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Original Research Article

Adverse drug reactions of antibiotics and it's management in a tertiary care hospital: a prospective observational study

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Abstract

Antibiotics are one of the widely used categories of drugs which have been used in clinical practice since last three decades. Adverse drug reactions (ADR) and antibiotic resistance are two main factors of concern while treating with antibiotics. In contrary of antibiotics being used for all kinds of infections, proper monitoring, escalation and de-escalation of doses of antibiotics, proper antibiogram and appropriate follow up should be carried out for patients. In this study, a total of 2.26% ADRs (50) were identified from 48 patients taken out of 2216 patients which was conducted in a tertiary care hospital of South India for a period of six months from February 2019 to July 2019. Descriptive statistics were used for data analysis. Out of 50 ADRs, 33 (66%) occurred in male patients and 17 (34%) in female patients. More adverse reactions were observed in general medicine department 16 (32%) and followed by cardiology department 13 (26%). Skin reactions 13 (26%) were found to be more followed by haemopoietic disorders 11 (22%), gastrointestinal system disorders 10 (20%), urinary system disorders 8 (16%) and few other systems. From the study, it was concluded that by reducing the adverse drug reactions of antibiotics, patients could avoid unnecessary hospitalization, increased waiting time, cost and disability or death. There could be improvement in patient safety.

Keywords: Adverse Drug Reactions, ADR, antibiotics, tertiary care hospital

1 Introduction

Drugs are mostly given because the primary medical intervention to alleviate sufferings. Drugs are effective for several diseased conditions, however, these are considered as "double edged weapons," so drugs themselves are recognized to be fatal. Adverse reaction monitoring and reporting are vital in identifying the adverse reaction trends in every population [1]. The term antibiotic was derived from the word "antibiosis", which suggests "against life", which was introduced by the French Bacteriologist Vuillemin. These were considered as "wonder drugs", because of its miracles in modern medicine [2]. Antibiotics are defined as substances produced from a microorganism or a similar substance produced by chemical synthesis and are capable of inhibiting the growth (bacteriostatic) or causing death (bacteriocidal) of other microorganisms in low concentrations. Thus, they are medicines used in the prevention and treatment of bacterial infections [3].

The most troublesome classes of drugs contributing to ADRs are antibiotics (16%) followed by antitumor agents (15%) [4]. The incidence and severity of ADRs may be influenced by age, sex, concurrent diseases, genetic factors, and drug related factors like type of drug, route of administration, duration of therapy, and dosage. The other important risk factors are gender, increased number of drug exposures, advanced age, length of hospital stay and function of excreting organs [5].

ADR is usually misread with adverse events and side effects of drugs. So, one of the main objectives was to distinguish ADR from side effects of antibiotics. For this, literature sources where used. ADRs are classified into different types based on different factors. Antibiotics are being used in hospital settings for past three decades and not much new drug developement has occured since then in antibiotics. So chances of antibiotic resistance and ADR is high. Taking this into account, proper monitoring and management of ADR is important.

Most of the antibiotics are likely to cause some side effects in patients such as diarrhoea, constipation etc. Antibiotics that are considered to cause more ADR from different studies includes fluoroquinolones, cephalosporins, penicillins etc. Allergy testing and test dose administration of the antibiotics can decrease the chances of getting hypersensitivity reactions in the patients to some extent.

High end antibiotics (antibiotics which are to be used with caution) are classified in different hospital settings based on the formulary of the hospital. These drugs need to be

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regularly monitored along with the clinical parameters for adequate escalation and deescalation of the drugs.
The aim of the study was to analyse the number of adverse drug reactions occuring in a tertiary care hospital due to different antibiotics and to estimate the effect of the reaction. The study also focused on drug charecteristics such as dose, frequency, route of administration etc. Various treatment approaches taken for such reactions and to what extent such reactions can be controlled, monitored and avoided in a clinical practice were also points of notice.

2 Materials and methods

The prospective observational study was conducted for six-month time period, in the inpatients of G Kuppusamy Naidu Memorial Hospital, Coimbatore, Tamil Nadu, India. ADR reporting form of Pharmacovigilance Programme of India (PVPI) was used to collect the data. The study was approved by the Institutional Ethics Committee and was conducted in accordance with good clinical practice (GCP) guidelines outlined in ICH guidelines (https://ichgcp.net/). The reports were collected by both active method (direct observation by clinical pharmacist) and passive methods (indirect observation by physician or other hospital staffs). The collected data were evaluated to gather information about the pattern with respect to the patient demographics, characteristics of the drugs involved, nature of the reactions and outcome of the reactions. ADRs were analysed based upon the severity, preventability and reaction causality.
In agreement with previous published research articles, age and sex of the patients were evaluated [6, 7], patients were grouped into age group of 20 years interval (0-20 years, 20-40 years, 40-60 years, 60-80 years and 80-100 years). Based on the Rawlins and Thompson scale, individual reactions were classified as Type A (augmented), Type B (Bizarre), Type C (Continuous drug use), Type D (Delayed), Type E (End of dose) and Type F (Failure of Therapy) [8].
Causality of the reaction was analyzed using Naranjo Scale. According to this scale, reactions were classified into definite, probable, possible and doubtful. Severity of the reactions were measured using the Hartwig and Seigel scale of severity assessment [9]. In the sight of this severity classification, ADRs may be classified as mild, moderate and severe. Preventability of the reaction was monitored using Schumock and Thronton's scale for preventability assessment. According to which, the preventability of the reaction was divided as definitely preventable, probably preventable and possibly preventable [10].

2.1 Data analysis

The data collected was evaluated and entered into Microsoft excel spreadsheet. Analysis was performed by using Statistical Package for Social Science (SPSS). The categorical data were presented in the form of frequency and percentage. For analyzing relation between the ADR and sociodemographic, disease and treatment related factors, Chi-square test was used. p value < 0.05 is considered as statistacally significant. Results are presented in the form of tables, figures and texts.

3 Results and discussion

Antibiotics are considered as the second most prescribed drugs in the world, only next to the drugs indicated for cardiovascular diseases [11]. Antibiotics are used in different hospital scenario for the treatment of various infective conditions and as prophylatic for various surgical and non surgical procedures. A total of 2216 patients who were admitted in the hospital with different disease conditions and those who are on antibiotics were followed up to check the adverse drug reaction of antibiotics. The incidence of ADRs were identified (Table 1) in 50 patients (2.26%) of which 33 were male patients (66%) and 17 were female patients (34%). Various studies carried out in northeast India by Lihite et al. [7] and in south Indian by Vijayakumar et al., [6] have reported only 8% more ADRs in females than in males. Patients from the age category of 60-80 years were observed with more number of ADRs, 24 (48%), followed by 40-60 years (26%), 0-20 years (20%) and 20-40 (6%). Analysis of the age-wise distribution showed the predominance of geriatric patients followed by adults and this result implied that the geriatric patients were more prone to antibiotic adverse drug reactions due to age related pharmacokinetic and pharmacodynamic changes, presence of co-morbid illnesses and multiple drugs along with infectious diseases. The study conducted by Jimmy Jose et al [12] and Suthar and Desai [13] also highlighted the geriatric predominance in ADR. The mean age group of the patients appeared with ADR was found to be 49.34 ± 5.87. These details are tabulated in Table 2.

Table 1. Analysis of ADRs based on gender

Gender	Number (%) of ADR reports
Male	33 (66%)
Female	17 (34%)
Total	**50**

Table 2. Analysis of ADRs based on Age and age wise distribution of ADRs

Age	Number (%) of ADR reports
0 to 20	10 (20%)
20 to 40	3 (6%)
40 to 60	13 (26%)
60 to 80	24 (48%)
Total	**50**

When reviewing by the departments, general medicine department had more number of ADRs, 16 (32%), which was followed by cardiology department (26%), ICU and pediatrics departments had 9 ADRs each (18%) and oncology department had 3 adverse reactions (6%) (Table 3). This resembles studies carried out in various hospitals in India [14, 15, 16, 17].
On analysing the antibiotics classes, it was observed that penicillins were reported with the greatest number of ADRs (28%) which was followed by glycopeptide antibiotics

(18%), cephalosporin antibiotics (12%), carbapenams and oxazolidinone (8%), flouroquinolones and lincomycins (6%), tetracyclins and aminoglycosides (4%), polymixin and nitrofuran antibiotics (2%) (Table 4). There are studies illustrating similar ADR pattern of antibiotics [18, 19].

Different types of reactions were observed in patients. Diarrhoea and thrombocytopenia were the most observed reactions (16.99%), followed by rashes and itching (15.09%), redmann syndrome (7.55%), fever (5.6%), chills and rigors (3.55%) and various other reactions were also observed which is mentioned in Table 5. Skin was the mainly affected organ system followed by gastrointestinal system, urinary system and haemopoetic system. Other studies conducted also have reported that the skin is most affected organ in the organ system [20, 21, 22, 23].

On analysing the type of ADR based on Rawlin's and Thomson's scale, it was found that 26 adverse reactions were type A (52%), 17 were type B (34%), 3 reactions from both type C and type D (6%) and 1 reaction from type F (2%).

On causality assessment based on Naranjo scale, most of the ADRs were probable (56%), followed by definite (24%), possible (18%) and doubtful (2%). This data correlates with the study of Stavreva et al. [24], Priyadharsini et al. [25], and Jimmy Jose et al. [12] and is opposite to the study by Oshikoya et al. 2007 [26] as they reported more number of definite reactions.

Severity assessment based on Hartwig and Seigel scale, ADRs were classified as mild (48%), moderate (44%) and severe (8%) which corresponds to studies conducted by Kumar BN et al. [27] and Roy K et al. [28]. Preventability assessment is carried out based on Schumock and Thornton's scale. According to this scale, ADRs were differentiated as defintely preventable (72%), probably preventable (24%) and not preventable (4%) [Table 6] which is in line with the study of Oshikoya et al. [26] and Priyadharsini et al. [25].

On observation of ADRs caused by antibiotics, various steps were taken to manage the reaction. In most of the cases the drugs were stopped after observing the reaction (58%), in other cases drugs were not stopped (36%) or the dose was reduced (6%). Most of the ADRs had duration of 1-8 days (89%). About 70% ADRs were recovered, 24% were recovering and 6% were not recovered represented in Table 6.

Analysis of fate of the suspected drugs showed that the drug was withdrawn in many of the cases and the dose altered in some while no change was made with the suspected drug in others because of considering the risk-benefit ratio in specific patients and in some cases, the use of antibiotic was according to the culture and sensitivity reports. Drug rechallenge was not done in any of the cases. Most of the patients have shown recovery (70%) after the withdrawal of offending drug and/or with the treatment of ADRs, and the outcome was unknown (30%) for a predominant number of ADRs. Only a fatal reaction was noted in this study.

In our study 3 ADRs were identified in patients who were given less number of drugs (1-5 drugs) and 47 ADRs were observed in patients who were on greater number of drugs (more than 6 drugs). In 88% of patients, the adverse reaction occurred within 9 days of drug administration. Majority of the patients (92%) got relieved from the reaction within 8 days of action taken for the ADR.

Perason Chi-square test was carried out to verify whether there is a correlation between treatment related or demographic variables with number of ADRs. The result showed that there was no significant relationship between age ($X2 = 3.07$, $df = 3$, $P = 0.38$), gender ($X2 = 0.52$, $df = 1$, $P = 0.47$) and polypharmacy ($X2 = 1.74$, $df = 2$, $P = 0.41$).

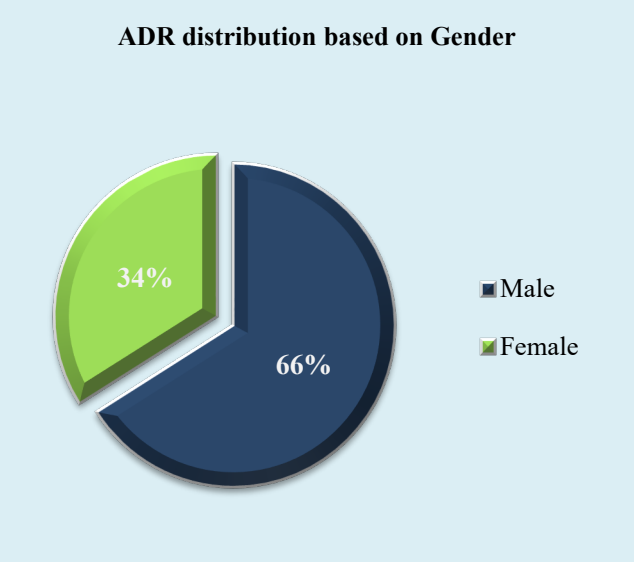

Fig. 1. Graphical representation of ADR based on gender

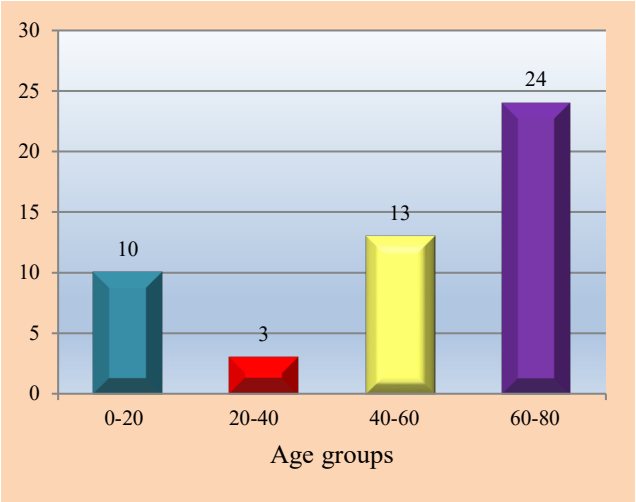

Fig. 2. Graphical presentation of ADR's based on age

Table 3. Occurance of ADR in different departments

Department	Number (%) of ADR reports
Cardiology	13 (26%)
ICU	9 (18%)
Pediatrics	9 (18%)
General medicine	16 (32%)
Oncology	3 (6%)

Table 4. Therapeutic class of antibiotics implicated to cause ADR

	Class of drug	Name of drug	Number (%) of ADR reports
1.1	Penicillins	Amoxicillin clavulanate	4 (8%)
1.2	Tetracyclines	Ampicillin	1 (2%)
1.3		Piperacillin tazobactum	8 (16%)
		Flucloxacillin	1 (2%)
		Minocycline	1 (2%)
1.4		Tigecycline	1 (2%)
1.5	Cephalosporins	Ceftriaxone	4 (8%)
1.6	Quinolones	Cefoperazone	2 (4%)
		Ofloxacin	1 (2%)
1.7	Lincomycins	Levofloxacin	1 (2%)
1.8		Moxifloxacin	1 (2%)
		Clindamycin	3 (6%)
1.9	Macrolides	Clarthiromycin	1 (2%)
1.10	Glycopeptide antibiotics	Vancomycin	6 (12%)
1.11	Aminoglycosides	Teicoplanin	3 (6%)
1.12		Gentamicin	1 (2%)
1.13		Amikacin	1 (2%)
1.14	Carbapenems	Meropenem	4 (8%)
1.15	Oxazolidinone	Linezolid	4 (8%)
1.16	Polymyxins	Polymyxin B	1 (2%)
1.17	Nitrofuran	Nitrofurontoin	1 (2%)

Table 5. Type of reactions observed

Reaction	No.of ADR	Percentage of ADR
Chills and rigors	2	3.7%
Vomiting	1	1.8%
Diarrhoea	9	16.99%
Nephrotoxicity	8	15.1%
Ototoxicity	1	1.8%
Thrombocytopenia	9	16.99%
Pancytopenia	1	1.9%
Thrombocytosis	1	1.9%
Fever	3	5.66%
Burning at infection site	1	1.9%
Rashes and itching	8	15.09%
Cough	1	1.9%
Loss of vision	1	1.9%
Redness of skin	1	1.9%
Anaphylatic reaction	1	1.9%
Bronchospasm	1	1.9%
Redmann syndrome	4	7.55%

Table 6. Classification of ADR

Rawlins and Thomsons scale (types) Type A- 26 (52%) Type B- 17 (34%) Type C- 3 (6%) Type D- 3 (6%) Type F- 1 (2%)
Naranjo Scale (Causality) Definite- 12 (24%) Probable- 26 (56%) Possible- 9 (18%) Doubtfull- 1 (2%)
Hartwig and Seigel scale (severity) Mild- 24 (48%) Moderate- 22 (44%) Severe- 4 (8%)
Schumock and Thornton's scale (Preventability) Definetly preventable-36 (72%) Probably preventable- 12 (24%) Not preventable- 2 (4%)

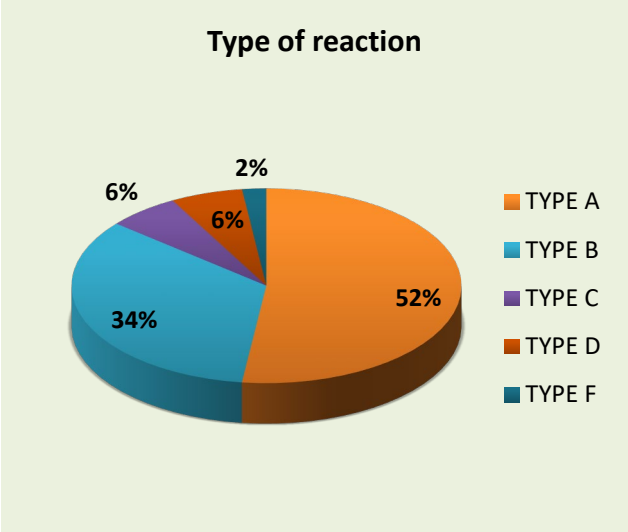

Fig.3. Graphical presentation of ADR's based on type of reaction

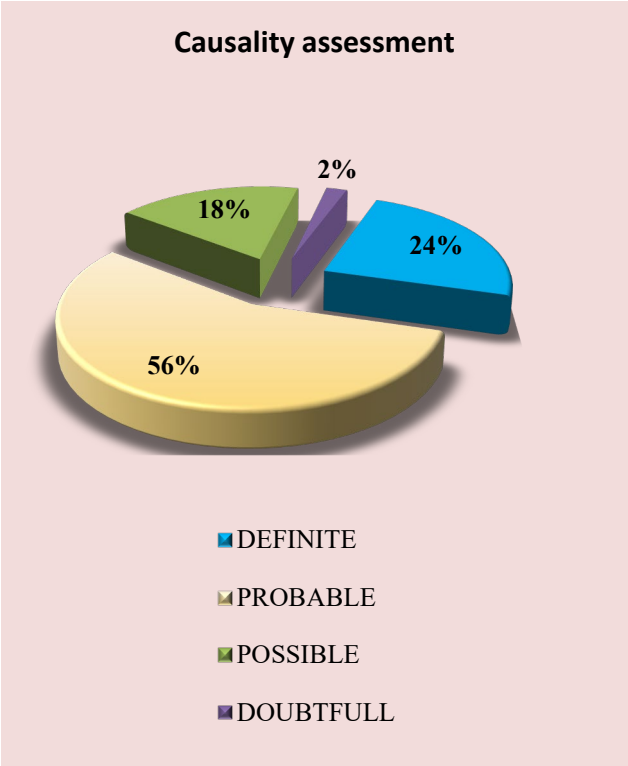

Fig. 4. Graphical presentation of ADR's based on causality

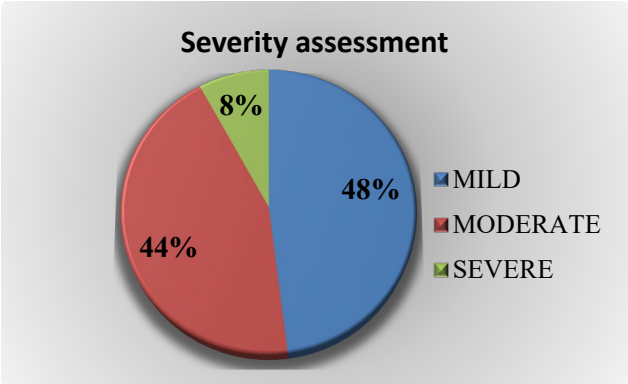

Fig. 5. Graphical presentation of ADR's based on severity

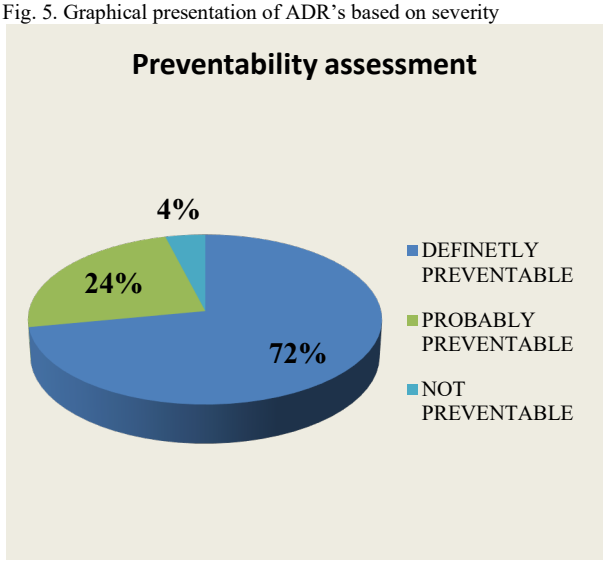

Fig. 6. Graphical presentation of ADR's based on preventability

Table 7: Further response of reaction

Drug stopped- 29 (58%) Drug not stopped- 13 (36%) Dose reduced- 3 (6%)
Duration of ADR <1-2 day- 23 (46%) 3-8 days- 22 (44%) <9 days- 5 (10%)
Recovery of ADR Recovering- 12 (24%) Recovered- 35 (70%) Not recovered- 3 (6%)

4 Limitations of the study

The study could not be carried out in all departments of the hospitals. Departments such as pediatric ICU, Neonatal ICU were avoided. One of the well-known limitations was under reporting in spontaneous reporting method which should be considered on analyzing the data.

5 Conclusion

Our study was based on the spontaneous reporting method to analyze the adverse drug reactions and included patients who developed ADR during the hospital stay and who are admitted for treatment of the ADR. From the study, it was concluded that antibiotics are one of the major medications that can produce adverse drug events. Periodic evaluation and appropriate follow up are necessary to complement hospital risk management as well as drug safety evaluation.

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Conflict of interest

None

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