitted to the hospital which is considerably low considering the number of inpatients. This shows the need for active participation of nurses, pharmacists, and physicians in monitoring and reporting ADRs as well as their need to be wary of possible medical complications by assessing the medicines that the patient has recently used. This should include not only medicines but the different kinds of food or food products that the patients may be allergic to, and whether the patient is breastfeeding, pregnant, or planning a pregnancy shortly. The frequency of ADRs found in this study could have been greater if every healthcare professionals were aware and participated in the process of ADR monitoring and reporting. The low number of reports

could also be attributed to the fact that data were obtained only from spontaneous reporting. Other elements that may have been the cause of low-level reporting include the non-reporting of very mild reactions and the nonexistence of bullet points and procedures for detection, registration, and reporting. Reluctance in reporting ADRs by nurses and physicians is also a factor that needs to be considered. This is due to the fact that reporting of ADRs could indicate clinical mistakes or low quality of care which could be believed to break the trust between a patient and his/her healthcare provider [9]. The majority of ADR in our study was related to the oral route [18]. This was in contrast to the study by Pathak *et al*., where the intravenous route was the major contributor [4].

In this investigation, there was no consensus on whether gender is a predisposing factor for ADR, which contrasts with a study by Pathak *et al*. [4], which found a higher frequency of ADR in males based on demographic data. Women are more sensitive to ADRs, according to some writers, potentially due to their high pharmaceutical use, obstetric problems, and metabolic changes due to hormone levels [10]. Other researchers have discovered that ADRs are unrelated to gender, which supports our conclusion that ADRs are not significantly different between men and women [13]. Several organ systems were observed to be influenced by various medications. The highest frequency of ADR occurred in the dermatological system (40.38%) manifested in the form of urticaria, rashes, SJS, skin lesions, and sweating. This is in contrast to a study done in Brazil where the orthopedic department reported the highest number of ADRs, however, this study result is similar to the result of a study done by Pathak *et al*., where the study showed the highest number of ADR in dermatology department [4, 13].

It was also observed that antibiotics caused the highest ADR rate (42.3%) followed by antitubercular drug (13.46%) and, analgesic - 9.61% of the total ADR reported. This is probably due to the high consumption and prescription of these drugs by physicians. However, in accordance with another study conducted by Pathak *et al*., the majority of ADR was caused by analgesics, followed by antibiotics [4]. In this study, the majority of the ADR was found to be a Type A reaction (55.76%), whereas, in the previous study, the majority of the ADR was found to be Type B [4].

In the current study, it was also observed that none of the patients are aware of their right or responsibility to report ADRs. Therefore, awareness regarding the importance of ADR reporting and guidance on how to report it must be taken up for the patients as well as for the other healthcare professionals and sensitize them to the importance and need of ADR monitoring and reporting. It was also observed that pharmacy students can be effectively utilized to strengthen the ADR reporting and monitoring as well as to educate the other healthcare professionals. If all the other healthcare professionals were to participate more actively in the process of ADR monitoring and reporting, this could widen the reporter base to a larger extent and strengthen the pharmacovigilance services more effectively in the hospital. This will ultimately lead to better patient care and decreased hospitalization.

Conclusion

The outcomes received will form a basis for the improvement of methods for the Pharmacovigilance services i.e., ADR monitoring and reporting at MMDU hospital and other hospitals countrywide. This will further improve and strengthen the quality and quantity of ADR reporting thus ensuring more benign use of drugs in Indian hospitals.

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