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Original Research Article

To Evaluate the Adverse Drug Reactions of Antibiotics in a Tertiary Care Hospital in Bihar

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Abstract

Background: It has been established long ago that the drug itself might be lethal; as the adage accurately goes, "Drugs are Double-Edged Weapons." As defined by the World Health Organization (WHO), an ADR is "any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function.

Aim and Objectives: The purpose of this research is to assess the adverse drug reactions to antibiotics in a tertiary care hospital.

Materials & Methods: The current prospective spontaneous reporting study was conducted under the supervision of treating physicians on 100 patients of both genders (60 males and 40 females) attending in all departments, Jannayak Karpoori Thakur Medical College & Hospital, Madhepura, Bihar (India), to investigate ADRs (adverse drug reactions).

Results: AMAs were responsible for 100 (20%) of the ADRs reported spontaneously during the course of the study. The antimicrobial medications associated with the development of ADRs were cephalosporins (40%), fluoroquinolones (20%), penicillins (14%), antitubercular medicines (12%), macrolides (10%), sulfonamides (2%), and tetracyclines (2%). The most common ADRs were produced by Ceftriaxone (25%), Ciprofloxacin (13%), Rifampicin (10%), and Azithromycin (8%). Fixed Dose Combinations (FDCs) were responsible for 14% of ADRs, with Amoxicillin+Clavulanic Acid accounting for 4% and the irrational combination (FDC) of Ciprofloxacin+Tinidazole accounting for 4% of ADRs, respectively.

Conclusion: As more and more medications reach the market, it is imperative that adverse event reporting (AER) remain a constant process. Most adverse drug reactions (ADRs) were traced back to cephalosporins and fluoroquinolones.

Keywords: Adverse drug reactions, Antimicrobial agents, Preventability, Severity, Predictability, Cephalosporins

Introduction

The most common medical procedure is the use of drugs to alleviate suffering. But it has been established long ago that the drug itself might be lethal; as the adage accurately goes, "Drugs are Double-Edged Weapons." As defined by the World Health Organization (WHO), an ADR is "any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function." This definition does not include overdose (intentional or accidental), drug abuse, treatment failure, or drug dependence [1, 2]. Adverse drug reactions (ADRs) are substantial causes of death and morbidity in both hospitalised and ambulatory patients. In several countries, ADRs are among the top 10 leading causes of death. To reduce the potential for harm, more research on ADRs is needed to raise patient awareness of the issue and encourage hospital staff to report any adverse reactions they see. Reducing patient harm and improving public health through better medication prescription necessitates early detection, evaluation, and monitoring of adverse drug reactions (ADRs) [3]. This topic has recently risen to the top of the medical agenda. Patients are a susceptible category with relation to rational medication prescription, as many new pharmaceuticals are launched onto the market without the benefit of even minimal experience. Due to this shortcoming, doctors often prescribe medications "off label," which might have dangerous consequences. The rate of adverse drug reactions is likely to keep rising as the number of pharmaceuticals on the market and the number of people taking various medications both rise. Therefore, improved methods for reporting, evaluation, and care are required to identify people who present with drug-induced diseases [3].

The harmful effects of ADRs on health and healthcare expenditures are substantial. ADR monitoring and reporting activity is in its infancy in India. There are a substantial number of drug users in India, which is a developing nation. There are more than 6,000 licenced medication producers and more than 60,000 branded formulations, making it the fourth biggest pharmaceutical producer in the world. Since this is the case, it is crucial that the medication be both effective and affordable. It is also becoming a major centre for medical research, meaning more people will have access to experimental medicines. The Ministry of Health and Family Welfare established the National Pharmacovigilance Program (NPP) on January 1, 2005, which was further revitalised in July 2010. Antibiotics come in a wide variety of classes, including penicillins, cephalosporins, sulfonamides, and amino glycosides, and each has its own unique mechanism of action and set of potential side effects; this initiative is managed by the Central Drugs Standard Control Organization (CDSCO), New Delhi [4]. Over half of all hospitalised patients are treated with antimicrobial agents, and their usage accounts for 20–50% of drug expenditures in hospitals.4 Antibiotics are widely used in general practise for the treatment and prevention of numerous disease conditions. Antibiotics are expensive because of the drugs they treat, the drugs they interact with, and the side effects those drugs might cause.

Aim and objectives:

The purpose of this research is to assess the adverse drug reactions to antibiotics in a tertiary care hospital

Materials & Methods

The current prospective cross-sectional spontaneous reporting study was conducted under the supervision of

treating physicians on 100 patients of both genders (60 males and 40 females) attending in all departments, in collaboration with the Department of Pharmacology, Jannayak Karpoori Thakur Medical College & Hospital, Madhepura, Bihar, India, to investigate ADRs (adverse drug reactions). The methods used to collect the study's data are both active (pharmacists actively looking for suspected ADRs) and passive (encouraging prescribers to report suspected ADRs). Case sheets, investigation reports of patients who had experienced an ADR, personal interviews with reporting parties or clinicians, personal interviews with patients or patients' attendants, and past histories of medication use—which were generally obtained from prescriptions from the past—were all used to collect data. The period of study was from March 2022 to September 2022. The ethical clearance of the study protocol was pre-approved by the institutional ethical committee of the institution and permitted by it. All patients gave detailed written consent to take part in the study. Data such as name, age, etc. was recorded.

Inclusion criteria

a. Patients of all age groups who developed adverse drug reactions to antibiotics
b. Patient with the ability to understand and provide written informed consent

Exclusion criteria

a. pregnant or lactating women,
b. Patients with hypertensive emergencies, unstable coronary heart disease, acute myocardial infarction, advanced kidney or liver failure, cerebral stroke, and severe infection

Patients receiving treatment with systemic corticosteroids. The Central Drug Standard Control Organization-Indian Pharmaco-poeia Commission (CDSCO-IPC) adverse drug event reporting form was used to gather patient demographics, clinical and drug data, details of ADRs, onset time, causal drug information, outcome, and severity [5-8]. The WHO-ADR likelihood scale and the Modified Schumock and Thornton scale were used to determine whether or not an adverse drug reaction might have been avoided [9,10]. The Hartwig and Siegel Scale was used to determine the level of severity of each ADR. Predictability was characterised as Type A and Type B ADRs [11-14].

Data thus obtained were subjected to statistical analysis through Microsoft Excel 16.

Results

A total of 500 ADRs were reported spontaneously throughout the research period; 100 (20%) of these were induced by AMAs. The male preponderance (60%) was noticed. The incidence of ADRs was highest in those aged 35–45 (35%), followed by those aged 25–35 (25%). Patients aged 55 and over saw the lowest incidence of ADRs (8%) (Table1).

Table 1: Age & Gender wise distribution of ADRs

Gender	Number	Percentage
Male	60	60
Female	40	40
Age(In years)		
Below 25	12	12
25-35	25	25
35-45	35	35
45-55	20	20
Above 55	8	8

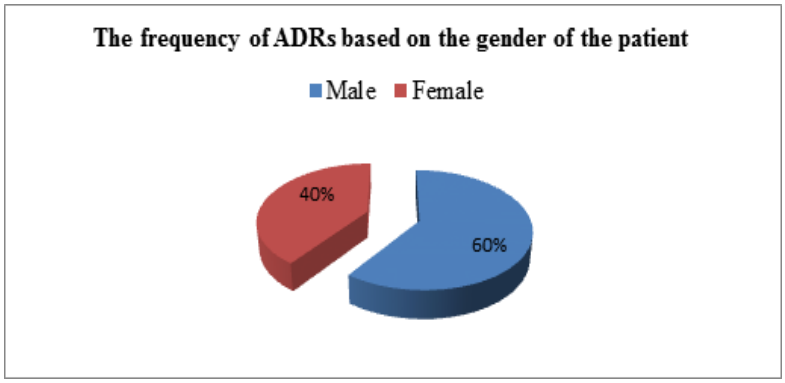

Figure 1: The frequency of ADRs based on the gender of the patient

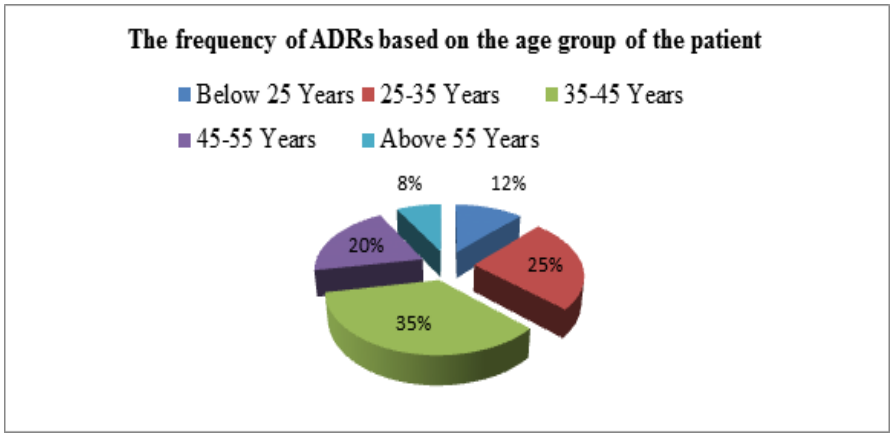

Figure 2: The frequency of ADRs based on the age group of the patient

Table 2: ADRs caused by different classes of Antimicrobial Agents

Causative drug class	Causative drug	Number	Percentage (%)
Cephalosporins	Ceftriaxone	25	25
	Cefotaxime	6	6
	Cefixime	6	6
	Cefpodoximeproxetil	1	1
	Cefoperazone + Sulbactam	2	2
Fluroquinolones	Ciprofloxacin	13	13
	Ciprofloxacin+Tinidazole	4	4
	Ofloxacin	1	1
	Moxifloxacin	1	1
	Norfloxacin	1	1
Penicillins	Amoxicillin	6	6
	Amoxicilln+Clavulanic acid	4	4
	Piperacillin +Tazobactam	4	4
Antitubercular drugs	Rifampicin	10	10
	Isoniazid	2	2
Macrolides	Azithromycin	8	8
	Clindamycin	2	2
Sulfonamides	Cotrimoxazole	2	2
Tetracycline	Doxycycline	2	2

Cephalosporins (40%), Fluoroquinolones (20%), Penicillins (14%), Antitubercular Medicines (12%), Macrolides (10%), Sulfonamides (2%), and Tetracyclines (2%), (Table 2).

Ceftriaxone (25%), Ciprofloxacin (13%), Rifampicin (10%), and Azithromycin (8%) were the pharmaceuticals with the highest prevalence of ADRs. Fixed Dose Combinations (FDCs) caused 14% of ADRs, with Amoxicillin+Clavulanic Acid and the illogical combination (FDC) of Ciprofloxacin+Tinidazole accounting for 4% and 4% of ADRs, respectively (Table 3).

Table 3: ADRs caused by Fixed Dose Combinations of AMAs

Fixed dose combinations	Type of ADR	Percentage (14%)
Amoxicillin+ Clavulanic acid	Maculopapular rash (3%) Diarrhoea (1%)	4
Piperacillin +Tazobactam	Vomiting (3%) Maculopapular rash (1%)	4
Ciprofloxacin+Tinidazole	Vomiting (2%) Fixed drug eruption (2%)	4
Cefoperazone + Sulbactam	Neutropenia (2%)	2

The dermatological system was impacted by the majority of the ADRs (60%), which varied from a simple macula-papular rash to life-threatening Steven Johnson's Syndrome (SJS), followed by the gastrointestinal system (40%), with diarrhoea (10%) being the most prevalent. The WHO probability scale for assessing the causality of ADRs found that 80% of ADRs were likely and 20% were plausible. Following the causality evaluation, the medicine was removed in 78% of instances, the dosage was not altered in 16% of cases, and the dose was reduced in 6% of cases. With drug cessation and medical therapy, 81% of patients recovered. According to the Hartwig and Seigel scale, 19% of ADRs were mild, 71% were moderate, and 10% were severe. According to the modified Schumock and Thornton scale, the majority of ADRs induced by AMAs were not avoidable (67%), 28% were possibly preventable, and 5% were definitely preventable. 67% of AMA-related ADRs were unexpected (type B), whereas 33% were predictable (type A).

Discussion

The advent of AMAs in the 20th century was the single most important development in the therapeutic realm. Their emergence shifted doctors' perspectives on the efficacy of medicines in treating illness. They are among the few medications that have the potential to treat disease rather than simply mask its symptoms. As infectious illnesses are more common in poorer regions, their value increases. When used responsibly, AMAs are thought to be safer than other regularly used drugs [9]. However, they are one of the most often used and abused drug classes. Yet, more ADRs are attributed to them than to any other medication class.

Similar to the studies by Jimmy Jose et al. and Suthar et al. [10,11] we found that adults accounted for the majority of ADRs in this study's age group (35–45 years), followed by those aged 25–35 years. The occurrence of ADRs among adults is cause for concern because of the potential economic impact on their families. Similar to the study of Kavitha et al. in Ghaziabad, India, the current research shows that men are more likely than females to experience ADRs from AMAs. Researchers Sudha Sharma et al. found no significant differences in ADR patterns across the sexes. However, research by Starveva et

al. and Hussain et al. demonstrated a gender bias against female participants [12-14].

The most common ADRs were associated with cephalosporins, followed by those associated with fluoroquinolones, penicillins, anti-tubercular medicines, and macrolides. Most adverse drug reactions (ADRs) were associated with ceftriaxone, which is consistent with the findings of studies by Mohammed Misbah Hussain et al. [14] Since cephalosporins are effective against both gram-positive and gram-negative microorganisms, they may be widely used at our facility. Cross-reactivity between penicillin and cephalosporin occurs in around 14% of penicillin-allergic individuals and may lead to ADRs. For deadly ADRs such as anaphylactic shock, a test dosage of cephalosporin before the full dose may be helpful.

Many adverse reactions were caused by using predetermined doses. Finding the offending medication in the FDC and taking it off the market might be challenging. In our investigation, ADRs were associated with the irrational FDC Ciprofloxacin+Tinidazole, while in the study by Sudhaaet al.12, ADRs were associated with the FDC Ofloxacin+Ornidazole.

Despite claims that Ciprofloxacin + Tinidazole FDC is broad-spectrum, using this combination in a patient with only one type of diarrhoea is harmful. Using both components together increases expenditures, risks, and resistance.

The majority of adverse drug reactions (ADRs) involved the skin, with maculopapular and vesiculobullous rashes being the most prevalent types of rash seen. The most often mentioned medicines were ceftriaxone and ciprofloxacin. Reena Verma et al. found that AMAs were responsible for 56% of CADRs in India, whereas research by Hsin-Yun-Sun et al. in Taipei, Taiwan, found that the most prevalent side effects were blood dyscrasias (32.1%), dermatomucosal effects (23.9%), and febrile responses (17.9%). Differences could be due to differences in study setting, study population, drug use, and route of administration (oral vs. intravenous). Qing-ping Shi et al. reported that cephalosporins accounted for a higher frequency of dermatological ADRs (43.5%), with the most common reaction being a skin rash (33%) [15-17]. CADRs are unpredictable and unrelated to dosage. They are responses that may occur. Most studies have found that parenteral administration leads to more ADRs than oral administration, but in the current study, more ADRs occurred after oral administration than before [12].

In the current study, 80% of ADRs were classified as probable, 20% as possible, and no cases were classified as certain because re-challenge of the causative drug was not performed. Comparable to the study by Shamna et al. from Saudi Arabia, which found 63.26 percent of ADRs to be moderate in severity, the study by Brahma Naidu et al [18] from Guntur, AP, India, found that 19% of ADRs were certain, 42% were probable, 29% were possible, and 10% were unlikely and unclassified using the WHO causality assessment scale. 18 Furthermore, 71% of the ADRs were noted to be moderate in 10% of ADRs were classified as severe in this research, with 8% resulting in extended hospitalisation and two percent posing a serious danger to life. The current investigation was performed in a referral centre, thus the incidence of severe ADRs may be greater than in the study by Jamunarani et al. [19] in which 6.5% of patients suffered severe ADRs.

Ceftriaxone was shown to have serious adverse effects in this research, including Stevens-Johnson syndrome and anaphylactic shock. Until now, the causes of SJS and TEN have been poorly understood. The CD8+ T-lymphocyte has

been shown to be crucial to this procedure. The Pharmaco-vigilance Programme of India (PvPI) recently (2016) recommended that Ceftriaxone's label be changed because it can cause SJS. This is because it has been demonstrated that ceftriaxone-specific MHC molecules induce specific T-cell receptor (TCR) activation, followed by the expansion of cytotoxic T lymphocytes that infiltrate skin lesions, resulting in autologous lymph node necrosis. Anaphylactic shock is a life-threatening, IgE-mediated type I hypersensitivity reaction that can be prevented with prompt medical attention. [20, 21] Although serious adverse drug reactions (ADRs) were reported, no deaths were reported in our study, in contrast to a study by Naidu et al. [18], which reported a mortality rate of 3% in patients taking anti-tuberculous drugs. As far as drug withdrawal symptoms go, hepatotoxicity is among the most prevalent. The most common causes of metabolic syndrome are an increase in reactive metabolite production as a consequence of phase I metabolism or a failure of detoxification as a result of phase II metabolism. These reactive metabolites cause lipid peroxidation and cell death by causing an excessive generation of reactive oxygen species (ROS). [22, 23] The risk of anti-tubercular drug-induced hepatitis has been linked to acetylator phenotypes and other genetic polymorphisms, such as cytochrome P4502E1 and glutathione S-transferase M1, and certain MHC Class II-associated HLA-DQ alleles. [24] The Indian Pharmacopoeia Commission (IPC) and the Revised National Tuberculosis Control Program recommend that, due to a lack of prior medication history recording, 5% of ADRs are unavoidable. The majority of reported ADRs in the current research were unexpected, which is greater than the study by Jamuna rani et al. [19], in which only 21.8% of ADRs were unpredictable. This finding also runs counter to the commonly held belief that type A reactions are more prevalent than type B reactions. Why our patients showed a preponderance of type B responses is a mystery [25].

Unique and independent of the pharmacological effects of the drug, type B responses are possible. Treatment charts must always include the names of the agents responsible for such responses. Patients who have had an adverse drug response in the past may be able to avoid experiencing the same reaction again if they are given an alert card outlining the facts of the reaction and instructed to present the card prior to getting any medicine.

Limitation of study: The small sample sizes

Conclusion

As more and more medications reach the market, it is imperative that adverse event reporting (AER) remain a constant process. Most adverse drug reactions (ADRs) were traced back to cephalosporins and fluoroquinolones. The most common effects were on the skin and the stomach. In addition to ADRs, FDCs were also suspected as a possible cause. There was no recorded death despite the presence of significant ADRs. To lessen the impact of ADRs, early detection and control are crucial.

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