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A RETROSPECTIVE ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED TO AN ADVERSE DRUG MONITORING CENTRE OF PHARMACOVIGILANCE PROGRAMME OF INDIA IN A TERTIARY CARE HOSPITAL

Pharmaceutical Science

Dr. Darsana Suresh Kumar* Junior Resident, Sree Gokulam Medical College and Research Foundation *Corresponding Author

Dr. P. Shobha Professor, Sree Gokulam Medical College and Research Foundation

Dr. Messaline Sunitha Professor, Sree Gokulam Medical College and Research Foundation

ABSTRACT

Introduction: Pharmacovigilance plays an important role in the detection and analysis of new ADRs that occur once the drug enters the market. The objective of our study is to retrospectively analyze the adverse drug reaction (ADRs) reported to our tertiary Care Hospital over a period of six years. **Methods:** The ADRs were recorded in the Suspected Adverse Drug Reporting Form issued by the Indian Pharmacopoeia Commission, which was categorized as per the system affected and type of ADRs. Causality assessment, seriousness of reaction, and management were also analyzed. **Results:** Female patients (68%) were more affected than male patients (32%). Patients between the ages of 18- 65 most commonly experienced ADRs (65.6%). The most commonly affected organ system was skin and connective tissue (65.1%) followed by the immune system (9.9%). Amoxicillin-clavulanic acid (28) followed by tramadol (22), were the most commonly implicated drugs for causing the ADRs. The highest percentage of ADRs recorded were categorized as probable (95%). **Conclusion:** In conclusion, the skin and connective tissue was the most affected system followed by the immune system. The amoxicillin-clavulanic acid combination has caused maximum ADRs (28) followed by tramadol (22) and piroxicam (21). The causality analyses showed that the majority of ADRs were categorized as probable (95%). This pattern of ADRs is corresponding to results from other studies in India. These findings can be used to improve patient's safety and health outcomes in our demographic area. However, a more stringent ADR surveillance and reporting system should be implemented to overcome the disparity between occurrence and reporting of ADRs.

KEYWORDS

Pharmacovigilance, Adverse Drug reactions, PvPI, Drug Safety

INTRODUCTION

The World Health Organization (WHO) defines an Adverse Drug Reaction (ADR) as "a response to a medicine which is noxious and unintended and which occurs at doses normally used in man."(Jayanthi, 2018)

All drugs and vaccines go through extensive clinical trials to test their safety and efficacy before being available in the market. However, during the clinical trials, the drugs are studied for a relatively short period of time in a sample population. So, when these drugs enter the market and are used by a diverse population, including pregnant ladies, children, patients having comorbidities, other concomitant drug intake or for a longer period of time, previously unknown adverse drug reactions become apparent (*WHO Pharmacovigilance*, 2023). ADRs can cause significant morbidity, mortality, and financial burden for the patient. The significance of pharmacovigilance is to detect any adverse reaction occurring post- marketing, so that adequate guidelines may be implemented to ensure further safety(EMA, 2018; *Pharmacovigilance*, 2023). The research and practices around the identification, evaluation, comprehension, and prevention of side effects or any other concern pertaining to medications or vaccinations is known as pharmacovigilance (*WHO Pharmacovigilance*, 2023).

With the goal to monitor adverse drug reactions, CDSCO and the Indian Ministry of Health and Family Welfare established the National Pharmacovigilance Programme (NPP) in November 2004. The program was renamed the Pharmacovigilance Programme of India (PvPI) in 2010. The National Coordinating Center (NCC) for this program is the Indian Pharmacopoeia Commission (IPC), located in Ghaziabad. Throughout the nation, Adverse Drug Reaction Monitoring Centers (AMC) have been established to collect data on ADR, follow up with the reporter to check the completeness of the reports, and enter and report data to NCC through Vigiflow (*PvPI*, 2018). Through the program, the AMC at government and private medical colleges offers physicians training, feedback, and sensitization.

Our institution has been one of the AMC under the PvPI since April 21st,2016. The goal of the current study is to analyze ADRs that were reported to our tertiary care hospital.

METHODS

The ADRs that previously occurred in this AMC from the time of inception of the Pharmacovigilance unit (21/04/2016) onwards have been recorded in the Suspected Adverse Drug Reporting Form issued by the IPC.

The data until 31/12/2022 was entered into Microsoft Excel and analyzed. The results were categorized as follows:

1. Demographic profile of patients
2. Organ System Involved & Type and pattern as per Extended Rawlins–Thompson(Aronson & Ferner, 2003) classification of adverse drug reactions.
3. Causative drugs
4. Management: Drug withheld, drug continued with reduced dose, drug continued
5. Causality assessment: WHO-UMC scale (WHO, 2023) classifies ADRs as certain, probable, possible, or unlikely

Approval was taken from the Institutional Ethics Committee before the commencement of the study, and at every stage of the study, patient details and other identification were kept confidential.

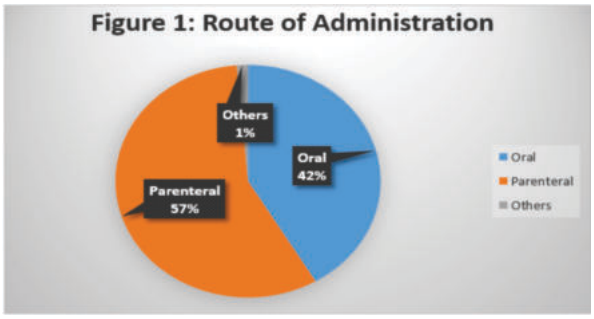
RESULTS

During our study period a total of 354 ADRs were reported, out of which 294 was analyzed. The remaining ADRs were excluded as per protocol due to incomplete data recorded. A total of 68 % of the ADRs were seen in female patients which was significantly higher than in male patients (32%). The highest number of ADRs was 193 (65.6%) recorded in patients of age group 18-65 years, while 75 (25.5%) ADRs were seen in patients above 65 years and remaining 26 (8.9%) was seen in the 0-17 years age group as shown in Table 1.

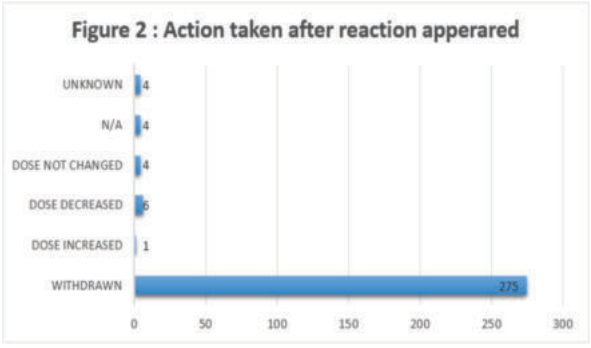
The most frequently used route of administration was parenteral (57%) followed by oral (42%) (Figure 1).

Table 1: Demographic Details of patients who experienced an ADR

Gender		
	Total no. 294	Percentage, %
Male	94	32
Female	200	68
Age distribution		
0-17 years	26	8.9
18-65 years	193	65.6
> 65 years	75	25.5



In 275 (93.5%) cases, the drug was withdrawn immediately after the reaction, while in 6 (2.2%) cases the dose was decreased (Figure 2).



We classified the ADRs according to the system that was affected which is shown in Table 2. It was found that the most commonly affected system was skin and connective tissue (191 (65.1%)), in which urticaria and Maculo-papular rashes were seen the most. Serous cutaneous reactions like Steven-Johnson Syndrome / Toxic Epidermo-necrolysis Syndrome (SJS/TENs) was seen in five patients. Immune system disorders were the next commonly occurring ADRs (9.9%). Anaphylactic shock and angioedema (12 cases) were the frequently encountered immune system disorders.

Table 2: Frequency of ADR symptoms based on the organ system involved

Systems	ADR symptoms n (%) 294 (100)	Most common ADRs (n)
Skin and connective tissue	191(65.1)	Urticaria (67), Induration (34), Maculo-papular rash (64), SJS-TENS (5)
Gastrointestinal System	15(4.9)	Abdominal Pain (4), GI Bleed (5), Vomiting (5)
Central Nervous System	8(2.7)	Vertigo (4), Tremor, Seizure, Numbness, Parkinsonism-1
Respiratory System	4(1.4)	Cough (2), Saturation fall (2)
General disorders	11(4.4)	Shivering (6), Fatigue (3), Facial puffiness (2)
Blood and lymphatic system	3(1.02)	Agranulocytosis (3)
CVS	7(2.4)	Bipedal edema (4), Hypotension (3)
Renal	1(0.34)	Acute renal injury (1)
Endocrine	2(0.67)	Hyperglycemia (2)
Immune system disorders	29(9.9)	Anaphylaxis & Angioedema (12), Breathing difficulty (5), Generalized Itching (7), Fever (3), Generalized edema (2)
Electrolyte disorder	19(6.5)	Hypokalemia (5), Hyponatremia (14)
Musculoskeletal system	2(0.67)	Myalgia (2)
Ophthalmic	5(1.69)	Swelling (2), Eye Congestion (2), Edema (1)

According to our analysis as shown in figure 3, Amoxicillin-clavulanic acid combination has caused the highest number of ADRs (28), followed by tramadol (22) and piroxicam (21).

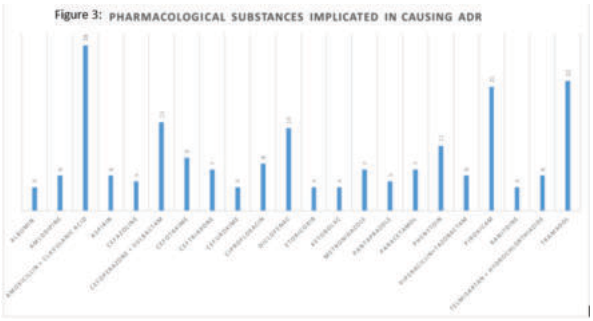


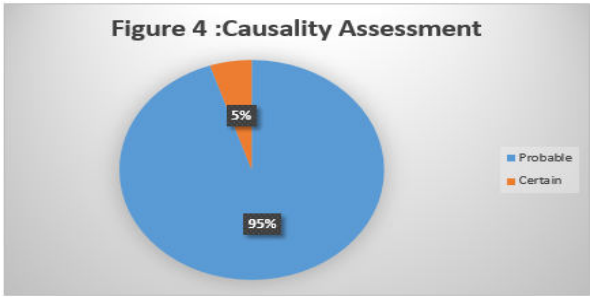
Figure 3:

The most frequently implicated drug causing specific ADR symptom is highlighted in Table 3. Urticaria was most commonly caused by Tramadol (9) and Amoxicillin-Clavulanic combination (8). Maculo-papular rash was most frequently associated with Amoxicillin-clavulanic acid combination (14). Hydrochlorothiazide (12) was frequently associated with hyponatremia.

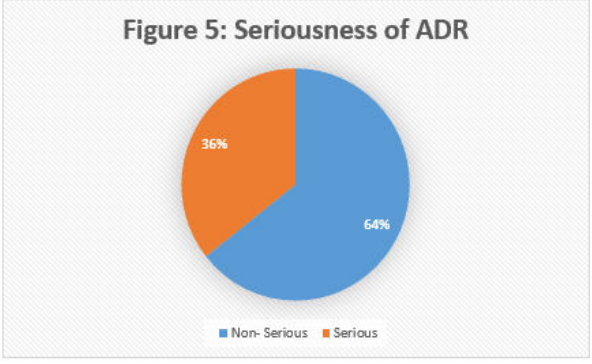
Table 3: ADR symptoms with the most frequently implicated causative drug

ADR symptom (n)	Name of the drug, suspected for the ADR symptom (n)
Urticaria (67)	Amoxicillin- Clavulanic (8), Cefoperazone + Sulbactam (7), Paracetamol (5), Tramadol (9)
Maculo-papular rash (64)	Amoxicillin- Clavulanic (14), Phenytoin (5), Piroxicam (8), Tramadol (6)
Induration (34)	Diclofenac (7), Piroxicam (8), Tramadol (5)
Hyponatremia (14)	Hydrochlorothiazide (12), Telmisartan (6), Losartan (3)
Anaphylaxis (10)	Cefazolin (3), Cefotaxime (2),
Shivering (6)	Pantoprazole (2), Albumin (2)

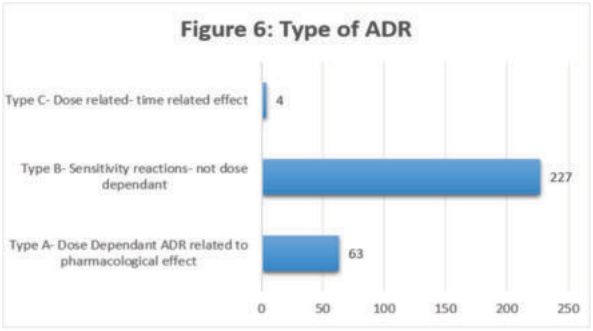
According to the WHO-UMC classification of ADRs, the largest number of ADRs (95%) recorded was probable and only 5% of ADRs satisfied the certain category (Figure 4). There were no ADRs satisfying the possible or unlikely category.



As depicted in Figure 5, 106 patients experienced a serious ADR, as they required hospitalization or prolongation of hospital stay, or experienced a life-threatening ADR. The remaining majority of patients (188) experienced a non-serious ADR.



On further analysis of the ADRs, as per extended Rawlins–Thompson classification of adverse drug reactions, 227 of the reactions were due to hypersensitivity and not dose-dependent (Type B), while 63 reactions were dose-dependent related to the pharmacological effect of the drug (Type A) and 4 ADRs occurred due to the dose-related and time-related effects of the drug (Type C) (Figure 4).



DISCUSSION

As per reports, India is the largest provider of generic drugs and has a robust domestic market(Government of India, 2022). A large number of novel medications are being introduced onto the market and hence, pharmacovigilance plays a significant role in detecting any new noxious effects of the drugs during the post-marketing phase. However, there is a significant difference between the occurrence and reporting of the ADR in our country and worldwide(Dutta et al., 2020; KC et al., 2013; Venkatasubbaiah et al., 2018). In our study, the ADRs reported to the institution for the past 6 years were analyzed.

The incidence of ADRs is influenced by a number of factors, including patient age, gender, and drug usage history, length of hospital stay, genetics, ethnicity, diet, and environment(Alomar, 2014; Yaya, 2016). The majority of the patients belonged to the age group of 18-65 years which is similar to the previous study (Sharma et al., 2021) where the common age group was 19- 65 years. This is due to the broad age range and the likelihood that this is the primary population receiving medication therapy and frequent hospital visits. There is also a higher proportion of patients having polypharmacy and concomitant diseases. This can be may be reduced by safe medication practices like rational prescription and deprescribing.

In accordance with previous research (Sundaran et al., 2018; Zopf et al., 2008), considerably more ADRs were recorded in female patients than in male patients in our study. However, a small number of studies have also noted a male preponderance (Sen et al., 2018; Sharma et al., 2021). Despite this, the impact of gender on the occurrence of ADRs cannot be explained in this context; it may be an incidental finding that has no bearing on the reporting of ADRs.

Parenteral route was the most frequently used route of drug administration which led to an occurrence of ADR, followed by oral route which was reflected in the study by Sen et al (Sen et al., 2018). However, this was in contrast to other studies where oral was the most common route of drug administration (Sona Bharti Kaushal, 2020; Sharma et al., 2021).

The most common organ system affected was skin and cutaneous tissue (65.1%). This finding is consistent with the study by Kirti Saxena et al (Saxena et al., 2017). Similarly immune system disorders were the second most commonly affected system which was in concurrence with other studies done (Sharma et al., 2021).

Amoxicillin-Clavulanic acid (28 cases) was the most commonly implicated medication specific to our center, in contrast to other researches that identified Zidovudine or Ceftriaxone as the most frequently suspected drugs (Sharma et al., 2021; Thakare et al., 2022). This may be due to the difference in prescription patterns between the centers.

In our study, the maximum number of ADRs were categorized as probable (95%) which reflects the results of previous studies (Saxena et al., 2017; Sharma et al., 2021). The remaining ADRs fell into the Certain category (5%). Patients who had a reappearance of the same ADR on re-exposure to the same drug was categorized as certain.

The greatest number of the cases in our research were categorized as sensitivity reactions and not dose-dependent (Type B) (227) ADRs, according to extended Rawlins and Thompson's classification, followed by Type A reaction (63), which dose-dependent reactions related to the pharmacological effect of the drug. This was comparable with results from another retrospective analysis (Sen et al., 2018).

This study analyzed the ADR reports recorded in the prescribed form by the Pharmacovigilance unit of the Institution during the past 6 years. Therefore, it was possible to identify the drugs most frequently associated with ADRs. These findings can be used to improve patients' safety and health outcomes. However, it may be possible that there is a disparity in the occurrence and reporting of ADRs, and hence the data may not be a true representation of the population. Therefore, more stringent ADR surveillance and reporting system should be implemented to overcome this lacuna.

CONCLUSION

In conclusion, the skin and connective tissue was most affected system followed by immune system. Amoxicillin-Clavulanic acid combination has caused maximum ADRs (28) followed by tramadol (22) and piroxicam (21). The causality analyses showed that majority of ADRs were categorized probable (95%). This pattern of ADRs is corresponding to results from other studies in India. These findings can be used to improve patients' safety and health outcomes in our demographic area. However, more stringent ADR surveillance and reporting system should be implemented to overcome the disparity between occurrence and reporting of ADRs.

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