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Research Article

A PROSPECTIVE OBSERVATIONAL STUDY OF MONITORING AND REPORTING OF ANTIMICROBIAL DRUGS ASSOCIATED ADVERSE DRUG REACTIONS AND THEIR SIGNIFICANCE ON PATIENTS SAFETY AND HEALTH-CARE OUTCOMES

ZEENATH UNNISSA[1]*, MAHER UNISSA[2], SHAISTA KHAN[3], NAZIYA THASLEEM[4], NIKHATH FATIMA[5]

[1]Department of Pharmacy Practice, Deccan School of Pharmacy, Dar-us-Salam, Hyderabad, Telangana, India. [2]Department of Pharmacy Practice, Deccan School of Pharmacy, Hyderabad, Telangana, India.
*Corresponding author: Zeenath Unnissa, Email: Zeenathunnissa9848@gmail.com

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ABSTRACT

Objective: Adverse drug reaction (ADR) surveillance and reporting practices are at an early stage of development within the Indian context. The pharmacovigilance rate in India falls below 1%, which is notably lower compared to the global average of 5%. India holds the position of being the fourth most significant contributor to the pharmaceutical industry worldwide. Therefore, there exists a pressing demand to enhance the pharmacovigilance framework for safeguarding the health of the Indian population. ADR is defined as the unintended, obnoxious, and unwanted reaction due to the use of a drug. The administration of antimicrobial agents causes various ADR that has been analyzed throughout the study. The main objective of the research is to monitor and report the adverse drug reaction caused by antimicrobial drugs

Methods: A prospective observational study was carried out in the various departments of the hospital with duration of 3 months including 100 patients using patient profile form and ADR reporting forms and analyzing with the scales for causality, severity, and preventability assessment.

Results: During the study, 29 ADRs were found among 100 patients, with an incidence rate of 9.6%, more common in females (52%) than in males (48%). ADRs were most frequently reported in the age group of 35–51 years (34%), then 18–34 years (28%), and 1–17 years (24%). The general medicine department reported the highest number of ADRs (66%), followed by the pediatric department (24%). Cephalosporins caused the most ADRs (35%). Common ADRs included constipation, diarrhea (34%) and rashes, nausea, and vomiting (34%). Naranjo scale indicated that the causality of ADRs was probable (52%). Hartwig severity scale showed 55% ADRS to be mild. Schumock and Thornton method found that 76% of ADRs were preventable.Management of most of ADRs included drug withdrawal (52%).

Conclusion: The majority of cephalosporin-related side effects, which included constipation, diarrhoea, and rashes, were observed. Most of the patients got better with the help of ADR monitoring and management. Finding and treating drug-related problems early make patients feel better and keep them safe. This study shows health-care system why it is important to monitor and report ADR caused by drugs.

Keywords: Pharmacovigilance, Adverse drug reaction, Antimicrobial agents, Patient safety, Assessment of adverse drug reaction

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INTRODUCTION

Pharmacovigilance refers to the monitoring and assessment of adverse effects related to pharmaceutical products. The Pharmacovigilance Programme of India (PvPI) is a flagship drug safety-monitoring program of the Government of India. The program aims to protect national health by identifying and responding to drug safety issues. PvPI is now recognized as a World Health Organization (WHO) collaborating Centre for Pharmacovigilance in Health Programs and Regulatory Services. By identifying adverse events and taking corrective actions, PvPI contributes to safer medication use in India [1].

It is imperative that harmful effects and toxicity are reported and examined, and their importance is clearly conveyed to the audience with the necessary knowledge to understand the information, particularly when they were previously unknown. At present, the impact of adverse drug reactions (ADRs) on public health is considerable, even with the advancements in pharmacovigilance. It is becoming more evident, nevertheless, that the socio-political, economic, and cultural aspects of society have a direct bearing on the safety profile of pharmaceuticals. These elements also influence public perceptions, access to pharmaceuticals, and patterns of their use [2].

ADR

As per the WHO (1972), ADRs are adverse and inadvertent reactions to drugs that are typically administered to humans for the purpose of disease prevention, diagnosis, treatment, or alteration of physiological function at doses that are typical [3]. Doctors, clinical pharmacists, and nurses play a crucial role in monitoring and reporting ADR among health-care professionals. It is essential to establish an effective system for reporting ADR to prioritize patient safety and high-quality care [4].

Antimicrobial agents (Fig. 1)

It refers to a group of agents working together to reduce the risk of infection and sepsis. Antibiotics, which are typically derived from molds or synthesized, are ingested to either kill or prevent the growth of bacteria [5]. Antimicrobial therapy aims to destroy or inhibit the infected organism without harming the host [6] shown in Fig. 1.

Adverse effects of antimicrobial drugs

There are two types of adverse effects caused by antimicrobial agents

01. Directly causing-Allergies, Toxicity, Drug–drug interaction, or Therapeutic failure
02. Indirect effects on commensal flora (e.g., Clostridium difficile infection in humans, higher risk of drug-resistant infections in animals) and environmental flora [7].

METHODS

The current prospective observational study was carried out at a tertiary care hospital for 4 months, from April to June 2024. All patient

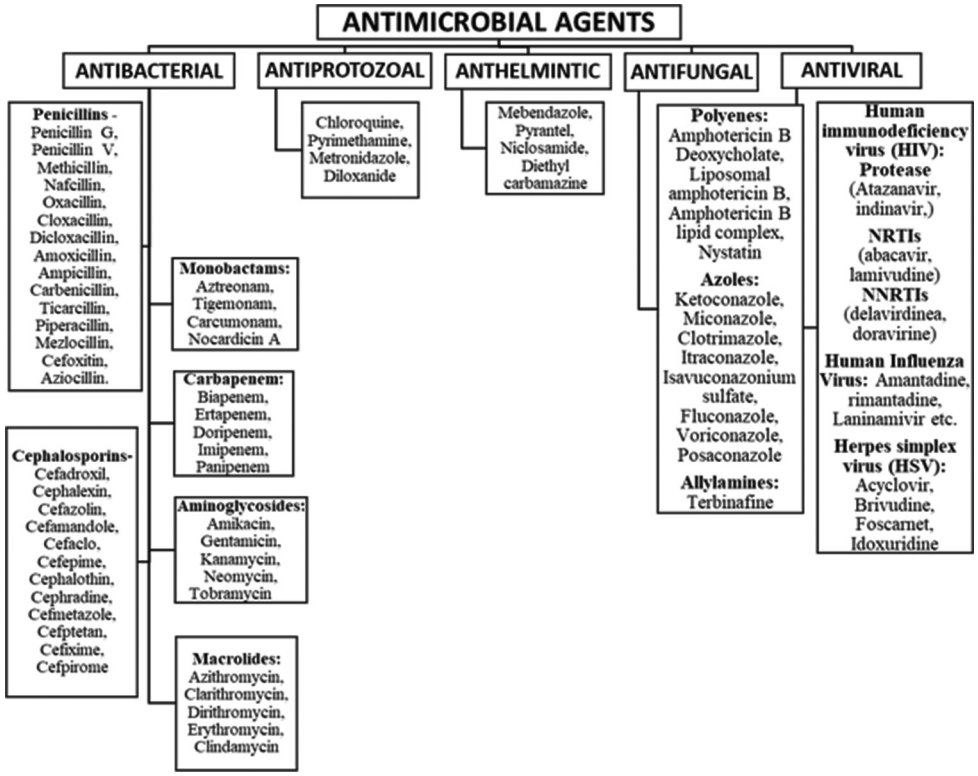

Fig 1: Classification of antimicrobial drugs

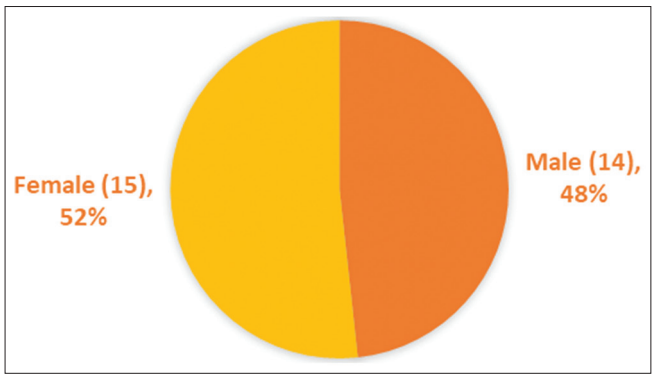

Fig 2: Gender distribution among adverse drug reactions

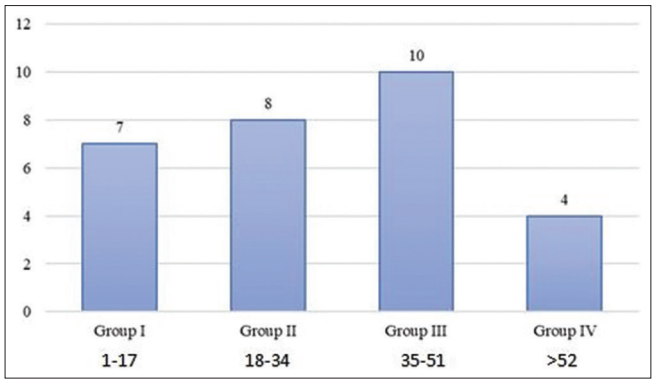

Fig 3: Age-wise distribution among adverse drug reactions

have given consent for involvement in the study. This study included 29 patients. Patients with inclusion criteria were divided into different age groups: 0–17 years, 17–34 years, 35–51 years, and >52 years, ADR

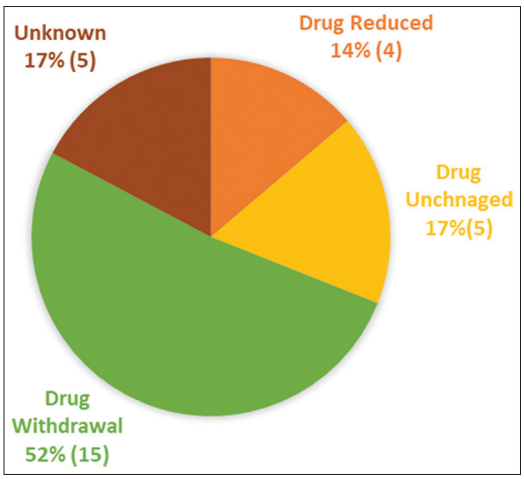

Fig 4: Management of adverse drug reaction with number of patient and percentages

reports of in patients of different departments of the hospital. Exclusion criteria included patients who were admitted in psychiatric ward and intensive care unit were excluded from the study. Some patients who were not willing to participate.

Data collection

All patients gave written informed consent before participation in the study. The patient data were collected through history interview and from the case sheets of in-patient then documented in a suitably designed case record form.

Study methodology

The type of ADR and other pertinent data, such as demographics, type of reaction, drugs used, management, and result of the reactions, were studied while data confidentiality of patient was preserved.

Statistical analysis

The causality assessment was determined using the Naranjo Probability Assessment Scale, the Severity Assessment was performed using the Hartwig severity assessment scale, and the Preventability Assessment was completed using the Schumock and Thornton approach. Data were presented in the form of tables and graphs/pie charts using Microsoft Excel.

Table 1: Departments affected by adverse drug reactions with percentages

Departments	Number of ADRs	Percentage (n=29)
General medicine	19	66
Pediatrics	07	24
Orthopedics	02	7
Gastroenterology	01	3

ADRs: Adverse drug reactions

Table 2: Classes of AMAs with percentages

Antimicrobials drugs	Number of ADRs	Percentage (n=29)
Cephalosporins	10	35
Antiprotozoal	04	14
Fluoroquinolones	03	10
Oxazolidinone	03	10
Penicillin	03	10
Aminoglycosides	02	7
Antitubercular	01	4
β-Lactamase inhibitor	01	4
Macrolide	01	3
Antifungal	01	3

ADRs: Adverse drug reactions

RESULTS

In this study, we have represented categorical data such as age, gender, department, different antimicrobials, types of ADRs, outcome of ADRs, causality, severity, and preventability assessment data as percentages. A total of 100 patients participated in our research. Data were gathered from in patients across various departments. The patients were accordingly chosen based on specific inclusion criteria which is grouping patients by age wise and department wise, and those who did not meet this criterion were excluded from the study.

Gender distribution (Fig. 2)

Among the 100 patients, 29 ADRs were monitored, resulting in an incidence rate of 9.6% out of which female patients were 15 (52%) when compared to male patients, which were 14 (48%) and is represneted in Fig. 2.

Age distribution (Fig. 3)

We observed that a greater number of ADRs were seen in 35–51 years of age group (Group III), i.e., 10 (34%), followed by 8 ADRs (28%) in the 18–34 years (Group II), 7 ADRs (24%) were observed in 1–17 years (Group I), and >52 years (Group IV) 4 ADRs (14%) were observed and that is shown in Fig. 3.

Distribution based on department (Table 1)

ADRs are differentiated according to the department, i.e., general medicine, pediatrics, gastroenterology, and orthopedics. ADRs were found majority in the general medicine department compared to the others. Out of 29 patients, 19 patients were of the general department, 7 patients of pediatric, 2 patients of orthopedic, and 1 case was reported in gastroenterology, that is seen in Table 1.

Distribution based on different antimicrobials frequency (Table 2)

Among all the classes of antimicrobials, antibiotics were found to cause majority of ADRs than other classes. Among antibiotics,

Table 3: Nature of reaction and distribution among systems

Systems affected and their ADR	Number of ADR (n=29)	Percentage	Suspected drugs
Gastrointestinal system disorder	n=19	66	
Diarrhea	5	17	Ceftriaxone Clarithromycin Ofloxacin Cefepime Linezolid
Constipation	5	17	Ceftriaxone Ofloxacin Metronidazole
Vomiting	3	10	Linezolid Neomycin
Nausea	3	10	Cefepime Amoxicillin Amikacin
Malena	1	4	Cefixime
Abdominal pain	1	4	Ceftriaxone
Metallic taste	1	3	Metronidazole
Skin disorders	n=4 (14%)	14	
Rashes	4	14	Ofloxacin Cefotaxime Rifampicin Caspofungin
Central nervous system disorder	n=3 (10%)	10	
Headache	1	4	Metronidazole
Dizziness	1	3	Metronidazole
Insomnia	1	3	Amoxicillin
Pulmonary system disorders	n=2 (7%)	7	
Difficulty in breathing	1	4	Amoxicillin
Cough	1	3	Piperacillin
Musculoskeletal disorder	n=1	1	
Joint pain	1	1	Ofloxacin

ADR: Adverse drug reaction

Table 4: Assessments of adverse drug reactions

Type of assessment	Number of ADR	Percentage (n=29)
Causality assessment (Naranjo scale)		
Probable	15	52
Possible	8	28
Unlikely	5	17
Certain	1	3
Severity assessment (Hartwig scale)		
Mild	16	55
Moderate	11	23
Severe	2	7
Preventability assessment (Schumock and Thornton Method)		
Definite	22	76
Probable	6	21
Unknown	1	3

ADR: Adverse drug reaction

Table 5: Common doses of antimicrobial agents causing adverse drug reactions

Suspected drug	Common dose	Adverse reaction
Fluoroquinolones Ex: Ofloxacin	200–400 mg PO	Rashes, constipation, diarrhea, pain in Joints
Cephalosporin Ex: Cefotaxime Ceftriaxone Cefepime Cefoperazone	250–500 mg PO	Rashes, constipation, malena, diarrhea abdominal pain, nausea
Penicillin Ex: Amoxicillin	250–500 mg PO	Insomnia, difficulty in breathing, nausea
Anti-tubercular Ex: Rifampicin	300–900 mg PO	Rashes
Macrolide Ex: Clarithromycin	500 mg IV	Diarrhea
Aminoglycosides Ex: Neomycin Amikacin	10 mg/kg QD	Vomiting, nausea
Antifungal Ex: Caspofungin	60–70 mg/kg PO	Rashes
Oxazolidinone Ex: Linezolid	600 mg PO/IV	Vomiting, diarrhea
Antiprotozoal Ex: Metronidazole	60 mg/kg PO	Headache, metallic taste, constipation, dizziness
β-lactamase inhibitor Ex: Piperacillin	250 mg BID	Cough

cephalosporins caused ADRs in 10 patients (35%), antiprotozoal caused ADRs in 4 patients (14%), fluoroquinolones, oxazolidinone, and penicillin caused 3 ADRs in each class (30%), 2 ADRs (7%) in aminoglycosides and β-lactamase inhibitor, antitubercular, and macrolides, and antifungal caused 4 ADRs (14%) which is represented in Table 2.

Nature of reaction and organ system affected (Table 3)

Type of ADR seen among 29 patients in different departments is as follows: 10 cases showed constipation and diarrhea as an ADR (34%), 4 cases of rashes (14%), 6 cases of nausea and vomiting (20%), and 1 ADR each of joint pain, malena, headache, dizziness, abdominal pain, metallic taste in mouth, insomnia, cough, and difficulty in breathing (32%). The disorders associated by ADRs that affect the body systems include the gastrointestinal system disorder causing 66% of ADRs, skin disorders causing 14%, central nervous system disorder accounting for 10% of ADR, pulmonary system disorder causing 7% of ADRs, and musculoskeletal system disorders causing 1% of ADRs which is shown in Table 3.

Assessment of ADRs (Fig. 4)

a. Causality: The causality assessment was performed using the Naranjo Scale, in which the causality of the ADRs was obtained. The current data show the probable, possible, unlikely, and certain about the causality of ADR among the patients.
b. Severity: The severity assessment of ADRs was categorized using the Hartwig severity assessment scale, in which the extent of the ADR was estimated predicting it to be mild, moderate, and severe.
c. Preventability: The preventability of such ADRs was calculated using Schumock and Thornton method, which indicated that a greater number of ADR caused by the suspected drug can definitely be prevented which is seen in Fig 4.

Management of ADR (Table 4)

The management of ADR was done by withdrawing the drug, reducing the drug, no change in the drug treatment, and unknown. About 15 patients experiencing ADRs had drug withdrawal (52%), and 5 patient's drugs remain unchanged (17%) while 4 patients had drugs with reduced dose (14%) and 5 ADRs had unknown outcome (17%) which can be seen in Table 4.

Some of the common antimicrobial agents and their doses which are leading cause of the Adverse drug reaction in patients are seen in Table 5.

DISCUSSION

The findings where females were reported more in number were in the study conducted by Kumar *et al*. [8] and Rani *et al*. [9] and male preponderance was seen in the study of Singh *et al*. [10] The present study monitored ADRs among inpatients across various departments in a tertiary care hospital over a 3-month period, documenting the reported cases. It is evident that women are more to experience ADRs than men. This disparity can be attributed to numerous physiological differences where women have divergent metabolism and comorbidities than men.

Age significantly influences the likelihood of experiencing ADRs. The highest incidence of ADR reported in the study conducted by Singh *et al*. [10] was the age group range of 41–50 (21.25%) and in study of Kumar *et al*. [8], age group 21–40 years were most commonly involved. In our analysis, patients aged 35–51 years had the highest incidence of ADRs, accounting for 34% of cases. This was due to the more visits of adults of age group 35–51 for antimicrobial use during the observational period.

The predominance of ADR can be seen in general medicine department and the Pediatric department in study conducted by Rani *et al*. [9] In our study, the highest number of ADRs were reported in the general medicine department, accounting for 19 cases (66%), followed by the Paediatrics department with 7 cases (24%).

According to the study by Kumar *et al*. [8] and Rani *et al*., [9] cephalosporin was most commonly prescribed as antimicrobial agent and in study conducted by Patel *et al*. [11] showed that more prescribed antimicrobial was β-lactamase inhibitors and fluoroquinolones. In our surveillance, maximum number of ADRs in antimicrobial agents was caused by cephalosporins having ADRs in 10 patients (35%) and antiprotozoal having ADRs in 4 patients (14%)

In the studies of Rani *et al.* [9] and Singh *et al.*, [10] most of the ADRs affected the skin and GI. This result was in concordance with our study where most of the adverse reactions (ADRs) were mild, with diarrhoea and constipation making up 34% of all reported cases, followed by skin rashes, nausea, and vomiting at 34%. This is because the adverse drug reaction caused by antimicrobial agents affects the skin and GI system. These ADRs can typically be managed by discontinuing the medication or switching to an alternative.

According to the study conducted by Alam *et al*., [12] the gastrointestinal system was more affected than other systems, which shows

concordance with our study accounting for 66% of GI system disorders such as constipation, diarrhea, vomiting, nausea, malena, metallic taste, and abdominal pains.

The causality of ADRs was determined using the Naranjo causality assessment scale. The result in studies conducted by Kumar *et al*. [8] and Patel *et al*. [11] shows that the most of the ADR was categorized under probable and was categorized under possible in the study of Belhekar *et al*. [13]. In our monitoring, the results indicated that most ADRs were categorized as probable (52%), followed by 8 ADRs as possible (28%), 5 ADRs as unlikely (17%), and 1 ADRs as certain (3%).

The pattern of severity assessment studies shows that the majority of the ADR were mild in Belhekar *et al.* [13] and moderate in Singh *et al.* [10] and Patel *et al.* [11]. In our findings, according to the Hartwig severity assessment scale, the majority of ADRs were mild and resolved during the study period. The adverse events observed ranged from mild to moderate severity, with about 7% classified as severe. No fatal cases were reported.

The preventability assessment was calculated using Schumock and Thornton method. In the study of Belhekar *et al*., [13] the majority of the ADRs were definitely prevented. In our scrutiny, about 22 ADRs were definitely prevented (76%), and 6 ADRs were probably prevented (21%) and 1 ADR was found to be not preventable (3%).

In the study conducted by Patel *et al.*, [11] the management of ADR was done by the withdrawal of the drug. In our observation, management of ADRs involved drug withdrawal in 15 cases (52%). Hence, the outcome suggests that the maximum ADRs can definitely be prevented in the study.

CONCLUSION

Antibiotics are among the most commonly prescribed medications in hospitals, accounting for a significant proportion of antimicrobial drug use. Studies have shown that around 30–50% of hospitalized patients receive antibiotics during their stay [14].

In this current study, 29 antimicrobial-induced ADRs were monitored and reported, from which the higher number of ADR was reported by antibiotics and antiprotozoal drugs where these drugs show significant effects such as gastrointestinal tract disturbances and allergic reactions such as skin irritation, rashes, and life-threatening anaphylaxis.

The process of ADR monitoring and reporting is continuous and ongoing. ADRs, which have the potential to be fatal or life-threatening, can happen to anyone taking any medication. By early and appropriate management, majority of ADRs could be treated. The primary barrier was under-reporting of ADR, which may be addressed by increasing knowledge and enhancing the culture of ADR monitoring and reporting among medical personnel to guarantee safe medication usage. As the most commonly prescribed medication, antibiotics necessitate closer monitoring of ADRs. An interdisciplinary approach, involving pharmacists, physicians, and nurses can enhance medication management, ensuring comprehensive care and reducing the risk of ADRs.

AUTHORS' CONTRIBUTIONS

Zeenath Unnissa - Manuscript preparation, protocol preparation, data analysis, editing, data collection, review, and correspondence. MaherUnissa - Manuscript preparation, protocol preparation, data analysis, editing, data collection. Shaista Khan - Manuscript preparation, protocol preparation, data analysis, editing, data collection. Naziya Thasleem - Manuscript preparation and data collection. Nikhath Fatima - Manuscript preparation and data collection.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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