RESEARCH ARTICLE

A Prospective Study on Antibiotics-associated Spontaneous Adverse Drug Reaction Monitoring and Reporting in a Tertiary Care Hospital

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Abstract

Background: The aim of the present prospective study was to determine the causality, preventability, and severity of adverse drug reactions (ADRs) occurring in various departments of the tertiary care hospital. **Materials and Methods:** This prospective, interventional study was undertaken in general medicine, surgery, respiratory medicine, intensive care unit care unit, and nephrology units in a tertiary care hospital, Coimbatore, and to assess preventability, severity, and causality assessment in antibiotics which caused ADRs, and to determine most commonly affected organ system. **Results:** A total of 143 ADRs were identified in 1138 patients, out of which 74 (51.75%) male patients were identified with ADRs, whereas 69 (48.25%) were female. The age wise distribution revealed that middle-aged patients showed more incidence of ADR 60 (41.96%), followed by geriatrics 41 (28.67%), adult 35 (24.47%), and pediatrics 7 (4.89%). Gastrointestinal tract 66 (46.15%) was the most affected organ system by ADR followed by others 21 (14.7%) skin and appendages disorder 15 (10.48%), central and peripheral system disorder 13 (9.09%), respiratory system disorder 13(9.09%), hematopoietic disorder 4 (2.8%), urinary system disorder 3 (2.09), and CVS 2 (14.7%). Maximum ADRs were reported with beta-lactams class 103 (72.04%) followed by miscellaneous 12 (8.4%), macrolides 10 (6.99%), quinolones 6 (4.99%), and aminoglycosides 5 (4.20%). **Conclusion:** Antibiotics comprise the major volume of the drug family and in prescriptions of hospitalized patients. Implementation of antibiotic guideline policy in hospitals and strict adherence to it should be ensured for safe and rational use of antibiotics. Furthermore, health system should promote spontaneous reporting of ADRs to regional pharmacovigilance centers which is detected in clinical practice.

Key words: Adverse Drug Reactions, Antibiotics, Pharmacovigilance

INTRODUCTION

Adverse drug monitoring and spontaneous reporting are important in recognizing adverse reactions in local population. Adverse reactions are recognized hazards of drug therapy. Adverse drug reactions (ADRs) are main causes for mortality and morbidity in both hospitalized and ambulatory patients. The current epidemiological studies have revealed that the ADRs are the fourth to sixth leading cause of death.[1] Sometimes, ADR-related costs, such as hospitalization, surgery, and lost productivity, exceed the cost of the medications.[2] However, detection of ADRs has become increasingly meaningful because of the introduction of large number of potent noxious chemicals as drugs in last two or three decades. Thus, it is very critical to oversee both the known and unknown adverse effects of medicines.

Adverse reaction can take place with any class of drugs. The most troublesome classes of drugs contributing to ADRs were antibiotics followed by antitumor agents.[3]

Antibiotics remain the most consistently prescribed group of drugs by all clinical specialties because of high predominance of infectious disease, specifically in developing countries. However, this group is also most extensively exploited in

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many forms such as self-medication, over-the-counter use, and irrationally prescribed many a times. The rational use of antibiotics is a greater health need.[4-6] Consequently, leading to increase in the prevalence of resistant pathogen, which has significant impact on the mortality and morbidity due to infectious diseases and can add unnecessary financial burden to the patient and community at large.

A systemic meta-analysis using Medline and Embase as databases for literature published between 1980 and June 2002 on the occurrence of ADEs and their preventability in hospital background showed that up to 56.6%; these events were judged to be preventable. An ADR was classified as preventable if the drugs involved were not relevant for the patient's clinical condition; the dose, route, or frequency of administration was not appropriate for the patient's age, weight, or disease; the patient requires therapeutic drug monitoring or other essential laboratory tests that were not completed or not completed repeatedly enough; the patient had a history of allergy or previous reaction to the drug; a known drug interaction was the suspected cause of the reaction; a serum drug concentration above the therapeutic range was documented; non-compliance was associated with the reaction; or a medication error was associated with the reaction.[7]

Antibiotics reside to distinct classes such as penicillins, cephalosporins, sulfonamides, and aminoglycosides and they differ in respect of their mechanism of actions and adverse effects. Antibiotics are worn prevalently in familiar practice for treatment and prophylaxis of many disease conditions.[8] Over half of all hospitalized patients are treated with antimicrobial agents and their use account for 20–50% of drug utilization in hospitals. More than 70% of intensive care unit (ICU) patients accept antibiotics for therapy or prophylaxis, with much of this use being empiric and over half of the recipients accepting multiple agents. The total costs correlated with antibiotics are not only related to antibiotic use itself but also to comedication and adverse drug events.[9,10]

The prevalence and severity of ADRs can be altered by patient-related factors such as age, sex, comorbid diseases, and genetic factors, and drug-related factors such as type of drug, route of administration, duration of therapy, and dosage. The other essential liable risk factors combined with ADRs are gender, increased number of drug exposures, advanced age, length of hospital stay, and function of excreting organs.[11] Healthcare professionals - doctors, dentists, pharmacists, and nurses are the most favored source of data collection associated to ADRs.

Prevention of ADRs is desirable by appropriate monitoring, which reinforced the national directive to institutionalize a pharmacovigilance center in every medical college in the country.[11] It is excessively necessary that institutions and hospitals have an antibiotic policy and assure that perfect choices are made by respective prescribers.[3] Thus, affording such studies shall absolutely prove useful in reconstructing hospital and national antibiotic policy in the concern of patient care and safety. Although India is a developing country, most hospitals in India do not have an ADR reporting and monitoring programmers. Judgment of the impact and possible for prevention of ADRs were narrow because various studies did not determine seriousness and preventability.

The aim of the present prospective study was to determine the causality, preventability, and severity of ADRs occurring in various departments of the tertiary care hospital.

MATERIALS AND METHODS

This prospective, interventional study was conducted in General medicine, Surgery, ICU, Respiratory Medicine, and Nephrology Departments in PSG Hospitals, Coimbatore, Tamil Nadu. ADRs with antibiotics were reported from February 6, 2017, to July 30, 2017, and analyzed using Microsoft Excel. All patients of either sex and of any age who developed an ADR were included in the study. Pregnant patients and nursing mothers were excluded from the study. Patients case notes/files and CDSCO (suspect ADR) forms were used as main sources of data collection. The protocol of the study was approved by Institution Human Ethics Committee (IHEC, PSG IMS&R) of the hospital. All statistical analysis was performed with Statistical Package for the Social Sciences version 16 statistical program. Categorical variables were described as percentages and continuous variables as mean and standard deviation. Association between demographic variables and score was performed using Chi-square test.

RESULTS AND DISCUSSIONS

A total number of patients treated with antibiotics were 1138, in which the predominance of male patients was high compared to females. Age wise distribution of the total study population (n = 1138) showed that middle-aged patients were high following geriatrics, adult, and pediatrics population. A number of hospitalized patients treated with antibiotic were 1138, in which patients treated with one antibiotic were 742 (45.02%), patients treated with two antibiotics were 576 (34.95%), patients treated with three antibiotics were 276 (16.64%), and patients treated with four antibiotics were 64 (3.86%).

Number of ADRs

The number of antibiotics given in the total study population patients was 1658, out of which 143 ADRs were identified [Figure 1].

Gender classification of ADR

During the study period, a total of 143 antibiotics-related ADRs were identified and reported among 1138 patients. Over the study period, it was found that ADRs were more

predominant in male patients over females. The similar study which was conducted shows the same predominance of ADRs in the study population. The predominance of male sex in occurrence of ADRs with antibiotics was more which may be due to larger number of male population enrolled into the study when compared to females.[9,12,13] It is depicted in Figure 2.

Department wise distribution of ADR

Maximum number of ADRs was reported from the general medicine, followed by surgery, respiratory medicine, nephrology, and ICU. This higher antibiotic ADRs in medicine and surgery departments may be due to frequent prescription of antibiotics in these units which are depicted in [Table 1].

Age wise distribution of ADRs

Age wise distribution of antibiotic-related ADRs in the study population revealed that the incidence of ADR is higher among middle-aged patients showing a rate of 41.96%, followed by geriatric patients 41 (28.67%), adults 35 (24.47%), and pediatrics 7 (4.86%) analysis which was done for the age wise distribution in another similar study, showing the same predominance of middle-aged patients. The result implied that the middle-aged patients were more prone to antibiotic ADRs. The reason for such findings might be changes in pharmacokinetic and pharmacodynamic parameters in various age groups and the presence of comorbid illnesses and multiple drugs along with infectious diseases[14] depicted in [Table 2].

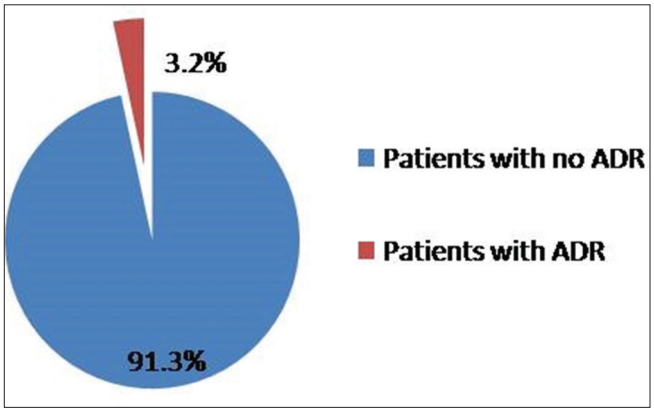

Figure 1: Number of adverse drug reactions

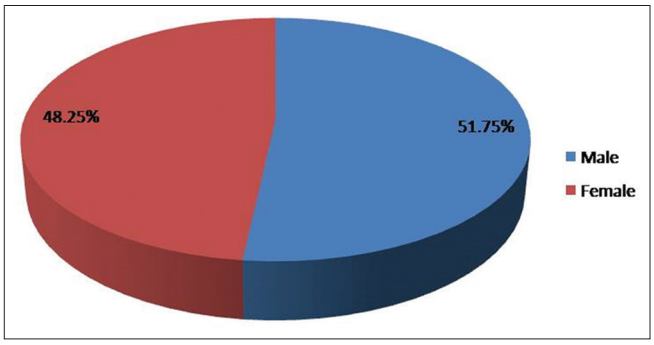

Figure 2: Gender classification of adverse drug reactions (*n* = 143)

Organ system affected due to ADR

Results revealed that gastrointestinal tract (GIT) was the most affected organ system by ADRs followed by others, skin and appendages disorder, central and peripheral system disorder, respiratory system disorder, hematopoietic system disorder, urinary system disorder, and CVS. GIT was the main organ system affected. Other studies conducted showed the same predominance of the gastrointestinal system followed by the skin in ADR occurrence[14-17] which is showed in [Table 3].

Table 1: Department wise distribution of ADRs (*n*=143)

Department	Number of ADRs (%)
General medicine	83 (58.06)
Surgery	31 (21.67)
ICU	5 (3.49)
Respiratory medicine	14 (9.79)
Nephrology	10 (6.99)

ICU: Intensive care unit, ADRs: Adverse drug reactions

Table 2: Age wise distribution of ADRs (*n*=143)

Age group (years)	Number of ADRs (%)
Pediatrics 0–18	7 (4.89)
Adult 19-45	35 (24.47)
Middle aged 45-65	60 (41.96)
Geriatrics>65	41 (28.67)

ADRs: Adverse drug reactions

Table 3: Organ system affected due to ADR (*n*=143)

Organ system affected	Number of ADRs (%)
Urinary system disorder	3 (2.09)
Gastrointestinal disorder	66 (46.15)
Respiratory system disorder	13 (9.09)
Skin and appendages disorder	15 (10.48)
Central and peripheral system disorder	13 (9.09)
Musculoskeletal system disorder	6 (4.2)
Hematopoietic disorder	4 (2.8)
CVS	2 (1.4)
Others	21 (14.7)

ADRs: Adverse drug reactions

Therapeutic class of Antibiotics Implicated to cause ADRs

Incidence of ADRs suspected to be caused by various classes of antibiotics is shown in Table 9. Compiled data revealed that maximum ADRs were noted with Beta-Lactams (Ceftriaxone, Amoxicillin/Clavulanic acid, Cefotaxime, Tazobactam, Cefazolin, Cefpodoxime, Cefixime, Cefuroxime,Piperacillin/ Tazobactam,Cefoperazone/Sulbactam,Carbapenems,and Vancomycin) followed by miscellaneous (Linezolid, Clindamycin, Metronidazole, and fungal antibiotic-Voriconazole), Macrolides (Azithromycin and Clarithromycin), Quinolones (Ofloxacin and Levofloxacin), and Aminoglycoside (Amikacin). The cephalosporins were the most used antibiotic class in this study. Another study which revealed the predominance of Cephalosporins, Vancomycin, and Penicillins[17,18] which is depicted in [Table 4].

Types of ADRs observed

Different types of ADRs observed during the study period which is depicted in [Table 5].

Causality assessment of the ADRs identified

Causality of each ADR was assessed using Naranjo scale. Assessment showed that out of 143 ADRs, possible ADRs were high, followed by probable ADRs, were as definite and doubtful was 0% which is described in [Table 6].

Preventability assessment

All the identified ADRs were analyzed for its preventability using Schumock and Thornton scale, which showed that not preventable ADRs were more and probably preventable was only 1%, while remaining 1% was definitely preventable [Table 7].

Severity assessment

Severity assessment was carried out using Hartwig and Siegel scale and found that out of 143 ADRs mild were high followed by moderate and severe. Another similar study conducted showed same prevalence of severity assessment in their study population[19] which is depicted in Table 8.

Seriousness assessment

Seriousness criteria assessment out of 143 ADRs, the ADRs coming under "others" category are upraised, followed by ADRs which prolonged the hospitalization of patients, subsequently required intervention to prevent permanent impairment or damage and next ADRs which were life-threatening which is depicted in Table 9.

Outcomes of the reaction

Of 143 ADRs, ADRs which were classified as recovering are higher, followed by recovered and others were 0%. Vast majority of the patients recovered from ADR because the reported reactions were not fatal [Table 10].

Actions taken to resolve ADR

In actions taken, out of 143 ADRs, "drug not changed" were upraised followed by drug withdrawn and subsequently actions taken were unknown. Another study conducted was showing a careful analysis of the fate of the suspected drugs showed that the drug was not changed in many of the cases and drug withdrawn was made in others keeping the risk–benefit ratio in consideration[20] [Table 11].

Table 4: Therapeutic class of antibiotics implicated to cause ADRs (*n*=143)

Beta-lactams	Number of ADRs (%)
Ceftriaxone	24 (16.78)
Cefazolin	4 (2.80)
Cefuroxime	1 (0.70)
Cefpodoxime	2 (1.40)
Cefixime	1 (0.70)
Piperacillin	20 (13.99)
Amoxicillin	9 (6.29)
Cefoperazone	24 (16.78)
Cefuroxime	2 (1.40)
Carbaperam -imepenem+cilastation	3 (2.10)
Carbaperam – meropenam	6 (4.20)
Carbaperam – ertapenam	1 (0.70)
Vancomycin	3 (2.10)
Quinolones – ofloxacin	2 (1.40)
Colistin	3 (2.10)
Tazobactam	5 (3.50)
Quinolones – levofloxacin	2 (1.40)
Quinolones – oflamax	3 (2.10)
Macrolites – azithromycin	8 (5.59)
Macrolites – clarithromycin	2 (1.40)
Aminoglycoside – amikacin	6 (4.20)
Miscellaneous - linezolid	3 (2.10)
Miscellaneous - clindamycin	4 (2.80)
Miscellaneous - metronidazole	3 (2.10)
Fungal antibiotic - voriconazole	2 (1.40)

ADRs: Adverse drug reactions

Table 5: Types of ADR observed (*n*=143)

Types of reactions observed	Number of ADRs (%)
Vomiting	21 (14.69)
Loose stools/diarrhea	17 (11.89)
Rashes in upper limb	1 (0.70)
Decreased WBC and platelet count	2 (1.40)
Encephalopathy	1 (0.70)
Dizziness	3 (2.10)
Nephrology	1 (0.70)
Tendinitis	1 (0.70)
Itching	2 (1.40)
Throat soreness	2 (1.40)
Joint pain	1 (0.70)
Burning sensation at the site of application	1 (0.70)
Lower limb pain	2 (1.40)
Allergic reaction/itching	1 (0.70)
Maculopapular erythematous itchy rashes on both thigh	2 (1.40)
Abdominal pain - Severe abdominal pain	5 (3.50)
Numbness of legs	2 (1.40)
Tiredness and weakness	4 (2.80)
Pain at the site of injection	3 (2.10)
Constipation	10 (6.99)
Hypersensitivity reaction	3 (2.10)
Breathlessness	1 (0.70)
Decreased appetite	3 (2.10)
Headache	5 (3.50)
Hypokalemia	1 (0.70)
Swelling	1 (0.70)
Muscle soreness	2 (1.40)
Leucopenia	1 (0.70)
Fever	5 (3.50)
Trouble sleeping	1 (0.70)
Lower back pain	1 (0.70)
Black colored stools (melena)	1 (0.70)
Thrombocytopenia	1 (0.70)
Severe headache	1 (0.70)
Hypotension	1 (0.70)
Fever/tiredness	3 (2.10)
Ulcers in mouth	1 (0.70)
Throat soreness	1 (0.70)
Transient pain in abdomen	1 (0.70)
Vomiting/constipation	1 (0.70)
Pruritus	1 (0.70)
Difficulty in passing urine	1 (0.70)
Diarrhea/vomiting	13 (9.09)
Cough producing mucus	1 (0.70)
Decrease in hemoglobin and thrombocytopenia	1 (0.70)
Sore throat	1 (0.70)
Increased cough and cold	1 (0.70)
Pricking pain at the site of injection	2 (1.40)
Fever and diarrhea	1 (0.70)
Anxiety and depression	1 (0.70)
Nausea	1 (0.70)
Rashes	0 (0.00)
Nasal blockage	2 (1.40)

(*Contd...*)

Table 5: (***Continued***)

ADR: Adverse drug reaction, WBC: White blood cell

Table 6: Causality assessment of the ADRs identified (*n*=143)

Type of reactions	Number of ADRs (%)
Possible	129 (90)
Probable	14 (10)
Definite	0 (0)
Doubtful	0 (0)

ADRs: Adverse drug reactions

Table 7: Preventability assessment (*n*=143)

Type of reactions (%)
Not preventable (98)
Definitely preventable (1)
Probably preventable (1)

Table 8: Severity assessment (*n*=143)

Type of Reactions	Number of ADRs (%)
Mild	127 (89)
Moderate	15 (11)
Severe	0 (0)

ADRs: Adverse drug reactions

Table 9: Seriousness of the reaction (*n*=143)

Seriousness of the reaction	Number of ADRs (%)
Required intervention to prevent permanent impairment/damage	8 (5.6)
Others	110 (76.92)
Hospitalization/prolonged	21 (14.68)
Life-threatening	4 (2.8)

ADRs: Adverse drug reactions

Association between gender and ADR

Total number of patients treated with antibiotics during their in-hospital stay was 1138. Out of which, 735 were male, 403 were female. Association between gender and ADRs was analyzed using Chi-Square statistic. *P*-value was found to be 0.000597 implicsating a significant association between gender and ADR [Table 12].

Association between age and ADR

Association between age and ADRs was analyzed using Chi-square statistics ($P = 0.902167$). This result is significant at $P < 0.05$. There is significant association between age and ADR [Table 13].

Table 10: Outcomes of the reaction (*n*=143)

Outcomes	Number of ADRs (%)
Recovering	132 (92.30)
Recovered	11 (7.70)

ADRs: Adverse drug reactions

Table 11: Actions taken to resolve ADR (*n*=143)

Actions taken	Number of ADRs (%)
Drug withdraw	24 (16.79)
Drug not changed	110 (76.92)
Unknown	9 (6.29)

ADRs: Adverse drug reactions

Table 12: Association between gender and ADR (*n* = 1658)

Gender	ADR		Total
	Yes	No	
Male	74	661	735
Female	69	334	403

ADRs: Adverse drug reactions

Table 13: Association between age and ADR

Age	ADR		Total
	Yes	No	
<45	42	406	448
>45	101	589	690

ADRs: Adverse drug reactions

Table 14: Association between antibiotic class and ADR

Antibiotic	ADR		Total
	Yes	No	
Beta-lactam antibiotics	80	820	900
Non-beta-lactam antibiotics	32	716	748

ADRs: Adverse drug reactions

Association between antibiotic class and ADR

A total of 900 beta-lactams were prescribed for 1138 patients, of which 80 patients developed ADR, and 748 non-beta-lactams were prescribed, of which 32 patients developed ADR. The association between the antibiotic class (beta-lactams and non-beta-lactams) was the presence of ADR was analyzed using Chi-square test. The Chi-square statistic was utilized to check for the association ($P = 0.000213$). This result is significant at $P < 0.05$. Hence, beta-lactam inhibitors are more prone to cause ADRs than non-beta-lactams [Table 14].

CONCLUSION

ADRs are one of the drug-related problems in the hospital setting and are a challenge for ensuring drug safety. The result provides an insight into the healthcare providers on the importance of monitoring and reporting of ADRs.

Although the use of non-prescription drugs, self-medication and drug abuse remains significant cause problem for the occurrence of ADRs. The ADRs encountered in this study were non-serious and not preventable, and severity assessment showed mild and moderate ADRs and causality assessment using Naranjo scale showed only possible and probable ADRs. Moreover, there is a significant association between gender and ADR, age and ADR, and antibiotic class and ADR.

Healthcare professionals have an important responsibility in monitoring the ongoing safety of medicines. Polypharmacy needs to be discouraged for a good number of ADRs results from drug-drug interaction. Pharmacovigilance needs to be enforced in our country for better and safe use of drugs. Our ability to anticipate and present ADRs can be facilitated by the establishment of standardized approaches. Although it would be prudent to initially focus on the more serious ADRs, it is important to consider even so-called non-serious ADRs as they can have a significant impact on the patient's quality of life.

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