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RESEARCH ARTICLE

An intensive monitoring of adverse drug reaction in indoor patients of medicine department at tertiary care teaching hospital: A single center, prospective, multisource observational study

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ABSTRACT

Background: Adverse drug reactions (ADRs) have been evolved as a serious and major health-care problem affecting the quality of life of patients and increasing burden over the health-care system. Studying the pattern and spectrum of ADRs can help to find measures to address the problem and possibly prevent it effectively. **Aims and Objectives:** The study aimed to intensively monitor ADRs in indoor patients of medicine wards and estimate the incidence rate with documentation of the spectrum of ADRs in studied patients in terms of causality, severity, and preventability. **Materials and Methods:** This was prospective, observational, and single-center study, conducted at internal medicine wards of Sir Sayajirao General Hospital, Vadodara, over a duration of 8 months, after taking prior permission from the Institutional Ethics Committee. The necessary data were obtained and recorded on a pre-designed "case record form" and "Indian Pharmacopoeia Commission-ADR reporting form" after taking written informed consent and analyzed with Microsoft Excel-2016. **Results:** A total 11,400 admissions recorded during the study period in all nine wards of medicine department, of which 66 patients developed 88 ADRs with the incidence of 0.5789%. They were classified into Group A (38, 57.58%), ADR developed after hospitalization and Group B (28, 42.42%), ADR is the reason for hospitalization. The most common category of causality assessment was "probable" according to both WHO-UMC criteria (53, 54.65%) and Naranjo scale (54, 55.68%). According to modified Hartwig-Siegel scale majority, ADRs (43, 48.32%) fall into "moderate" category, and according to modified Thornton and Schumock criteria, the "preventable" ADRs were (29, 30.85%). **Conclusion:** The drug safety seems to be well considered in this setup with lower incidence rate found in our study, but there is still a need for improvement to reduce the huge portion of preventable ADRs.

KEY WORDS: Drug Safety; Intensive Adverse Drug Reaction Monitoring; Medicine Indoor Patients; Pharmacovigilance

INTRODUCTION

Adverse drug reaction (ADR), as defined by the WHO,[1] is "a response to a drug that is noxious, unintended and occurs at doses normally used in man for prophylaxis, diagnosis or treatment of disease, or for modification of physiological function." The activity of ADR monitoring is known as "Pharmacovigilance" which is defined by the WHO as "the science and activity relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems."

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In 1950s, thalidomide was initially introduced as an effective medication for influenza. Later on, it was marketed as a new, mild sedative with an amazing absence of acute toxicity even

at high doses.[2] During the years following the marketing of thalidomide, the drug was prescribed to thousands of people, including fertile women. In 1961, McBride in Australia reported in a short letter to the editor of the Lancet about the cases of limb malformations among babies and that a common denominator seemed to be the intake of thalidomide by their mothers.[3] Near the same time, two reports were published by German physicians describing the similar kind of limb malformations.[4] In the wake of this public health disaster, governments in many countries established procedures for a collection and systematic evaluation of suspected ADRs.

ADRs have been implicated as a major cause of considerable morbidity and mortality.[5] They are a serious clinical problem, accounting for increased resources.[6] The incidence of ADR varies with studies ranging from as low as 0.15% to high as 30%.[7,8] Apart from the medical impact, it also have an economic impact. The patients who developed adverse effects during hospitalization were hospitalized for an average of 1.2–3.8 days longer than patients who did not, with a substantial increase of the healthcare costs.[9] Up to 57% of the community-acquired ADRs are not being recognized by the attending physician on hospital admission, leading to inappropriate management of the adverse event and exposure of the patient to additional hazards of the drugs and prolonged hospitalization.[10]

At present, only spontaneous reporting of ADRs is practiced in India, which plays major role in the identification of safety signals once the medicine is marketed and it may also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known and serious ADRs. However, it captures only a small fraction of the adverse events that actually take place (underreporting).[11] There are strong biases in reporting.[12] Most of these problems can be overcome by undertaking a hospital based intensive monitoring. In India, very few intensive monitoring studies are published.

The present study was carried out to study the incidence and the pattern of ADRs and to shed light on their extensiveness and pattern of occurrence in the local population. It was also considered to provide opportunities for interventions, especially for the preventable ADRs, which will help in promoting safer use of drugs. The observations made, if disseminated to other health-care professionals, can help to improve the quality of patient care by ensuring good pharmacovigilance practice. Furthermore, similar reporting exercises may become necessary to educate and to increase the awareness about ADRs to all the concerned patients.

MATERIALS AND METHODS

This prospective, observational, and single-center study was undertaken with the objectives of conducting intensive monitoring and to estimate the incidence of ADRs in hospitalized patients of internal medicine wards of a tertiary care teaching hospital and to document the spectrum of ADRs in studied patients in terms of causality, severity, and preventability. It was carried out at internal medicine wards of government medical college and Sir Sayajirao General (SSG) Hospital, Vadodara. All the recorded admissions who either develop a clinically suspected ADR after admission or those who are admitted primarily because of an ADR in internal medicine wards were included over a period of 8 months from September 2014 to April 2015. All the patients enrolled during this period were followed up until they were discharged. No formal sample size was calculated for this study, and all the patients with suspected ADR during the study period were enrolled.

Inclusion Criteria

The following criteria were included in the study:

1. All patients of both sex and age more than 12 years admitted in internal medicine wards.
2. Patients transferred from the intensive care unit and intensive coronary care unit to internal medicine wards.
3. Patients referred to the higher center or discharged against medical advice but in whom the outcome of ADR was known were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. <12 years of age groups patients.
2. Patients referred to the higher center or discharged against medical advice and in whom outcome of ADR was not known.
3. Patients who developed an ADR during transfusion of blood or blood products and vaccines.
4. Patients with intentional or accidental poisoning, drug abuse, and patients with non-compliance.
5. Patients who had not developed ADR during his/her drug treatment and get transferred to some other department or those directly admitted to intensive care unit, dialysis unit, TB chest ward or isolation ward were excluded from the study.

Prior permission from the Institutional Ethics Committee of SSG Hospital, Vadodara, and head of the Medicine Department was obtained. The investigator visited the wards regularly and observed patients with case record data from admission to discharge. The attending doctors and the paramedical staff were appraised about the study objectives and requested to inform the investigator about any ADRs. The detection of the ADRs was, therefore, done by both the investigator, as well as the attending medical and paramedical personnel. In all the ADR-related patients, the necessary data were obtained and recorded on a pre-designed case record form (CRF), national coordinating center (NCC)-PvPI ADR form along with written informed consent.

The data recorded include general details, for example, name, age, sex, present history, general and systemic examination, laboratory investigation, diagnosis, and treatment were recorded in "CRF form." If required, patients were interviewed at the time of enrolment into the study. In case that was not possible, relatives of the patients were asked to provide the desired information. An ADR was documented in details in a "NCC-PvPI ADR form" which is prescribed by Indian Pharmacopoeia commission. This form contains the details of general patient characteristics, adverse drug event, suspect medication, treatment of ADR, and its outcome. The assessment of ADRs was carried out by (1) causality analysis: All the observed ADRs were undertaken as per the WHO-UMC (1972)[13] and Naranjo *et al*.[14] probability score. (2) Severity analysis: The severity of an ADR was evaluated by Hartwig *et al*.[15] severity assessment scale and (3) preventability analysis: The preventability of an ADR was estimated by using the modified Schumock and Thornton[16] criteria. The data collected in the manner described above were analyzed under incidence, age, and gender distribution of patients, onset, resolution time, categorization according to the anatomical system, according to drug class, route of administration of suspected drugs, seriousness, outcome, causality, severity and preventability of ADRs. Results were expressed in absolute number and percentages. Analysis of results was done using Microsoft Excel 2016.

RESULTS

For the study purposes, the patients were divided into two groups, (1) patients that were admitted for other ailments (other than an ADR) but developed the ADRs during hospitalization (Group A) and (2) those patients that were admitted primarily due to the ADRs developed outside the hospital (Group B).

A total number of 11,400 patients were admitted during the study period; of these, 11,334 patients had no ADR. In the remaining 66 patients, 38 (57.58%) developed the ADRs during hospitalization (Group A) and 28 (42.42%) patients were admitted primarily for the treatment of ADRs that developed outside the hospital (Group B). Thus, the incidence of ADRs in this study was 0.58% (n = 11,400). This reflects the number of patients in medicine wards with ADRs that may have developed before or after their hospitalization. It was observed that 38 patients (0.33%) developed the ADRs during hospitalization (Group A) while in 28 patients (0.24%), ADRs themselves were the reason for their hospitalization (Group B). The flow chart showing recruitment of patients is depicted in Figure 1. A further analysis of the data revealed that a total number of 87 ADRs were reported in 66 patients. Out of this 87 ADRs, 47 (54.02%) were reported in Group A and the remaining 40 (45.98%) in Group B.

Majority of ADRs reported were in 31–60 age groups (44, 66.67%). ADRs in geriatric age group (>65 years) were (8, 12.12%). The mean age of the patients in whom ADRs were reported was 45.38 years. Out of 11,400 patients, 7214 patients were male and the remaining 4186 were females. The incidence of the ADRs in male patients was 0.62% (45/7214) and in case of females it was 0.50% (21/4186). The male:female ratio was 1.24. Out of 66 patients more ADRs were reported in male patients (45, 68.18%) than in female patients (21, 31.81%). Most of the ADRs in Group A 36 (41.37%) developed within 10 days of drug intake, while in Group B most reaction 27 (31.03%) developed after a period of 1 month of drug administration [Figure 2]. Most of the ADRs, 59 (67.81%), were resolved within a week after starting treatment. A total of 28 (32.18%) ADRs, however, did not subside, were abating or persisting at the time of discharge. No death was reported due to the ADRs [Figure 3]. Out of 87 ADRs, 53 (60.92%) ADRs required some form of treatment to resolve with or without withdrawal of the suspected drug, while in the remaining 34 (39.08%) ADRs, no treatment was given because of mild nature of ADRs or resolution occurred just by the withdrawal of the suspected drug. On assessing the outcome of all the ADRs, majority of ADRs 59 (67.81%) recovered completely, while remaining 28 (32.18%) were either in recovering stage

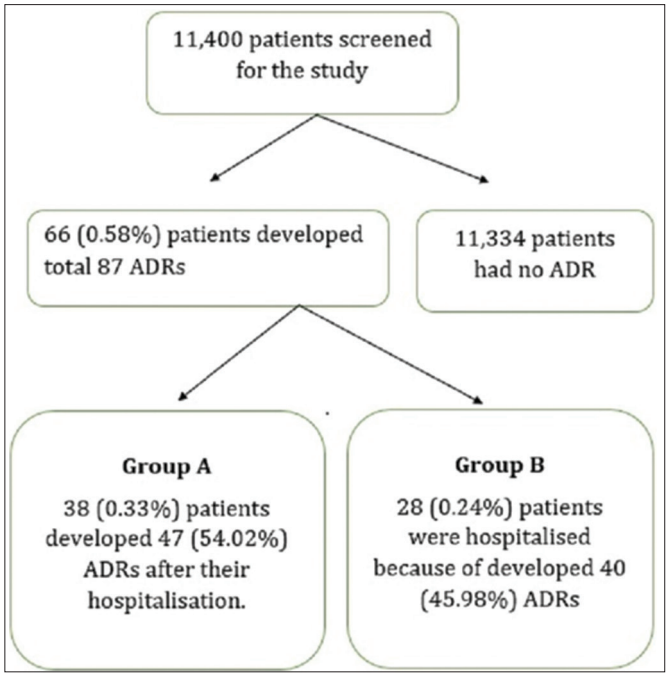

Figure 1: Recruitment of patients

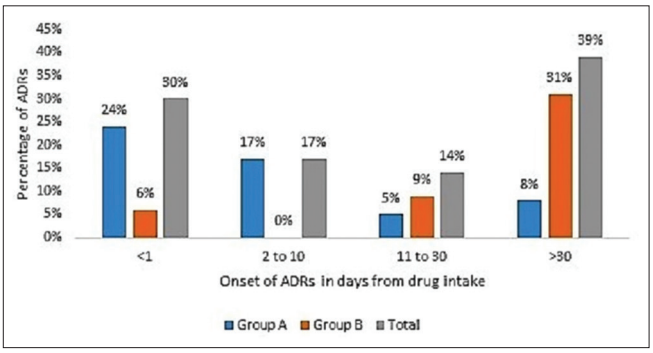

Figure 2: Drug administration and appearance of adverse drug reaction

or discharged from hospital before any outcome could be identified. No ADR associated with fatal outcome or led to any sequelae [Table 1]. ADRs were categorized as serious or non-serious based on the WHO classification. Out of 87 ADR reports, 58 (66.66%) ADRs were considered to be serious and 29 (33.33%) ADRs to be non-serious. It was further divided into serious and non-serious ADRs in Groups A and B. It was observed that among them, 29 non-serious ADRs 26 (89.65%) belonged to Group A and 3 (10.34%) in Group B. In the same manner, out of 58 serious ADRs, 27 (46.55%) serious ADRs were seen in Group B and 21(36.20%) serious ADRs in Group A [Table 2]. However, there was no report of any death, disability and congenital anomaly in any of the groups during the study period.

The ADR categorization according to anatomical system shows that large number of ADRs reported was from central nervous system (CNS) 22 (25.28%), gastrointestinal tract 13 (14.94%), skin 12 (13.79%), and hematology 12 (13.79). This was followed by cardiovascular system (CVS) and electrolyte imbalance [Table 3]. According to drug class, out of total 100 drugs suspected for the total 87 ADRs reported in the study, in majority of the cases, the drug implicated was antimicrobial agents 37 (37%) followed by drugs acting on CNS 14 (14%) and drugs of CVS 14 (14%) [Table 4]. Individual drugs responsible for ADRs in both the groups are displayed in Tables 5 and 6. The suspected medication was usually administered by oral route (76%) in most the ADRs reported followed by intravenous route (20%). Other routes of administration were found to be uncommon [Table 7].

As per WHO-UMC criteria, the majority of the cases in Group A 46 (97.87%) and B 39 (97.50%) were either probable or possible. Only 1 case (1.14%) was certain, which was in Group B while 1 case (1.14%) was unlikely, which was in Group A. There was not any case which can be categorized in either conditional or unassessable category [Figure 4]. As observed in WHO-UMC criteria, in Naranjo scale also most of the causality assessments were either probable or possible 47 (100.0%) in Group A and 39 (97.50%) in Group B. Only 1 case (1.15%) was categorized in the doubtful category from Group B, while no case could be found to be labeled as definite in either group [Figure 5]. According to Hartwig Siegel's scale, a total number of 15 (17.24%) ADRs were severe in nature. Out of 42 moderate ADRs, there were 18 (20.69%) ADRs in Group A and 24 (27.58%) ADRs in Group B, while out of 15 (17.24%) severe ADRs, majority of them 12 (13.79%) were exhibited in Group B and very few 3 (3.44%) in Group A [Figure 6]. As per Thornton and Schumock preventability criteria, majority of the ADRs 63 (72.41%) were not preventable. Out of total 24 preventable ADRs 23(26.43%) were probably preventable while 1 (1.14%) was definitely preventable [Figure 7].

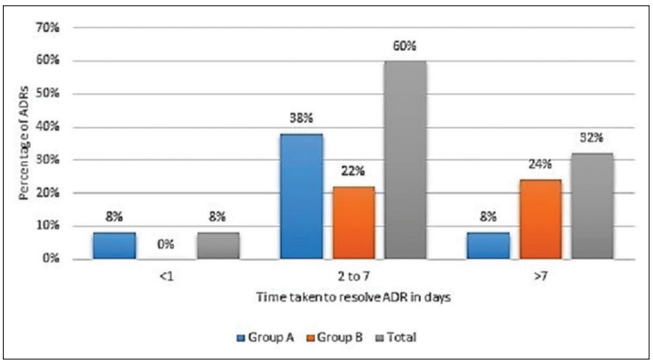

Figure 3: Time taken to resolve adverse drug reaction

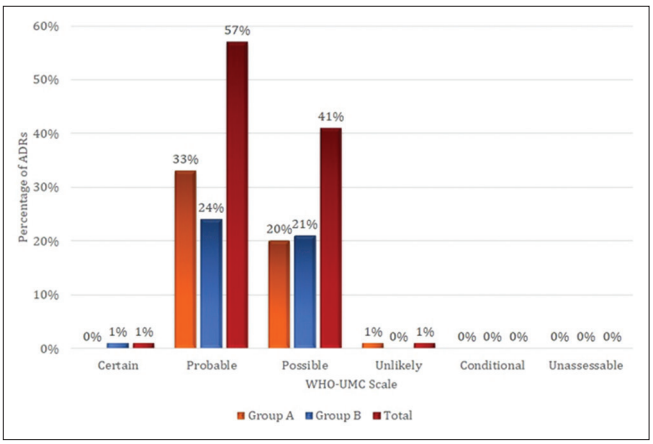

Figure 4: Adverse drug reaction analysis as per the WHO-UMC criteria

Table 1: Outcome of ADRs

Outcome	Group A *n* (%)	Group B *n* (%)	Total *n* (%)
Fatal	00 (0.00)	00 (0.00)	00 (0.00)
Recovered	38 (43.68)	21 (24.14)	59 (67.82)
Recovering	04 (4.60)	08 (9.20)	12 (13.79)
Unknown	05 (5.75)	11 (12.64)	16 (18.39)
Recovered with sequelae	00 (0.00)	00 (0.00)	00 (0.00)
Total	47 (54.02)	40 (45.98)	87 (100.0)

ADRs: Adverse drug reactions

Table 2: Seriousness of the ADRs

Seriousness	Group A *n* (%)	Group B *n* (%)	Total *n* (%)
Death	00 (0.00)	00 (0.00)	00 (0.00)
Life-threatening	00 (0.00)	08 (9.20)	08 (9.20)
Hospitalization/prolongation	08 (9.20)	19 (21.84)	27 (31.03)
Required intervention to prevent permanent damage	13 (14.94)	10 (11.49)	23 (26.44)
Disability/congenital anomaly	00 (0.00)	00 (0.00)	00 (0.00)
Non-serious	26 (29.89)	03 (3.45)	29 (33.33)
Total	47 (54.02)	40 (45.98)	87 (100.0)

ADRs: Adverse drug reactions

DISCUSSION

The overall incident rate in this study (0.58%) is low as compared to 2.4% and 2.12%, incidence published in previous studies done by Darji *et al*., 2016[17] in Gujarat and Doshi *et al*., 2012[18] in Maharashtra, respectively. It can

Table 3: ADR categorization according to anatomical system

Anatomical system	Total *n* (%)	Symptom	Total *n* (%)
CNS	22 (25.29)	Dizziness	7 (31.81)
		Convulsion	6 (27.27)
		Altered sensorium	5 (22.72)
		Headache	2 (9.09)
		Sedation	2 (9.09)
GIT	13 (14.94)	Diarrhea	9 (69.23)
		Vomiting	2 (15.38)
		Gastritis	1 (7.69)
		Abdominal pain	1 (7.69)
Skin	12 (13.80)	Rashes	5 (41.66)
		Pruritus	5 (41.66)
		Petechie	1 (8.33)
		Phlebitis	1 (8.33)
Hematology	12 (13.80)	Hematuria	4 (33.33)
		Melena	3 (25.0)
		Hemoptysis	2 (16.66)
		Coagulopathy	2 (16.66)
CVS	8 (9.20)	Hypotension	4 (50.0)
		Left ventricular failure	1 (12.5)
		Right bundle branch block	1 (12.5)
		Hypertension	1 (12.5)
Electrolyte imbalance	6 (6.90)	Hypokalemia	3 (50.0)
		Hyponatremia	3 (50.0)
Renal	4 (5.75)	Renal impairment	4 (100.0)
Liver	3 (3.45)	Hepatic impairment	3 (100.0)
RS	3 (3.45)	Cough	2 (66.66)
		Pleural effusion	1 (33.33)
Miscellaneous	4 (4.60)	Fever	1 (25.0)
		Weakness	1 (25.0)
		Chills with rigor	1 (25.0)
		Hyperglycemia	1 (25.0)
Total	87 (100.0)	Total	87 (100.0)

ADR: Adverse drug reactions, CNS: Central nervous system, CVS: Cardiovascular system, GIT: Gastrointestinal tract, RS: Respiratory system

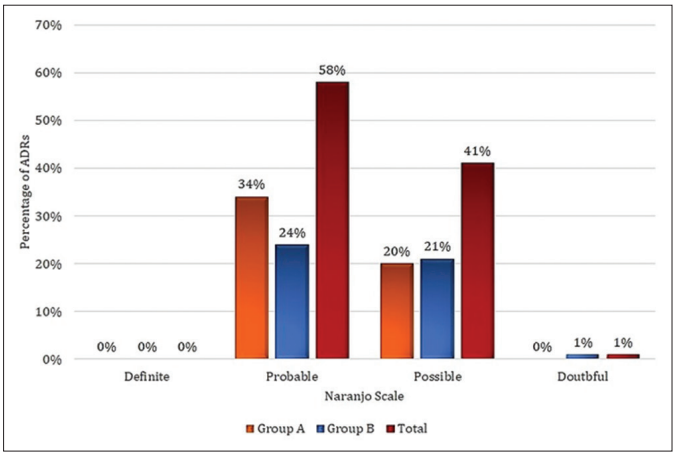

Figure 5: Adverse drug reaction analysis as per Naranjo scale

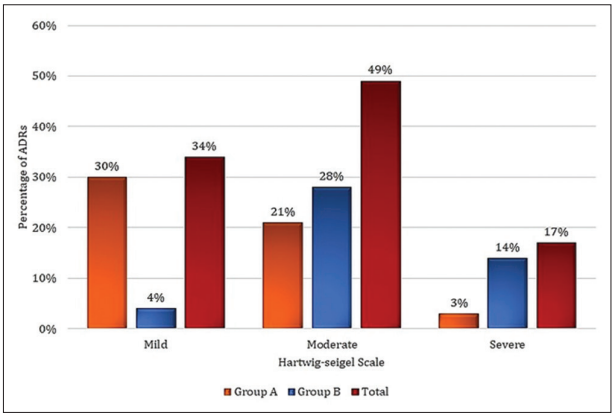

Figure 6: Severity analysis of adverse drug reaction according to Hartwig Siegel's scale

Table 4: ADRs distribution according to the drug class

Drug class	Group total	Sub class	Total
AMA	37	Antibacterial	16
		Antitubercular	5
		Antimalarial	4
		Antiretroviral	6
		Antiprotozoal	3
		Antileprotic	2
		Antiviral	1
CNS	14	Antiepileptic	9
		Opioids	3
		Antidepressant	2
CVS	14	Antihypertensive	11
		Antianginal	1
		Diuretics	2
Blood	9	Anticoagulant	8
		Antiplatelet	1
Endocrine	5	Antidiabetic	4
		Steroid hormone	1
Autacoids	4	NSAIDs	3
		Antihistaminic	1
Cancer chemotherapy	3	Anticancer	3
GIT	2	Laxatives	2
RS	1	Bronchodilator	1
FDCs	11	Antibacterial	6
		Antidiabetic	4
		Antiallergic	1
Total	100	Total	100

ADRs: Adverse drug reactions, CNS: Central nervous system, CVS: Cardiovascular system, GIT: Gastrointestinal tract, FDCs: Fixed-dose combination, NSAIDs: Nonsteroidal anti-inflammatory drugs, AMA: Anti microbial agents

Table 5: Individual drug suspected for ADRs in Group A

Drug	*n*
Amlodipine	3
Amoxicillin+Clavulanic acid	3
Artesunate	1
Aspirin	2
Atenolol	1
Clopidogrel	1
Dapsone	2
Efavirenz	2
Enoxaparin	1
Ethambutol	1
Glibenclamide+Metformin	3
Glipizide	1
Furosemide	2
Gefitinib	3
Glyburide+Metformin	1
Heparin	1
Isoniazid	1
Lactulose	2
Levofloxacin	1
Metronidazole	3
Nitroglycerine	1
Phenylephrine+Chlorpheniramine+Paracetamol+Caffeine	1
Piperacillin+Tazobactam	3
Prednisolone	1
Streptomycin	2
Tramadol	3
Sodium valproate	1

ADRs: Adverse drug reactions

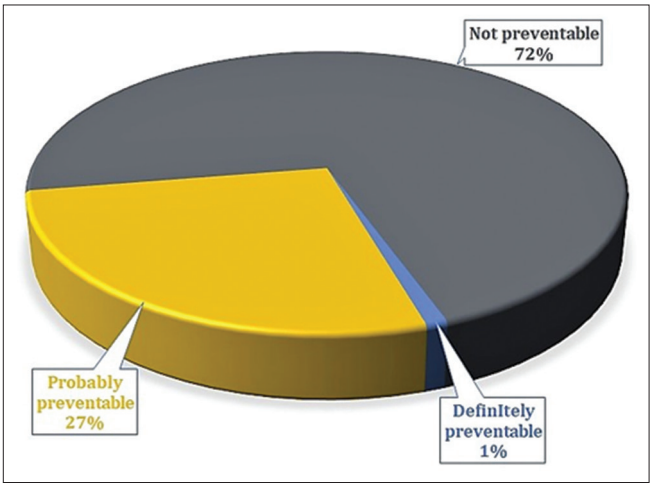

Figure 7: Preventability analysis of adverse drug reaction as per Thornton and Schumock preventability criteria

be partially explained by the fact that out of total 11,400 admissions recorded in medical records and statistics department of the hospital during the study period included a large number of admissions of day care procedures such as blood transfusion in patients of sickle cell anemia, hemophilia, and thalassemia. Furthermore, the common ADRs such as nausea, vomiting, and gastritis were very less due to appropriate preventive measure taken by prescribing H_2 blockers, proton pump inhibitors, and anti-emetics along with medication which could have caused such ADRs. The majority 66.6% of our patients belonged to the age group of 31–60 years and around 12.12% of the patients belonged to geriatric age group (>60 years) agrees with Ramesh *et al*., 2003[19] 67% adults versus 30% geriatric age group. In a North Brazilian study, Lobo *et al*., 2013[20] also reported that nearly 61% of the patients showing ADRs in their study belonged to the adult age group. The higher number of incidences of ADRs in males (0.62% vs. 0.50% females) observed in this study is in accordance to the results of a study conducted by Vora *et al*., 2011[21] (3.37% males vs. 2.05% females).

The majority of the ADRs in Group A (24.13%) developed within 1 day of drug intake, while in Group B most reaction (31.03%) developed after a period of 1 month of drug administration. Similar findings have also been reported by

Table 6: Individual drug suspected for ADRs in Group B

Drug	*n*
Acyclovir	1
Amlodipine	1
Artesunate	2
Aspirin	1
Azithromycin	3
Cefixime	2
Cefoperazone+Salbactum	1
Cefotaxime	2
Ceftriaxone	1
Chlorpheniramine	1
Chlorthalidone	2
Chloroquine	1
Cotrimoxazole	3
Doxycycline	1
Enalapril	2
Isoniazid	3
Lamivudine	2
Levetiracetam	2
Lithium	1
Metformin	2
Nortriptyline	1
Phenytoin	2
Pioglitazone	1
Telmisartan	1
Tenofovir	2
Theophylline	1
Sodium valproate	4
Warfarin	6

ADRs: Adverse drug reactions

Table 7: Routes of drug administration

Route of administration	Group A (*n*)	Group B (*n*)	Total (*n*)
Oral	27	49	76
Intravenous	20	0	20
Intramuscular	2	0	2
Subcutaneous	1	1	2
Total	50	50	100

Doshi *et al*., 2012, i.e., 46% (Group A) and 56% (Group B). The possible explanation for this observation could be the fact that hospitalized patients are usually admitted for acute conditions, and in these patients, any new symptoms or laboratory abnormalities are quickly observed, documented, and treated. On the other hand, patients developing the ADRs outside the hospital are usually on chronic medication and hence they either develop the ADRs after a substantial lag period or they report them quite late. The most commonly reported ADRs are affecting the nervous system followed by the gastrointestinal system, skin, and hematology in that order. It is also observed that most of the ADRs that led to hospitalization, i.e., in Group B patients were from the CNS and hematology. Javedh *et al*., 2013,[22] and Arulmani *et al*., 2007,[23] have published similar observations.

A large number of ADRs (particularly those belonging to Group A) resolved quickly and within a week of their appearance while ADRs in Group B took a much longer time (8–30 days) to resolve can be explained by the fact that most of the non-serious ADRs were in Group A and the serious ADRs belonged to Group B. Patients in Group A were already in hospital and therefore their ADRs were quickly spotted and treated which may not the case with the patients of Group B. The antimicrobial agents are a frequent cause of ADRs followed by drugs acting on CNS, CVS, and hematology in that order. These findings agree with (Patil *et al*., 2016)[24] study conducted in Telangana and (Thakare *et al*., 2019)[25] in Maharashtra as antimicrobial drugs are among the most frequently prescribed drugs in the hospital and to a great extent the large amount of their use may be considered injudicious and irrational. They are, therefore, quite likely to be the most common offending agents. In the WHO-UMC criteria, majority of the ADRs in Group A and Group B were "probable" and assessment according to Naranjo scale also resulted in majority of ADRs in both Groups A and B categories as "probable" supporting Mankiandan and Kesavan, 2007[26] study reported approximately 90% of the ADRs "Probable" in their study. The majority of the ADRs (48.2%) observed are moderate in nature according to Hartwig-Seigel severity scale. On comparison between both Group A and Group B, severe ADRs are most commonly seen in Group B patients. In a number of other studies, a major component of ADRs are similarly moderate in nature as observed in the present study (Darji *et al*. study; 2016, Doshi *et al*. study; 2012. The preventability assessment by Thornton and Schumock criteria shows that most of ADRs (72.4%) are "not preventable," however; considerable ADRs (26.4%) are "possibly preventable." A similar study, primarily focused on preventability by Raut *et al*., 2012[27] found as many as 56% preventable ADRs. This forms the most important basis of this study to collect statistics of preventable ADRs that would eventually help us to actually prevent all the "preventable" ADRs.

The present study has generated very useful data for our hospital as well as other tertiary care teaching hospitals, particularly in the Indian context. This helps to prevent undesirable drug effects and to undertake the right steps in the right direction. However, this study had a few shortcomings like it was limited to the medical wards only while it would have been ideal to cover all sections of the hospital, and the duration of the study was not long enough to be able to cover all the seasons in a year.

CONCLUSION

Intercurrent illnesses, longer hospital stay, and polypharmacy play a major role in the occurrence of multiple ADRs. This study concludes that prevention, early identification, and management of such ADRs can result in better patient outcome. Furthermore, strengthening of an ongoing ADR reporting system with continuous motivation and creating awareness among the health-care professionals for reporting suspecting ADRs can help to increase ADR reporting and form a strong database, which in term will improve the patient safety.

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