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Adverse Drug Reaction Monitoring in a North Indian Public Teaching Hospital

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Abstract

Background: ADRs are a significant cause of morbidity and mortality. Hospital-based monitoring is one of the methods to identify and assess the ADRs. The aim of this study is to monitor the incidence, causality, preventability and severity of ADRs occurring in the wards of a public teaching hospital.

Method: A prospective-observational study was conducted in medical wards of a public teaching hospital to assess the Causality, level of severity and preventability of identified ADRs. All the relevant information was collected from patients' record file in a standard case record form. To find out the incidence of ADRs between different gender and age groups, chi- square was applied.

Results: 60 ADRs in 56 patients were detected in 520 patients admitted to the hospital. The most commonly occurring ADRs were constipation, hypokalemia and diarrhea. Most troublesome classes of drugs contributing to adverse drug reactions were antibiotics. All the ADRs were Type 'A' reaction (100%). According to Naranjo's ADR probability scale, 13% ADRs were 'possible' and 87% ADRs were 'probable'. Severity assessment, using Modified Hartwig criteria, showed that 53% ADRs were mild and 47% ADRs were moderate respectively. Preventability of ADRs was assessed using modified Shumock and Thornton method; and, it was found that all the 95% ADRs were not preventable.

Conclusion: The results of this study concluded that adverse drug reactions were significant cause of increase burden on health care system, decrease quality of life, and increase hospitalizations. The results would help in the early detection and to ensure safer drug therapy.

Keywords: Adverse Drug Reaction, Pharmacovigilance, India, In-Patient Department (IPD)

Introduction

Pharmacovigilance is defined by the World Health Organization (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [1]. Drugs are double edged weapons drugs. Therefore, drugs offer great benefit to patients, but they can come with great risks when not administered or managed properly [2].

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition is independent of the mechanism of the adverse reaction and includes allergies, idiosyncrasies, pharmacological and toxicological mechanisms and interactions between different drugs. Adverse drug reactions are the most frequently reported causes of morbidity and mortality during hospitalizations affecting up to 20% of all hospitalized patients [3]. All drugs can produce ADRs, but not all patients develop the same level and type of ADRs. The majority of ADRs occur as a result of the extension of the desired pharmacologic effects of a drug, often due to the substantial variability in the pharmacokinetics and pharmacodynamics seen among patients. Factors that predispose to ADRs include age, polypharmacy, gender; immune system and pharmacogenetics have shown more propensity to cause morbidity and mortality [4].

In order to insure safer use of drugs, there is a need for a vibrant pharmacovigilance system at all the levels of health care. Hence, the development of a better system of reporting ADRs has been recommended as a top priority action to prevent ADRs in hospitals. Hospital based monitoring is one of the systems used to collect data on drug prescriptions and this data have become an important component of monitoring and evaluation activities performed in hospitals [5-7].

The aim of present prospective study was to determine the incidence, causality, preventability and severity of ADRs occurring in the wards of a public teaching hospital. Our research group has shown that, 10% ambulatory elderly patients were found to have ADRs in the same setting [8].

Methods

A prospective observational study was carried out at the three general wards of medicine department of a public teaching hospital over a period of 6 months.

All patients admitted to the wards were included in the study irrespective of sex and all age. The ADRs that had occurred outside the hospital or the reason for admission in hospital was excluded from the study. The patients with intentional or accidental poisoning with drug abuse and medico legal cases were excluded from the study. Patient files with incomplete data (such as lab values, progress notes, and incomplete prescription) were also excluded from the study. All relevant information was collected from patients' record files in a standard case record form. The information included reason and date of admission in hospital, date of discharge, drug allergies, and diagnosis and co morbid conditions. All laboratory investigations, vital values, daily progress notes from doctors and nurses were recorded. All the patients were followed until discharge from the general wards. All prescribed drugs including dose, frequency and route of administration were noted in the case record form.

ADRs were identified by three methods. First method was objective finding; include changes in laboratory values and changes in vital signs which are not related to the disease pathology. Second method was subjective findings; include increase in the severity of symptoms or appearance of new symptoms, identified during the treatment which was not present when the therapy was started. If it is not related with the disease pathology but related with drug, then it considered as an ADR. Third method was spontaneous reporting; the ADRs which were recorded in the patients record file identified by doctors or nurses.

Causality assessment was performed by using Naranjo's ADR probability scale. This scale categorizes ADR into Definite (score ≥ 9), probable (score=5-8), possible (score=1-4) and unlikely (score=0) [9]. Causality was also assessed by WHO-UMC causality category which categorizes ADRs into certain, probable/likely, possible, unlikely, conditional/unclassified, unassesable / unclassifiable [10]. ADRs were classified into mild, moderate and severe reactions using the Modified Hartwig criteria for severity assessment [11]. ADRs were categorized into definitely preventable, probably preventable and not preventable using the criteria of Schumock and Thornton criteria [12].

Individual reactions were classified depending on the type of reactions as type A (Augmented) and type B (Bizarre) reactions based on the classification by Rawlins and Thompson [13]. Drugs involved in the ADRs were codified into various drug classes according to anatomical therapeutic chemical (ATC) classification based on WHO–ATC Index 2013 [14].

Statistical Analysis

All the data was represented as average±SEM, and percentages. Chi-square test was applied for comparing categorical variables. Statistical analysis was performed using SPSS version 20.

Results

The results were based on data collected from the records of 533 inpatients from medicine wards. 13 patients were excluded from the study; 5 were medico-legal cases and 8 had incomplete files. Therefore, the results presented are based on data obtained from 520 inpatients.

The average age of patients was 42.41±0.78 years. The average length of stay was 8.64±0.19 days; average number of diagnosis 2.52±0.05, and average number of medication 9.16±0.16 (Table 1).

Parameters	Avg age (yrs)	Avg length of stay (d)	Avg no. of diagnosis	Avg number of medications
Male (n=344) Range	42.03±0.94 (13-90)	8.83±0.24 (2-40)	2.15±0.06 (1-7)	9.24±0.19 (1-21)
Female (n=176) Range	43.12±1.4 (13-87)	8.26±0.32 (3-27)	2.15±0.08 (1-5)	9.02±0.31 (1-28)
Children (n=44) Range	15.52±0.26 (13-18)	7.81±0.49 (3-18)	1.68±0.15 (1-4)	7.88±0.41 (1-14)
Adults (n=377) Range	38.39±0.59 (19-59)	8.68±0.23 (2-40)	2.12±0.05 (1-6)	9.25±0.19 (1-28)
Geriatric (n=99) Range	69.57±0.75 (60-90)	8.78±0.46 (3-26)	2.52±0.13 (1-7)	9.43±0.44 (1-22)

Table 1: Demographic profiling of the patients.

Of the 520 patients in the study, 56 patients experienced only one ADR and 2 patients had more than one ADR, a total of 60 ADRs. Incidence rate of ADRs was found to be 12%. ADRs were more frequent in males (75%) than in females (25%). All patients were classified on the basis of age into three groups.

The first group had 45 children (1-18 years), second group had 377 adults (19-59years) and the third group had 20 patients (over 60 years of age). The rates of ADRs in pediatric, adult and geriatric patients were 3%, 60%, and 37%, respectively.

The patients in age group of 19-59 years showed the highest number of ADRs, i.e. 36 (60%). There was a statistically significant difference in the incidence of ADRs among different age groups ($\chi 2=29.08$, $p=0.01$; Table 2).

Age group	Number of ADRs
Children (1-18 years)	2 (3%)
Adult (19-59years)	36 (60%)
Geriatric (≥ 60 years)	22 (37%)
Total	60

Table 2: Patient characteristics.

Most of ADRs were found to be 'Type A' reaction. The class of drugs most commonly involved in ADRs was infections and infestations drug class that showed the highest number of ADRs. The details regarding classes of drugs classified according to ATC are represented in (Figure 1).

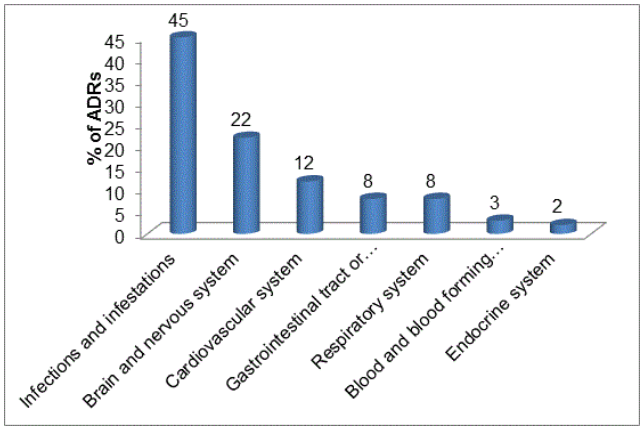

Figure 1: Profile of classes of drugs classified according to ATC.

The gastrointestinal system was found to be the most commonly affected organ system, followed by the metabolic and cutaneous system. The least affected system was found to be hematological system (3%) and cardiovascular system (2%; Table 3).

Organ system	Number (%) of ADRs	ADR number of times
Gastrointestinal	44 (73%)	Vomiting (1), diarrhea (24), constipation (19)
Metabolic	10 (17%)	Hypokalemia (10)
Cutaneous	3 (5%)	Edema (1), rash (2)
Hematological	2 (3%)	Thrombocytopenia (2)
Cardiovascular	1 (2%)	Tachycardia (1)
Total	60	60

Table 3: Organ system affected by ADRs.

Majority of ADRs were noted with parenteral route of administration (60%). Drugs administered by oral route accounted for 33%, while nebulized route accounted for 7% of the ADRs.

The top three most commonly reported ADR was diarrhea followed by constipation and hypokalemia (Table 4)

Commonly occurring ADRs	Number of ADRs	% of ADRs
Diarrhea	24	40%
Constipation	19	32%
Hypokalemia	10	16%
Thrombocytopenia, rash	2 each	6%
Tachycardia, edema, vomiting	1 each	6%

Table 4: Most commonly occurring ADRs.

Out of 60 ADRs, 24 ADRs were caused by antibiotics alone. Antibiotics are used commonly in routine practice for treatment and prophylaxis of various disease conditions. In this study, the most commonly prescribed antibiotic was ceftriaxone. Out of 24 ADRs, 15 ADRs were caused by ceftriaxone and 6 by Piperacillin+Tazobactum (Table 5).

Drug Class	Name of ADRs	Number
Antimicrobials Cephalosporins (Ceftriaxone, Ceftazidime)	Diarrhea(15 instances and 1 instance, respectively)	27 16
Quinolones (Ofloxacin)	Diarrhea(1)	1
Penicillins (Piperacillin+Tazobactam, Piperacillin+ Tazobactam, Imipenem +Cilasatin)	Maculopapular rash(1), Diarrhea(5), Skin rash(1)	7
Antifungal (Fluconazole)	Vomiting	1
Other antibiotics (Nitrofurantoin)	Diarrhea(2)	2
Antihypertensive (Amlodipine)	Edema(1)	1
NASIDs (Aspirin)	Thrombocytopenia	2
Diuretics Furosemide, Furosemide+Spironolactone	Hypokalemia(5), Constipation(1)	6
Analgesics (Tramadol)	Constipation(13)	13
Antiasthamatic Ipratropium bromide, Ipratropium bromide+Levosalbutamol	Constipation(5)	5
Antiemetic (Ondansetron)	Hypokalemia(1)	1

Antidiabetic (Insulin)	Hypokalemia(3)	3
Thyroid Hormone (Levothyroxine)	Tachycardia(1)	1
Vitamin and Minerals (Folic acid)	Hypokalemia(1)	1

Table 5: Class of drugs involved.

Out of the 60 identified ADRs, 52 of the reactions were 'probable' (87%) and 8 of the reactions were 'possible' (13%) according to Naranjo's ADR probability scale (Table 6). According to WHO-UMC causality categories, 28 ADRs were 'probable' and 32 were 'possible'.

The preventability was assessed using the modified Schumock and Thornton's criteria; 57 were 'not preventable' (95%) and 3 were 'probably preventable' (5%). The severity of the ADRs was evaluated using modified Hartwig's classification; it was found that 32 were 'mild' and 28 were 'moderate' (Table 6).

Parameters	Number (%) of ADRs
Causality (Naranjo's scale) Probable Possible	52 (87%) 8 (13%) 28 (47%)
Causality (WH0-UMC scale) Probable Possible	32 (53%)
Severity Mild Moderate	32 (53%) 28 (47%)
Preventability Probably preventable Not preventable	3 (5%) 57 (95%)

Table 6: Characterization of ADRs.

Discussion

Adverse drug reactions adversely affect the health care system and quality of life of patients in many ways. The present study was conducted in order to identify and assess the ADRs occurred in the wards of a public teaching hospital.

Overall incidence of ADRs was found to be 12%. The incidence rates of ADRs differ widely across different studies. This wide variation was attributed to different methodology adopted to collect information on ADRs. Lazarou et al. showed that the total incidence of both categories of serious ADRs was 6.7%, of which 4.7% were responsible for admission and 2.1% occurred after admission, with an overall fatality rate of 0.32% [3]. One study conducted on hospitalized patients by Jose et al. (2006) in Karnataka showed that the overall incidence of ADR calculated from the patient population was only 0.15%. The reason for this low incidence was that information on the ADRs was collected only if physicians reported through the spontaneous reporting system and patients were included from both the settings i.e. in-patients and out-patients [15,16]. A total of 520 cases were studied during the study period, including 66% males and 34% were females. ADRs were more frequent in males 45 (75%) than in females 15 (25%). No significant difference was observed in the ADRs between males and females during the hospital stay ($\chi 2 = 3.30$, $p = 0.07$). This may be due to more number of admitted patients were males. This finding is concurrent with the results of the study carried out by Lobo et al. who reported ADRs were more dominant in males (55.7%) than in females (44.3%) [5]. Various studies have reported that the percentage of ADRs found was higher in adults than geriatric population. The present study also revealed predominance adult (60%) over the geriatric (37%) and pediatric (3%) populations. This may be due to the fact that most patients who were admitted to the hospital were adults. This might be due to the fact that most adult patients received multiple drug therapy and also presented with other co morbidities such as diabetes, hypertension, tuberculosis, and asthma. It is known that multiple drug therapy and co-morbidities predispose patients to adverse drug reactions. Within the 'adult' age group, most reported cases were from the patients who were ≥ 40 years. This finding is consistent with the results of the study carried out by Ramesh et al. Their study reported that adults (67.1%) were most affected by ADRs followed by the geriatric (29.9%) population [17]. A similar study was carried out by Lobo et al. they reported that drug related hospitalization was significantly higher in the adults (61%) than geriatric (20%) population [6].

Almost all ADRs were found to be 'Type A' reaction. 'Type A' (augmented) reaction means that ADRs were dose related and related to a pharmacological action of the drug. Study carried out by Lobo et al. gave the consistent finding as above result. This study showed that (82.1%) ADRs were classified as 'Type A' reactions [6]. Study carried out by Mjorndal et al. gave the consistent finding as above result. This study showed that 90 (90%) ADRs were classified as 'Type A' reactions, and seven (7%) were of 'Type B' [18]. The most common category associated with ADRs was infections and infestations 27 (45%). This might be associated with the fact that antibiotics were the most commonly used class of drugs in this study. Patidar et al. showed same finding as above. His study showed that drug class most commonly implicated with ADRs was antibiotics 13 (40.62%) [6]. Another study conducted by Rehan et al. also showed the same finding who reported that antibiotics (35.7%) were the commonest group of drugs causing ADRs [19].

The system most commonly affected by an ADR was the gastrointestinal system (73.3%) followed by the metabolic system (16.6%). In gastrointestinal system, ADRs reported were diarrhea (24), constipation (19) and vomiting (1). This finding is similar to the study conducted by Ramesh et al. who reported that the system most commonly affected by an ADR was the gastrointestinal system (36.3%) followed by the nervous system (24.4%) [17]. Maximum numbers of ADRs were caused by parenteral route of administration of drugs (60%) followed by oral route (33%) and nebulized route (7%). The present study is in contrast to study done by Srivastava et al. Their study reported that majority of ADRs were noted with oral route of administration (83.74%). Drugs administered by parenteral route accounted for 8.14% of ADRs, while 8.07% of the drugs given topically caused ADR [7]. This difference might due to different hospital setting

and different diagnosis and different prescribing pattern by physicians. The most commonly occurring ADRs was diarrhea 24 (40%) followed by constipation 19 (31.6%). The above results are in accordance with the study conducted by Halon et al. [20,21].

Antibiotics are used for treatment and prophylaxis of various infectious conditions and are considered as safer drugs when used rationally. But, like all other drugs, they also show some adverse drug reactions in various patient conditions [22,23]. According to a study conducted by Shamna et al. showed that the most affected antibiotic class was cephalosporins 17 (34.69%) followed by fluoroquinolones 15(30.61%), penicillins 7(14.28%), others 3(6.12%) [22]. This study is accordance with my present study, reported that cephalosporins 16 (27%) was most commonly accounted antibiotic class followed by penicillins 7 (12%). A study done by Ren et al. showed the similar finding as in above results. Third-generation cephalosporin was responsible for maximum ADRs (55.87%), in particular, associated with (15.56%) ceftriaxone. Cefaclor was found to be safer than other cephalosporins, whereas ceftriaxone was found to be less safe [20]. To strengthen and further emphasize the validity of the findings of the study, causality assessment was done by using the Naranjo's scale and WHO-UMC causality. According to WHO-UMC causality, there is a slight difference in causality, 28 (46.6%) ADRs were found to be 'probable' and 32 (53.3%) ADRs were 'possible'. Jose et al. in their study found that about 49.5% of the ADRs were 'possible' and about 38.14% of the ADRs were 'probable' [16].

On evaluation of the severity of ADRs by the Hartwig severity assessment scale, it was evident that most of the ADRs reported in the study were of 'mild' severity 32 (53.3%) and 'moderate' were 28 (46.6%). No ADR was found to be 'severe'. This finding is consistent with the results of the study carried out by Jose et al. showed 50.5% ADRs were 'mild'and 44% ADRs were 'moderate' [16]. Modified Schumock and Thornton's criteria were used to determine the preventability of ADRs. Around 95% ADRs were 'not preventable' 5% of the ADRs were 'probably preventable'. It suggest that if proper monitoring system in the hospital is developed than around most of the ADRs can be prevented from taking place. Study carried by Jose et al. showed the same finding as above, 72% ADRs were 'not preventable' followed by 18% 'probably preventable' [16].

Conclusion

The results provided awareness to the healthcare providers on the importance of monitoring and reporting of Adverse Drug Reactions in a public teaching hospital. Adverse Drug Reactions are one of the major drug related problems in the hospital setting and is a challenge for ensuring drug safety. Antibiotics amount to the major volume of the drug family and inpatient prescriptions and thus are the most irrationally prescribed drug class. So, Adverse Drug Reactions related to antibiotics use should be closely monitored for the ADRs to avoid any harmful consequences.

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