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A profile of adverse drug reactions to antimicrobial agents at a tertiary care hospital

C.R. Jayanthi[1], Chaithra K.N[2,*], Narayana Reddy S.[3]

[1]Professor & HOD, [2]Post Graduate Student, [3]Professor, Dept. of Pharmacology, Bangalore Medical College & Research Institute, Bangalore

***Correspondence Author:**
Email: dr.chaithra@gmail.com

Abstract

Background: The study was undertaken to identify the Patterns, Predictability, Preventability and Outcomes of Adverse Drug Reactions (ADRs) caused by Antimicrobial agents (AMAs) in a tertiary care hospital.

Material and Methods: A retrospective cohort study was carried out to analyze the Adverse Drug Reactions due to AMAs reported spontaneously from Hospitals attached to Bangalore Medical College & Research Institute to ADR Monitoring centre under Pharmaco vigilance Programme of India (PvPI) from 2012 (Jan) to 2015 (Dec). Patient demographics and other relevant details were collected as per Central Drug Standard Control Organization form. Causality was assessed by WHO ADR probability scale, preventability by modified Schumock & Thornton scale and severity by Modified Hartwig and Seigel scale.

Results: A total of 505 ADRs were reported spontaneously during the study period, 100 (19.8%) ADRs were caused by AMAs. Male predominance (58%) with majority (57%) from age group of 21-40 years was noted. ADRs reported were mainly dermatological (58%), followed by gastro-intestinal (35%). Maculopapular rash (46%) contributed the most. Cephalosporins (35%), Fluoroquinolones (21%), Penicillins (16%) Antitubercular drugs (14%) and Macrolides (11%) contributed to the ADRs. 78% of the ADRs were of probable causality. 67% of ADRs were unpredictable, 5% were definitely preventable and 72% were of moderate severity. Causative drug was withdrawn in 80% and 79% of the patients recovered after medical treatment.

Conclusions: Most of ADRs were caused by Cephalosporins and dermatological system was affected the most. Majority of the patients recovered with medical treatment. Early detection and treatment of ADRs improves patients care and drug safety. This study provides an insight to the healthcare providers on the importance of monitoring and reporting of Adverse Drug Reactions.

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

Introduction

Adverse Drug Reactions (ADRs) are a major cause of morbidity and place a substantial burden on limited healthcare resources.(1) According to WHO, an adverse drug reaction is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of a disease or for modifications of physiological function."(2)

The prevalence of reported admissions resulting from ADRs accounts for approximately 5% (0.2 to 21.7%) in the developed countries, and at least one ADR has been reported to occur in 10-20% of hospitalized patients.(3,4) An incidence of fatal ADRs is 0.23 -0.41%. ADR is associated with a significantly prolonged length of hospital stay, increased economic burden, and almost two fold increased risk of death.(5) It is fourth to sixth leading cause of mortality in the United States of America.(6) In India (South India), 0.7% ADRs are responsible for hospital admissions and 3.7% of the hospitalised patients experience ADRs with 1.8% ADRs being fatal.(7)

More than 50% of hospitalized patients and >70% of ICU patients receive Antimicrobial Agents (AMAs) for therapy or prophylaxis of infections and their use accounting for 20-50% of drug expenditures in hospitals. The total cost associated with AMAs are related to both use of the AMAs and their ADRs.(8) In India 35-40% of ADRs were due to AMAs and most of them were unpredictable.(9,10)

ADR related information of AMAs helps in identifying, minimizing the preventable causes to make the drug treatment safe, efficacious and cost effective. All the ADRs caused by AMAs are usually undetected during the premarketing clinical trials due to less sample size with controlled population, so the present study was undertaken to identify the Patterns, Predictability, Preventability and Outcomes of Adverse Drug Reactions caused by AMAs in a tertiary care hospital.

Materials & Methods

This retrospective cohort study was carried out from 2012 (Jan) to 2015 (Dec) to analyze the ADRs reported spontaneously from the hospitals attached to Bangalore Medical College & Research Institute to the ADR monitoring centre of Bangalore Medical College and Research Institute, Bangalore. Patient demographics, clinical & drug data, details of ADRs, onset time, causal drug details, outcome and severity were collected as per Central Drug Standard Control Organization- Indian Pharmacopoeia Commission (CDSCO-IPC) adverse drug event reporting form**.**

Assessment tools: Causality of ADR was assessed by WHO-ADR probability scale and preventability was assessed by using Modified Schumock & Thornton scale. Severity of each ADR was assessed using Hartwig

and Siegel Scale. Predictability was categorized as Type A and B ADRs.[11-14]

Statistical analysis: Data were analysed using percentages.

Ethics: The study protocol was assessed and approved by the Institutional Ethics Committee of Bangalore Medical College & Research Institute **(Ref.no: BMCRI/ PS/ 105/ 2016-17)**. Confidentiality of data was maintained**.**

Results

A total of 505 ADRs were reported spontaneously during the study period, 100 (19.8%) ADRs were caused by AMAs. Male predominance (58%) was noted. Higher number of ADRs were noted in the age group of 21-40 years (57%) followed by 41-50 years (18%). Least number (9%) of ADRs were observed among the patients aged between 51-60 years (7%). (Table 1).

Table 1: Age & Gender wise distribution of ADRs

Age	Male	Female	Frequency (100 %)
≤ 20y (n=9)	7	2	9
21-30y (n=26)	10	16	26
31-40y (n=29)	20	9	29
41-50y (n=18)	10	8	18
51-60y (n=7)	5	2	7
>60y (n=11)	6	5	11

Antimicrobial agents implicated in causing ADRs were Cephalosporins (n=35), Fluoroquinolones (n=21), Penicillins (n=16), Antitubercular drugs (n=14), Macrolides (n=11), Sulfonamides (n=2) and Tetracycline (n=1). (Table 2) Ceftriaxone (23%), Ciprofloxacin (16%), Rifampicin (13%), Azithromycin (10%) were the drugs accounted for higher frequency ADRs. (Fig. 1) 14% of ADRs were caused by Fixed Dose Combinations (FDCs), in which Amoxicillin+Clavulanic acid and irrational combination (FDC) of Ciprofloxacin+Tinidazole accounted for 5% and 2% of ADRs respectively. (Table 3).

Table 2: Frequency of ADRs caused by different classes of Antimicrobial Agents

Causative drug class	Causative drug	Number of patients(n)	Frequency (%)
Cephalosporins (n=35)	Ceftriaxone	23	23
	Cefotaxime	5	5
	Cefixime	5	5
	Cefpodoxime proxetil	1	1
	Cefoperazone + Sulbactam	1	1
Fluroquinolones (n=21)	Ciprofloxacin	14	14
	Ciprofloxacin+Tinidazole	2	2
	Ofloxacin	2	2
	Moxifloxacin	2	2
	Norfloxacin	1	1
Penicillins (n=16)	Amoxicillin	7	7
	Amoxicilln+ Clavulanic acid	5	5
	Piperacillin +Tazobactam	4	4
Antitubercular drugs (n=14)	Rifampicin	13	13
	Isoniazid	1	1
Macrolides (n=11)	Azithromycin	10	10
	Clindamycin	1	1
Sulfonamides (n=2)	Cotrimoxazole	2	2
Tetracycline (n=1)	Doxycycline	1	1

Table 3: Frequency of ADRs caused by Fixed Dose Combinations of AMAs

Fixed dose combinations	Type of ADR	Frequency (14%)
Amoxicillin+ Clavulanic acid	Maculopapular rash (4%) Diarrhoea (1%)	5
Piperacillin +Tazobactam	Vomiting(2%) Maculopapular rash (1%) Injection site reaction(1%)	4
Trimethoprim+ Sulfamethoxazole	Vesics rash(1%) Gastritis(1%)	2
Ciprofloxacin+Tinidazole	Vomiting(1%) Fixed drug eruption (1%)	2
Cefoperazone + Sulbactam	Neutropenia(1%)	1

Most of the ADRs reported were affected the dermatological system (n=58), ranged between the simple maculopapular rash to life threatening Steven Johnson's Syndrome (SJS) followed by the gastrointestinal ADRs (n=36) in which diarrhoea (n=11) was the most common. (Table 4).

Table 4: Organ-system wise distribution of ADRs

Systems involved	ADRs	Number of patients(n)	Frequency (%)
Dermatological System (n=58)	Maculopapular rash	46	46
	Vesiculobullous rash	05	05
	Injection site reaction	03	03
	Fixed drug eruption	03	03
	Steven Johnson's syndrome	01	01
Gastro Intestinal System (n=36)	Diarrhoea	12	12
	Gastritis	11	11
	Vomiting	07	07
	Hepatotoxicity	06	06
Central Nervous system	Headache	02	02
Cardiovascular system	Anaphylactic shock	01	01
Respiratory system	Dry cough	01	01
Ophthalmological System	Conjunctival congestion	01	01
Haematopoietic System	Neutropenia	01	01

Causality assessment of ADRs by WHO probability scale revealed that 78% of ADRs were probable and 22% of ADRs were possible. After the causality assessment was made, in 80% of cases drug was withdrawn, 15% of cases dose was not changed and in 5% of cases dose reduction was made. (Fig. 1) 79% cases recovered with drug withdrawal and medical treatment. Severity assessment of ADRs by Hartwig and seigel scale showed that 21% were mild, 70% were moderate and 9% were severe ADRs. (Fig. 3) Serious ADRs like Anaphylactic shock (n=1) and SJS (n=1) were caused by Ceftriaxone, Neutropenia (n=1) by Cefoperazone+Sulbactam combination and Hepatotoxicity (n=6) by Antitubercular drugs were reported in the study. (Table 5).

Table 5: AMAs implicated in Serious ADRs

Causative drug	Serious ADR (9%)
Ceftriaxone	Anaphylactic shock(1%) Steven Johnson's syndrome (1%)
Cefoperazone + Sulbactam	Neutropenia (1%)
Antitubercular drugs	Hepatotoxicity(6%)

Preventability assessment by modified schumock and thornton scale showed that most of the ADRs caused by AMAs were not preventable (67%), 28% of ADRs were probably preventable and 5% were definitely preventable. 67% of ADRs caused by AMAs were unpredictable (Type B) and 33% were predictable (Type A) reactions.

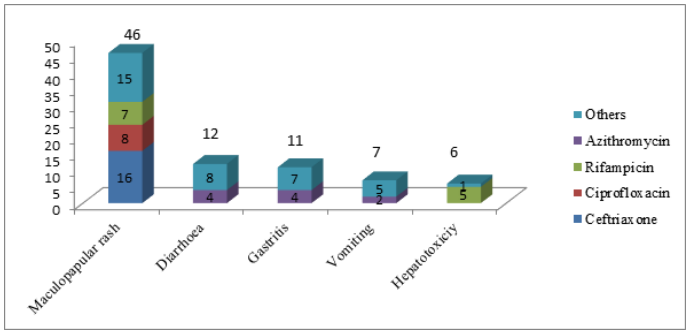

Fig. 1: Spectrum of ADRs related to commonly implicated AMAs

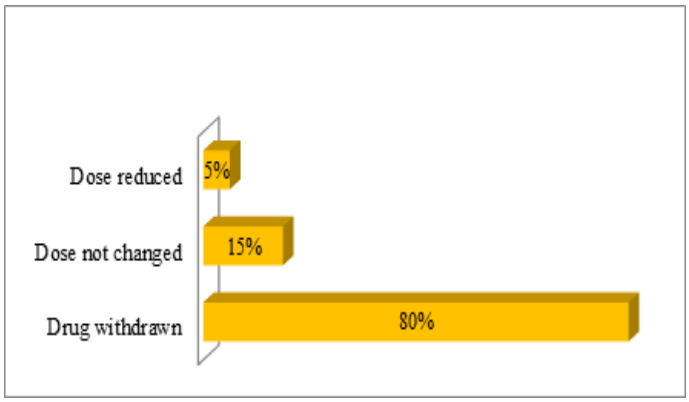

Fig. 2: Actions taken after the development of ADRs

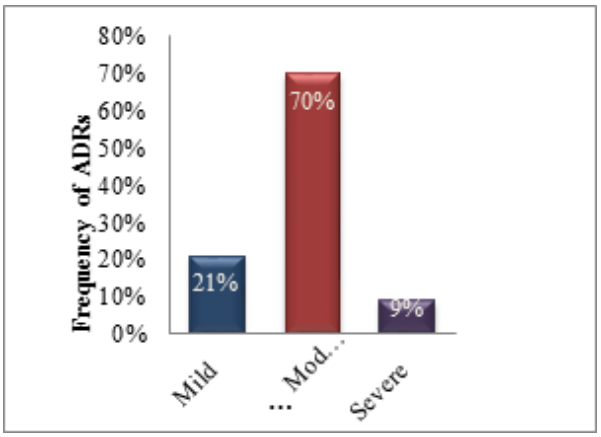

Fig. 3: Severity of ADRs

Discussion

AMAs are the greatest contribution of the 20th century to therapeutics. Their advent changed the outlook of the physician about the utility of drugs on diseases. They are one of the few drugs which can cure, and not just palliate disease. Their importance is magnified in the developing countries, where infective diseases predominate. As a class, they are one of the most frequently used as well as misused drugs.[15] AMAs being the most commonly used drugs are considered to be safer when used rationally. However, they are implicated in causing higher number of ADRs compared to other class of drugs.[10]

In the present study, analysis of the age wise distribution showed the predominance of ADRs in the age group of 31-40 years followed by 51-60 years which is similar to the study conducted by Jimmy Jose et al and Suthar et al where in, the age group most accounted were adults.[16,17] Occurrence of ADRs among adults is of concern, as their families could be affected economically. Present study shows occurrence of ADRs due to AMAs are predominant in males, which is similar to the study conducted by Kavitha et al in Ghaziabad India. Sudhaa Sharma et al noted no major gender related differences in the ADR patterns. But, studies conducted by Starveva et al and Hussain et al showed female predominance.[8,18-20]

Cephalosporins accounted for the higher incidence of ADRs, followed by Fluoroquinolones, Penicillins, Anti-tubercular drugs and Macrolides. Maximum number of ADRs were caused by Ceftriaxone, which is similar to the studies conducted by Kavitha et al and Mohammed misbahhussain et al.[8,20] Cephalosporins are effective against both gram positive and gram negative micro-organisms and therefore could be widely used in our hospital. About 10% patients allergic to Penicillin may show cross reactivity to Cephalosporin and thus could contribute to ADRs. Administration of test dose before administering the full dose of Cephalosporin may help to prevent fatal ADRs like Anaphylactic shock.

Fixed dose combinations contributed to significant number of ADRs. It is difficult to identify and withdraw the causative drug in FDC. Irrational FDC, Ciprofloxacin+Tinidazole contributed to ADRs in our study, where as in the study conducted by Sudhaa et al Ofloxacin+Ornidazole FDC was accounted for ADRs.[18]

Though Ciprofloxacin+Tinidazole FDC is claimed to be broad spectrum, combining Antiamoebic with Fluoroquinolone is irrational because patient suffers only from one type of diarrhoea. Using this combination adds to cost, adverse effects and resistance.

Cutaneous Adverse Drug Reactions (CADRs) accounted for majority of ADRs, with most common presentation being maculopapular and vesiculobullous rash. Ceftriaxone, followed by Ciprofloxacin were the commonly implicated drugs. Reena Verma et al from India reported that 56% of CADRs were caused by AMAs, where as in a study conducted Hsin-Yun-Sun et al from Taipei, Taiwan showed that the blood dyscrasias (32.1%), dermatomucosal effects (23.1%), and febrile reactions (17.9%) were the most common manifestations. Qing-ping shi et al reported that Cephalosporins accounted for higher frequency of dermatological ADRs (43.5%), most common reaction being the skin rash (30.6%) which is noted in our study.[21,22,23] Differences in study setting, study population, drug use and route of administration (oral vs intravenous) might contribute to such variations. CADRs are unpredictable reactions and they are unrelated to the dose. Most of the studies revealed that parenteral route of administration accounts for higher incidence of ADRs compared to oral route, but in the present study more number of ADRs occurred after oral administration.[2,18]

In the present study, 78% of the ADRs were probable and 22% were possible with no cases as certain because re-challenge of causative drug was not done. In the study conducted by Brahma Naidu et al from Guntur, AP, India, the WHO causality assessment scale revealed that 19% of ADRs were certain, 42% were probable, 29% were possible and 10% were unlikely and unclassified.[24] 70% of the ADRs were noted to be moderate in severity which is similar to the study conducted by Shamna et al from Saudi where they found 63.26.% of ADRs to be moderate in severity, whereas in a study conducted by Jamuna rani M et al showed that most of the ADRs caused by AMAs were mild (73.1%) in severity.[2,25] Interventions of ADRs ranged from withdrawal of the causative agent to administration of medical treatment. In the current study, 9% of ADRs were termed as severe, of which 6% were lead to prolonged hospitalization and 3% were life threatening. Incidence of severe ADRs were slightly higher compared to the study done by Jamunarani et al, where 6.5% patients experienced severe ADRs.[25] As the present study was conducted in a referral centre, the incidence of severe ADRs could be higher.

Serious ADRs like SJS and Anaphylactic shock caused by Ceftriaxone were noted in the present study. Pathophysiology of SJS/ TEN is still unknown. CD8+ T-lymphocyte have been identified to play an important role in the process. It is documented that Ceftriaxone-specific Major Histocompatibility Complex (MHC) molecule induce specific T-Cell Receptor (TCR) activation, followed by expansion of cytotoxic T lymphocytes which infiltrate skin leasions leading to necrosis of autologous lymphocyte and keratinocytes.[26] Recently (2016) Pharmacovigilance Programme of India (PvPI) recommended CDSCO for label change of Ceftriaxone that it can cause SJS. Anaphylactic shock is a Ig-E mediated type I hypersensitivity reaction which requires emergency treatment to avoid mortality.[27] The incidence of severe allergic reactions related to Ceftriaxone is 1-3%, and the incidence of anaphylaxis still lower at 0.1-0.0001%.[28] Even though serious ADRs occurred, no mortality was reported in our study whereas, 3% mortality was reported in a study conducted by Naidu et al.[24]

Hepatotoxicity was noted mainly among patients on Anti-tubercular drugs. Hepatotoxicity is considered to be the commonest reason for drug discontinuation. Increased formation of reactive metabolites generally as a result of phase I metabolism or failure of detoxification usually a function of phase II metabolism is likely to be an initiating event. These reactive metabolites induce the production of excessive reactive oxygen species (ROS) leading to lipid peroxidation and cell death. Cellular environment can modulate the threshold for hepatocytes death secondary to oxidative stress.[29] Anti-tubercular drug-induced hepatitis has also been found to be associated with acetylator phenotypes and other genetic polymorphisms, including cytochrome P4502E1 and glutathione S-transferase M1, and certain Major Histocompatibility Complex Class II associated HLA-DQ alleles.[30] The Indian Pharmacopoeia Commission (IPC) and Revised National Tuberculosis Control programme (RNTCP) are working together since 2013, to monitor the safety of Anti tubercular drugs.

Definitely preventable ADRs accounted for 5%, reason being the lack of documentation of previous drug history. Majority of reported ADRs were unpredictable in the present study, which is higher compared to the study conducted by Jamunarani et al where only 21.8% of ADRs were unpredictable.[25] This observation of present study also differs from the traditional concept that type A reactions are more common than type B reactions. It is difficult to explain why type B reactions were more commonly seen in our patients. Type B reactions are unrelated to pharmacological actions and are idiosyncratic. It is extremely important to record agents causing such reactions in the treatment charts. Issuing them an alert card with the details of reaction caused by the drug and informing the patient to show the card before receiving any medication, may prevent re-occurrence of such ADRs.

The study has a few limitations. It was a retrospective analysis of the spontaneously reported ADRs. The chance of under-reporting cannot be ruled out.

Computerised prescribing and monitoring systems and improving the awareness of ADRs among prescribers may reduce the incidence of ADRs.

Conclusion

Monitoring of ADRs is continuous process as the number of newer drugs entering the pharmaceutical market are increasing. Cepahalosporins and Fluroquinolones were implicated in majority of the ADRs. Cutaneous, followed by gastrointestinal systems were affected the most. FDCs were also implicated in causing ADRs. Though severe ADRs were noted, no mortality was reported. Early recognition and management of ADRs are essential to reduce the burden of ADRs.

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