Assessment of Adverse Drug Reactions due to Antimicrobial Drugs in Medicine Inpatients at a Tertiary Care Public Teaching Hospital

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ABSTRACT

Background: Adverse drug reactions (ADRs) represent the risk associated with the anticipated benefits of drug therapy and are known to be leading cause of morbidity and mortality worldwide. ADRs constitute an enormous clinical and economic burden on health care system.

Objectives: The objectives of this study were to identify the ADRs and to assess their causality, severity and preventability.

Methodology: This prospective observational study was conducted in the patients admitted to medicine wards of a public teaching hospital. Patients of all age groups and either sex admitted in medicine wards were included in this study. The ADRs were identified based on subjective and objective markers. The causality of suspected ADRs was assessed using Naranjo's ADR probability scale and WHO-UMC causality scale. Severity and preventability were assessed using modified Hartwig's severity scale and modified Schumock & Thornton criteria, respectively.

Results: Over the study period, data from 808 patients was collected. Of which 776 were analysed as they met the inclusion criteria. Out of 776 patients with complete documentation, 77 patients developed 82 ADRs during their stay in hospital with an incidence of 9.9%. The highest number of ADRs were associated with antimicrobial drugs (AMDs) (24.4%) followed by diuretics (15.9%) and opioid analgesics (14.6%). Overall 19 patients suffered adverse drug reactions due to administration of AMDs and a total of 20 ADRs were observed. Beta lactam AMDs were most frequently associated with ADRs. Among the organ systems affected, half of the ADRs due to AMDs were associated with GIT followed by cutaneous (40%). Hypersensitivity reactions (40%) were most commonly observed ADRs due to antimicrobial drugs. Based on Naranjo's scale 10% of ADRs were 'definite', 50% were 'probable' and 10% were 'possible' in nature. Further, based on WHO-UMC scale 20% of ADRs were 'certain', 30% were 'probable' and 50% were 'possible'. Modified Hartwig's severity scale showed 20% of ADRs were 'mild' and 80% were 'moderate'. Preventability assessment showed that 40% were 'probably preventable' and 60% were 'not preventable'. Also 60% of the ADRs were Type A in nature while remaining 40% were Type-B in nature.

Key points:

- β-lactam antibiotics were the lead class of AMDs involved in ADRs.
- Hypersensitivity reactions were most common ADRs observed.

- Female patients showed a higher incidence of ADRs compared to males.

INTRODUCTION

Medicines have been used since ages for the prevention, treatment, diagnosis of the diseases or alleviation of the symptoms. The disaster following the use thalidomide, used in 1960s for morning sickness by pregnant women appears to be the first planned step for safer drugs. The risk due to development of adverse drug reactions (ADRs) cannot be undermined. The World Health Organization (WHO) has defined an ADR as "a noxious, unintended and undesirable effect that occurs as a result of dose normally used in man for diagnosis, prophylaxis and treatment of disease or modification of physiological function"[1].The science and activities relating to detection, evaluation, understanding and prevention of ADRs or any other drug related problems is known as pharmacovigilance [2].

ADRs have been reported as leading cause of morbidity and mortality world wide. Lazarou et al. estimated that ADRs were the fourth to sixth largest cause of death in the United States of America and showed that the incidence of serious and fatal ADRs was 6.7% and 0.32%, respectively [3].Further, Pirmohammed et al. showed that over 2% of patients admitted with an adverse drug reaction died, signifying that ADRs may be responsible for the death of 0.15% of all patients admitted [4]. Evidence also indicates that death rates are 19.18% higher in patients who experience ADRs [5].

ADRs are also responsible for increased clinical and economic burden. ADRs continue to represent a significant clinical burden on health services, accounting for 1 in 16 hospital admissions and 4% bed occupancy [4]. This study also revealed that most reactions were either definitely or possibly avoidable. Evidence also suggests that ADRs are common during drug therapy but most of them are either definitely or possibly preventable. A meta-analysis by Hakkarainen et al. demonstrated that ADRs represent a significant burden on healthcare and approximately half of ADRs are preventable [6]. Davies et al. showed that ADRs directly increased length of stay in 26.8% patients [7]. The length of hospital stay in patients associated with ADRs is 8.25% higher and total medical costs for patients with ADRs are increased by an average of 19.86% [5].ADR monitoring studies conducted in India have reported the prevalence of ADRs between 2.12-32.7%[8-11].The total cost to the hospital due to ADRs was found to be Rs.1567397 (US$36451) and the average cost per patient hospitalized with an ADR was Rs.4945 (US$115) [12].

The development of ADRs has been associated with various risk factors like age, gender, number of drugs and length stay [8]. Davies et al. had shown that patients experiencing ADRs were more likely to be older, female, taking a large number of medications and had a longer length of stay than those without ADRs [7].

Although ADRs have been associated to range of drug classes but antimicrobial drugs [AMDs] have been more frequently associated with the development of ADRs. Novotny et al. has reported AMDs as the most troublesome class of drugs responsible for almost 16% of ADRs followed by antitumor and anticoagulant agents [13]. Kranthi et al. and Singh et al. have reported the incidence of 49.3% and 28.57%, respectively, due to AMDs [14, 11]. The higher incidence of ADRs associated with the use of AMDs is most probably due to the fact that these are the most frequently prescribed drugs in treatment and prophylaxis of infectious diseases; and, the available reports show that more than half of the hospitalized patients are prescribed with AMDs and

their use account for 20.50% of the drug expenditure in the hospitals.

This study is an attempt to identify characterize the ADRs taking place due to the use of antimicrobial drugs a tertiary care public teaching hospital.

MATERIALS AND METHODS

This prospective observational study was conducted at general medicine wards of a tertiary care public teaching hospital for a period of six months. The study was approved Institutional and Hospital Human Ethics Committees. Informed consent was obtained from every patient participating in the study.

Patients of all age groups, and either sex, admitted in the hospital wards were included in this study. The patients in which adverse drug reaction was the reason for admission, patients with incomplete information/ documentation and those unwilling to participate and not able to give informed consent were excluded from this study. For the purpose of this study, an ADR was defined according to the definition provided by World Health Organization [1].

Patient information including demographic details, diagnosis, medical history, laboratory data, vital values, and medicines prescribed their route of administration, dose, frequency and other necessary data were recorded on a pre-designed case record form (CRF). A daily visit to the wards was undertaken to assess the patient's clinical progress and all the patients were followed until discharged from the ward. The ADRs were identified based on subjective and objective markers like changes in laboratory values, vital values, and increase in severity or appearance of new symptoms not related to the disease pathology. Medical and nursing notes were also reviewed from the patient files for evidence of ADRs.

The suspected ADRs were analysed for their causality, severity and preventability using different scales. The assessment of causality was performed using WHO-UMC causality assessment criteria [13] and Naranjo adverse drug reaction probability scale [14]. The severity of ADRs was determined using Modified Hartwig's severity scale [15] and the preventability was assessed using modified Schumock and Thornton criteria [16]. ADRs were also classified as either Type-A (dose dependent and predictable from known pharmacology) or Type-B (idiosyncratic, unpredictable and non-dose dependent).

For the purpose of classification of diseases and medications prescribed, International Classification of Diseases was used (ICD-10) [17].Statistical analysis was performed using Microsoft Excel® 2013. Mean was supported by the standard deviation.

RESULTS

Over the study period, data from 808 patients was collected; and,32 patients were excluded as they did not fulfil the inclusion criteria.776 patients included in the study were followed up daily till discharged.

486 male patients, comprising 62.6% of the sample, had an average of 49.5±17.2 years and the female patients had an average age of 51.4±16.9 years. Further, a little more than one third of the patients were elderly (over 60 years of age; 36%) with the average age 68.2±8.6 years. The average number of drugs prescribed was 8.2±3.5 and the average length of stay was 8.7±4.4 days.

The average number of diagnoses was 2.2±1.0. Based on ICD-10, the major organ systems involved in diagnoses were: CVS 264 (34.0%), GIT 262 (33.7%), endocrine & metabolic 226 (29.1%), genitourinary 179 (23.0%), respiratory 99 (12.7%), blood and blood forming organs 85 (10.9%), infectious and parasitic diseases 77 (10.0%).The top ten diagnoses of the patients admitted were: DM2 255

patients (22.0%), HTN 195 (16.8%), CKD 189 (16.3%), CLD 158 (13.6%), acute pancreatitis 93 (8.0%), anaemia 97 (8.3%), CAD 91 (7.8%),UTI 76 (6.6%), COPD 63 (5.4%), CHF 37 (3.2%). Other diagnoses were malaria, tuberculosis, dengue and pneumonia.

A total of 776 patients were evaluated for adverse drug reactions. 699 patients did not suffer from any adverse drug reaction. Only 77 patients (45 male and 32 female) experienced at least one ADR during their stay in hospital. Therefore, the incidence of ADRs in this study was found to be 9.9%. The total number of ADRs observed in this study was 82. Among these 82 ADRs, 47 were observed in male and 35 were observed in females.72 patients (43 male, 29 female) experienced only one ADR while 5 patients (2 male, 3 female) suffered 2 ADRs each. None of the patients suffered from more than two ADRs. The most common class of drugs responsible were antimicrobial drugs 20 (24.3%) followed by diuretics 13 (15.9%) and opioid analgesics 12 (14.6%).More
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than 50% of the observed ADRs were associated with AMDs, diuretics and opioid analgesics. Almost one third of the patients were prescribed with one or more antimicrobials and 17.4% of all the prescribed drugs belonged to antimicrobial drugs. The average number of AMDs prescribed was 1.5±1.2.

Only 19 patients (9 male, 10 female) suffered adverse drug reactions due to administration of antimicrobial drugs and a total of 20 ADRs (9 in male and 11 in female patients) were observed. 15 patients belonged to adult category while only 4 belonged to elderly category. The different classes of AMDs involved in ADRs were further studied. Among these β-lactam antibiotics were the major offending class followed by fluoroquinolones. The individual AMDs, frequency of adverse drug reactions and nature of adverse drug reactions observed are shown in Table 1. The denominator in column 3 shows the number of patients who received the particular AMD

Table 1: Distribution of AMDs, ADRs and incidence

Drug involved	ADRs observed	Frequency	Incidence(%)
Imipenem	Hypersensitivity, Hepatic Impairment	3/24	12.5
Ciprofloxacin	Hypersensitivity, Diarrhea	3/91	3.3
Piperacillin + Tazobactam.	Hypersensitivity, Vomiting	3/175	1.7
Ceftriaxone	Hypersensitivity, Diarrhea	2/175	1.1
Azithromycin	Abdominal pain	2/60	3.3
Levofloxacin	Hypersensitivity reaction	1/29	3.4
Gentamycin	Renal impairment	1/2	50
Streptomycin	Vomiting	1/15	6.7
Ofloxacin	Diarrhea	1/3	33.3
Cefexime	Hypersensitivity reaction	1/2	50
Metronidazole	Dizziness, Restlessness	1/135	0.7
Rifaximin	Constipation	1/65	1.5

Antimicrobial drugs were responsible for different types ADRs affecting different organ systems. Hypersensitivity reactions, elevated liver enzymes, diarrhea, vomiting, abdominal pain, constipation and anxiety were the most common ADRs observed. The observed ADRs due to antimicrobial drugs affected a range of organ systems among which gastrointestinal system was the major organ system, followed by cutaneous(Figure 1).
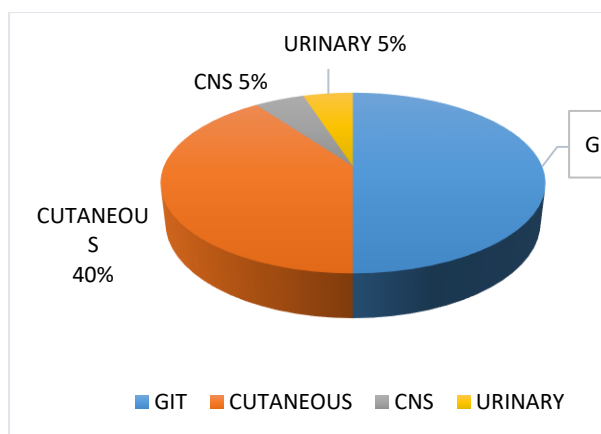

Figure 1: Organ Systems Affected Due to ADRs

Hypersensitivity reactions to antimicrobial drugs were the most frequently observed ADR and constituted 40% of the total

Causality Assessment

The suspected ADRs were assessed for causality, preventability and severity. Based on Naranjo adverse drug reaction probability scale, 10% of ADRs were "definite", 50% were "probable" and 40% were "possible" in nature. Further, on the basis of WHO-UMC causality assessment, 20% of ADRs were "certain", 30% were "probable" and 50% were "possible" in nature.

Severity Assessment

The analysis of severity of ADRs, using Modified Hartwig's severity scale,showed that 20% of the ADRs were "mild" and 80%were "moderate" in nature.

Preventability Assessment

ADRs. The class of AMDs associated with hypersensitivity reactions are shown in Figure 2. Among β-lactam antimicrobials, Imipenem (1), Pipercillin/Tazobactam (2) and Cephalosporins including Ceftriaxone (2) and Cefexime (1) were the most offending AMDs involved in hypersensitivity reaction. Among fluoroquinolones, Ciprofloxacin, Levofloxacin and Ofloxacin were involved in hypersensitivity reactions.
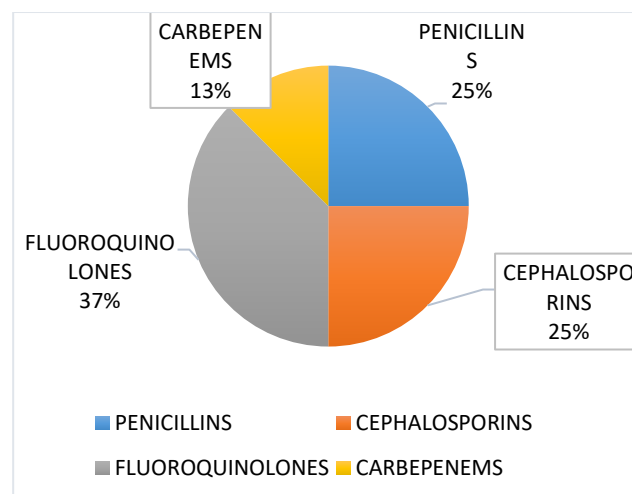

Figure 2: Class of AMDs associated with hypersensitivity reactions

Preventability assessment using Modified Schumock & Thornton criteria showed that 40% ADRs were "probably preventable" and 60% were "not preventable".

Moreover 60% of the observed ADRs were Type-A reactions while the remaining 40% were Type-B in nature.

DISCUSSION

The results of this study are based upon data obtained from a set of 776 patients admitted to the wards of a tertiary public teaching hospital. Antimicrobial drugs were second most frequently prescribed drugs in this study. This study showed that antimicrobial drugs were most frequently associated with almost one fourth of the ADRs.

Haile et al. and Singh et al. have also reported AMDs as the most offending drug class [8, 11]. The percentage of ADRs due to antimicrobials in this study was comparable to Haile et al. (24.4% vs. 24.3%). The consistency of results with Haile et al. (n=1460) may be due to fact that both studies were conducted in the same region of north India [8]. Singh et al. have reported ADRs as high as 28.57% on a study involving 4850 patients [11].

ADRs were also analysed with respect to the gender. The number of observed ADRs was found to be 11 in female patients and 9 in male patients. The number of female patients who suffered an ADR was 10 (out of total 290 female patients in the study). However, in male patients ADRs were noted in only 9 out of a total of 486. On this basis, it is appropriate to conclude that female patients showed a higher incidence of ADRs compared to males.

Singh et al. has also reported higher prevalence of ADRs in female patients when compared to male counterparts [11]. This may be due to hormonal changes in females like menstrual cycle and menopause, difference in fat composition, body mass index and weight which can affect the distribution and metabolism of drugs. On the contrary, Shamna et al. and Dhar et al. have reported predominance of male patients for ADRs with antibiotics which could be due to the fact that majority of the patients in these studies were male with high antibiotic use during study period [20,21].

β-lactam antibiotics were the major offending AMDs. β-lactam antibiotics (penicillins, cephalosporins and carbapenems) were responsible for 45% of the ADRs. The studies carried out by Shamna et al. and Dhar et al. and Nagaiah et al. have also reported predominance of β-lactam antibiotics involved in ADRs [20-22].

Hypersensitivity reactions were the most common (40%) ADRs observed with the use of β-lactam antibiotics.

Hypersensitivity reactions which includes rashes, itching, urticaria and fever are the major problem in the use of β-lactam antibiotics particularly penicillins; and, in current study 62.5% of the observed hypersensitivity reactions were associated with β-lactam antibiotics. Ravichandar et al. has also reported predominance of Type-B reactions compared to Type-A due to AMDs [23].

This study has also shown fluoroquinolones as second most offending AMD which is in concurrence with Shamna et al. that has also accounted fluoroquinolones as second most offending AMD [20]. Dhar et al. Have, however, reported vancomycin as second most offending AMD [21]. Fluoroquinolones have broader spectrum of activity and cover gram-positive bacteria and even anaerobes. Literature shows a number of fluoroquinolones have been withdrawn from the market previously because of serious adverse reactions. Leone et al. also concluded that difference in safety profiles should be taken into account when prescribing a fluoroquinolones to an individual [24].

According to the results of this study, Type A reactions which are dose-related, more common and potentially preventable accounted for 60% of the ADRs while 40% were of Type B nature which are unpredictable, less common and include hypersensitivity reactions. This result is consistent with the findings of, Haile et al. Shamna et al and Khan et al. who have reported similar results [8, 20, 25].

In this study, gastrointestinal system was the most commonly affected organ system due to ADRs followed by cutaneous and metabolic systems. The study conducted by Shamna et al. also reported predominance of gastrointestinal system followed by skin in the ADR occurrence [20]. Dhar et al. and Khan et al. have also reported gastrointestinal system as most affected organ system but the second most affected organ system in these studies were respiratory and central nervous system

respectively [21,25]. However, Nagaiah et al. has reported dermatological system as the most affected system [22].

No re-challenge was performed in this study. The causality assessment has been performed using Naranjo scale and WHO-UMC causality assessment scale. The results, using Naranjo scale, showed that 50% of the reactions were 'probable', 40% were 'possible' while 10% ADRs were in the 'definite' category. Haile et al. have reported 71.9% ADRs as 'possible', 26.1% as 'probable' and 2% as 'definite' [8]. Moreover, Shamna et al. and Ravichandar et al. have reported majority of ADRs in 'probable' category and less number of ADRs in 'possible' and 'definite' categories [22, 23].

On the other hand, analysis using WHO-UMC scale revealed that half of the observed ADRs were 'possible' while 30% were 'probable' and 20% ADRs belonged to 'certain' category. This does not match the findings of Nagaiah et al. which reported most of the ADRs belonged to 'probable' category followed by 'possible' category [22].Both Naranjo scale and WHO-UMC causality assessment scale used in this study showed that none of the ADRs were unlikely due to a drug.

Almost all the ADRs required treatment. The Hartwig severity scale showed that majority of the ADRs belonged to 'moderate' category (80%) followed by 'mild' category (20%).These results are in agreement with results of Shamna et al. who also reported majority of ADRs in 'moderate' and 'mild' category [20]. The incidence of 'severe' ADRs reported by Shamna et al. was 8%, 7.5% by Haile et al. and in this study, none of the observed ADRs was in 'severe' category [20, 8].

This study showed 40% of the ADRs were 'probably preventable' and 60% ADRs were 'not preventable'. The most common ADR observed in this study were hypersensitivity reactions which are Type B reactions and are unpredictable hence not preventable. These results are consistent with Shamna et al. which reported majority of the reactions were 'probably preventable' [20].

CONCLUSION

This study has shown that β-lactam antibiotics are the lead class involved in development of ADRs followed by Fluoroquinolones. In this study, gastrointestinal system was the most commonly affected organ system due to ADRs followed by cutaneous and metabolic systems. Finally, we conclude that female patients showed a higher incidence of ADRs compared to males.

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