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Research Article

Adverse Drug Reactions(ADRs)

Monitoring and Evaluation of Adverse Drug Reaction In Emergency Medicine Department: A Prospective Observational Study

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Background: Any deviation from the intended beneficial effect of medication results in a drug-related problem. Adverse drug reactions (ADRs) are negative consequences of drug therapy. It is the fourth to the sixth leading cause of mortality in the United States of America. **Aims:** To find out the proportion of medical emergency admissions that are secondary to Adverse Drug Reactions(ADRs). **Settings and Designs:** An observational, prospective study conducted at the Emergency Medicine Department, at Tertiary Care Teaching Hospital for 12 months, daily from 9 am to 5 pm. **Materials and Methods:** Patients aged ≥ 18, who have given written informed consent were included and patients not able to give willing consent and women presented with pregnancy were excluded from the study. The data was recorded in the case record form, The causality assessment was performed using the WHO causality assessment scale. To determine the ADR severity, the Modified Hartwig and Siegel scale was used. **Statistical Analysis:** The statistical evaluation was done with the help of Statistical Package for Social Science (SPSS) version 21.0 manufactured by IBM (demo version) and Microsoft Excel 2016. $p < 0.05$ was considered statistically significant. **Results:** Elderly patients were having a higher incidence of ADRs. Among all drug groups, the highest incidence was antimicrobials and drugs acting on blood. The majority of patients either recovered or were in a recovery phase. Most of the ADRs were not preventable. **Conclusions:** Reporting ADRs systematically allows appropriate analysis and intervention which will improve the patient's safety. Many ADRs could be preventable by avoiding certain drug/drug combinations, hospitalization, dose-dependent side effects, appropriate individual dosing and applying for the Antimicrobial Stewardship Programme.

Keywords: Adverse Drug Reactions(ADRs), Antimicrobials, Emergency Medicine Department

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Introduction

Nowadays, the use of medicines is increasing day by day. Every year there will be so many new drugs approved by the Central Drugs Standard Control Organization (CDSCO). Most commonly, the patient benefits from pharmacotherapeutic interventions. But sometimes adverse drug reactions (ADRs), adverse events, ranging from minor side effects to serious effects such as hospitalization, prolongation of hospitalization, intervention, congenital anomaly and death may occur. Any deviation from the intended beneficial effect of medication results in a drug-related problem.[1] In recent years patient safety has become a major concern for healthcare providers, and medication management is one of its more relevant aspects. Studies on ADR identified that approximately 6.5% of ED visits were due to drugs.[2]

According to World Health Organization (WHO), an Adverse drug reaction (ADR) is defined as "A noxious, unintended and undesirable effect that occurs as a result of a dose normally used in man for diagnosis, prophylaxis and treatment of disease or modification of physiological function."[3] Adverse drug reactions (ADRs) are negative consequences of drug therapy.

It is the fourth to the sixth leading cause of mortality in the United States of America. ADRs and events constitute a serious problem increasing morbidity and mortality and health care costs worldwide. The overall incidence of ADRs in hospitalized patients in the United States in 1998 was 6.7% and fatalities were 0.32%.[4]

Adverse drug reactions may also result in diminished quality of life, increased physician visits, hospitalizations, and even death. In addition, they result in increased healthcare costs. Polypharmacy, chronic medical problems, frequent acute illnesses and medications used without prescriptions increase the risk for ADRs and make detection more difficult.

Adverse drug reactions impose significant burdens on hospitals by prolonging patient stay and increasing admission rates.[5]

The occurrence of ADEs significantly prolongs the length of hospital stay and increases costs. Although there is an enormous amount of data regarding the incidences of ADEs, the precise frequency is unknown. Previous studies,

However, have estimated that approximately 2.0 – 6.5% of all hospital admissions are due to ADEs and that 2.0 – 20.0% of patients suffer from ADEs while staying in the hospital. Rates in outpatients range from 5 to 35%.[6]

The study of ADRs is the concern of the field known as pharmacovigilance.

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.[7]

Systematically reporting ADRs allows appropriate analysis and intervention which will improve the patient's safety. ADRs could be monitored through active participation or a voluntary reporting system.

The objective of this study was to find out the incidence of ADR in patients of emergency medicine wards and study various aspects of ADR, e.g., causality, severity, age group of patients who are prone to ADRs, the gender-wise occurrence of ADRs, classification of ADRs based on the reaction, assessment of preventability of ADRs and drugs commonly causing ADR in a tertiary care hospital.

Aims and Objectives

1. To determine the proportion of medical emergency admissions that are secondary to Adverse Drug Reactions(ADRs).

2. To estimate the frequency of Adverse Drug Reactions(ADRs) among cases of the Emergency Medicine Department.

3. To identify drug classes implicated and to analyze the putative causes for all the cases.

Methods

This was an observational, prospective, non-interventional, uni-centric study. The study was conducted at the Emergency Medicine Department, at Tertiary Care Teaching Hospital. The study was conducted for a total duration of 12 months. The study was approved by the Institutional Review Board (IRB). The investigator attended the Emergency Medicine Department daily from 9 a.m. to 5 p.m. All patients were diagnosed with Adverse Drug Reactions(ADRs) by the clinician and they were taken up for the study.

All the cases were evaluated based on the categories. We have included patients aged ≥ 18 Years and of either gender, patients who were admitted because of Adverse Drug Reactions(ADRs) to treatment and patients who have given written informed consent and are willing to participate in the study. We have excluded the patients not able to give willing consent and women who presented with pregnancy. The data were recorded in Microsoft Excel worksheet version 2007. The statistical evaluation was done with the help of Statistical Package for Social Science (SPSS) version 21.0 manufactured by IBM (demo version) and Microsoft Excel 2016. *P< 0.05* was considered statistically significant. Causality assessment is the method through which the relationship between the drug and the suspected ADR is determined. There are two types of scales which are used widely in performing the causality assessment they are Naranjo's causality assessment scale[8] and the WHO probability assessment scale.[9] To determine the ADR severity depending on its nature of occurrence mild, moderate or severe is assessed by the Modified Hartwig and Siegel scale.[10]

Results

Among 208 patients, 71 patients with Adverse Drug Reactions (ADRs) were included in our study.

Table 1: Demographic data of the patients presented with Adverse drug reactions (ADRs).

Sr. No.	Age Distribution(Years)	Male	Female
1.	Adolescents (0-20)	04(11.11%)	01(2.85%)
2.	Adults (21-40)	11(30.55%)	07(20%)
3.	Middle Age(41-60)	11(30.55%)	10(28.57%)
4.	Geriatric(>60)	10(27.77%)	17(48.57%)
	Total	36	35

Table 1 shows the demographic data of ADRs. Out of 208 patients, 71(34.13%) patients were admitted because of ADRs. The mean age of the study group was 64.5 years, ranging from 20 to 90 years. The mean age for men was 62 years and for women 67 years. Regarding the gender-wise distribution of patients reported with ADRs, there was an equal distribution of ADRs among males (n=36) and females (n=35) suggesting no statistically significant difference among genders reporting ADRs. This means there was no gender-related difference in ADRs related to admissions in our study.

Out of 71 patients admitted because of ADRs, 27(38.03%) patients above 60 years of age had a higher incidence of ADRs as compared to age groups less than 60 years of age.

Figure: 1 and Table: 2 indicate different drug groups administered to the patients showing ADRs. Following drug groups were given such as Antimicrobials, Blood, CVS, CNS, Endocrine, GIT, and Miscellaneous. Out of 71 patients reporting ADRs, a total of 80 drugs were prescribed. Out of that 27(38.57%) patients reported ADRs to antimicrobial drugs, followed by 15(18.75%) patients with drugs acting on blood group and so on. Among antimicrobials (n=27), the incidence of ADRs was more with antibiotic group 14 (51.85%), followed by antitubercular drugs 8 (29.62%). Among drugs acting on blood (n=15), higher incidences of ADRs were reported with anticoagulant drugs 14 (93.33%). Other drugs most commonly implicated to produce ADRs were drugs acting on CVS, CNS, Endocrine and GIT systems. Haemorrhage induced by anticoagulant agents was the commonest ADR reported in our present study.

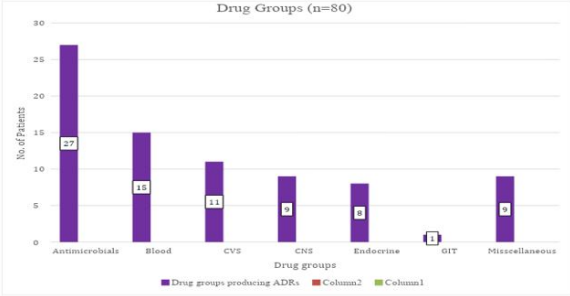

Figure 1: Drug groups of the ADRs.

Table 2: Classification of drugs according to their respective drug groups and drug class.

Antimicrobials (N=27)	Blood (n=15)	CVS (n=11)	CNS (n=9)	Endocrine (n= 8)	GIT (n= 1)	Miscellaneous (n=9)
Antibiotics- (14)	Anticoagulants- (14)	Antiarrhythmics- (3)	Antiepileptics (6)	Antidiabetics (7)	Antacids (1)	Calcium Supplements (1)
Antimalarials- (2)	Hematinics-(1)	Antihypertensives-(8)	Antipsychotics (1)	Anti-thyroids (1)		Corticosteroids (1)
Anti-parasites- (3)			Sedatives(1)			Contrast media(1)
Antitubercular- (8)			Skeletal muscle relaxants(1)			Analgesics(2)
						Immunoglobulins(1)
						Immunosuppressants (2)
						Statins (1)

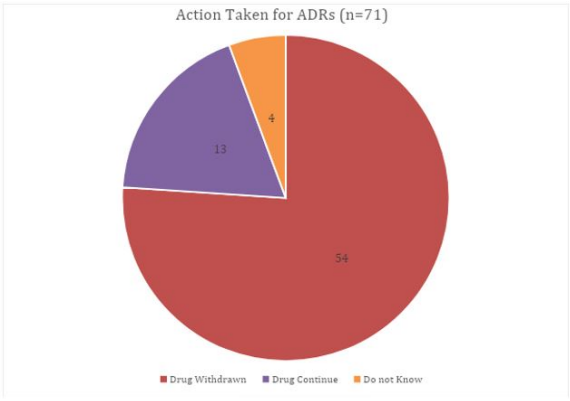

Figure 2: Action taken by a clinician for the ADRs.

Figure: 2 shows the action taken by the clinician on 71 patients suffering from ADRs. Out of 71 patients reporting, the culprit drug was withdrawn in 54(76.05%) patients, whereas the same drugs were continued in 13(18.31%) patients without any interruption of the culprit drug. On the contrary, actions taken by physicians in 4(5.63%) patients were not known in our study.

Table 3: Outcome of ADRs.

Outcome	No. Of Patients	Percentage
Recovered	29	40.85%
Recovering	36	50.70%
Unknown	6	8.45%
Total	71	100%

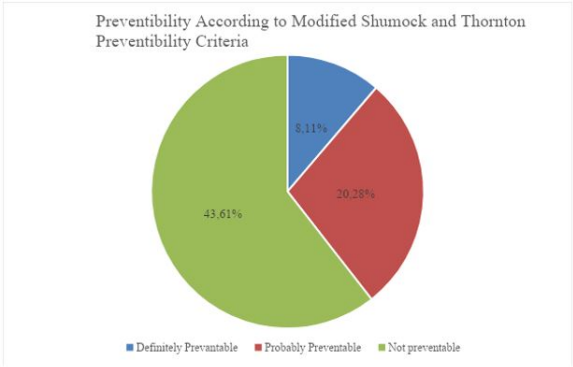

Figure: 3 Preventability of patients with ADRs according to Modified Schumock and Thornton Preventability Criteria

Table: 4 Preventability of ADRs according to Schumock and Thornton Preventability criteria

Definitely Preventable	Insulin- Hypokalemia, Hypoglycemia Penicillin- Anaphylactic shock Phenytoin- Gum hyperplasia, Ataxia
Probably Preventable	ATT- Hepatitis, Jaundice Phenytoin- Withdrawal Seizures Antihypertensives- rebound hypertension
Not Preventable	Cefoperazone- Diarrhea, SGPT increased, rash Ceftriaxone- rash, anaphylactic shock

In 34.13% of the patient's population, ADRs were the reason for hospitalization or had contributed to admission and 11% of ADRs were assessed as preventable.

The most commonly reported preventable ADR was inappropriate dosing and choice of Insulin and Antibiotics.

Preventability assessment was restricted to ADRs causing or contributing to hospital admissions. (n=71). In this population, 28% (20) of the ADRs were considered "Not Preventable". whereas, 61% of ADRs were assessed as "Probably Preventable" and 11% (8) of ADRs were assessed as "Definitely Preventable". **(Figure: 3 and Table: 4)**

Causality Assessment According to WHO-UMC Criteria.

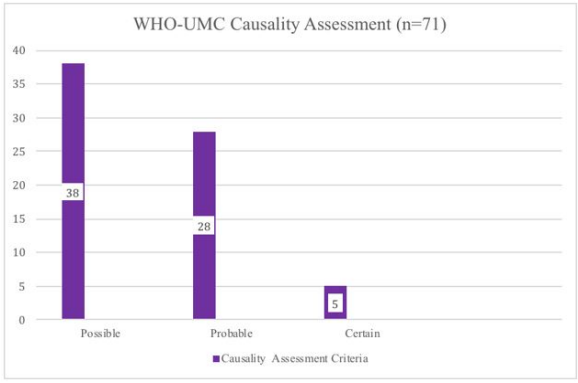

Figure: 4 Causality Assessment of the Adverse Drug Reactions (ADRs).

According to the WHO-UMC causality assessment score, out of 71 patients, 38(53.52%) ADRs fall into the category of possible, while 28(39.43%) were in the category of probable/ likely and 5(7.04%) were certain/likely. Whereas, no patients reported other causality assessment criteria such as unlikely, unclassified and unclassifiable. **(Figure: 4)**

Table: 4 Predictors of ADRs.

	Un-adjustable Odds Ratio	Adjustable Odds Ratio
Age	1.076 (2.028: 2.194)	1.058 (1.024 : 1.082)
Number Of Drugs	1.60 (1.44: 1.76)	1.50 (1.32: 1.70)
Gender (M/F)	0.89 (0.74 : 1.25)	0.86 (0.70:1.15)

1.095 confidential interval.

Gender was not identified as a significant predictor of ADRs (P=0.03).

In the multivariable regression model age and no. of drugs were significantly associated

With the risk of presenting with ADRs (P<0.01 & P<0.001 respectively)

Discussion

In our study, a total of 208 patients were studied, out of which 71 patients developed ADRs which was an incidence rate of 34.1% to develop ADRs. The incidence rate of ADRs in our study is significantly higher than those proposed in studies by Mohammed et al. and Lazarou et al. at a rate of 6% and 7% respectively.[1, 4] In the multicentric study, adverse drug reactions contributed to hospital admission in 10.5% of geriatric populations.[11]

The elderly population is more vulnerable to ADRs. Some studies show as high as a 25% incidence rate of adverse drug reactions in the elderly as compared to younger patients. Few studies have shown less incidence of ADRs rate in the elderly that evaluated age as a variable.[12] In our study, findings suggest that geriatric patients are more affected by ADRs because of polypharmacy and age-related retardation of drug metabolism. Age was found to be an important criterion in producing maximum ADRs, which was in concordance with findings similar to that of Mohammed. et al. and Ghufran et al. studies.[1]

Our findings correlating the association of gender with ADRs are not in consonant with the findings shown by Mohammed. et al. and Ghufran et al. studies,[1] where the male patients showed higher affected gender with ADRs more than females i.e. 56.14%Vs. 43.86%. In our study, ADRs categorized according to the gender of patients reflected that, among the various age groups of patients, geriatric patients with both the male and female gender respectively shared the similarity in the incidence of ADRs. i.e. geriatric males 50% of ADRs and geriatric females 49% of ADRs.

In this study, regarding ADRs commonly associated with certain drugs, it was found that ADRs were most commonly associated with antibiotics and drugs acting on blood. The reason may be due to misuse & overuse of antibiotics and lack of awareness regarding antibiotic stewardship programs among physicians.[13]

Several previous studies have addressed the prevalence of ADRs in an emergency setting. In our study, only 73% of the ADRs causing or contributing to admission to the emergency ward

Were assessed as definitely preventable (11%) and probably preventable (61%). Thus our results may not be comparable to the findings reported in two different reviews and one meta-analysis.[14,15]

Where the median preventability rate of all drug-related adverse events in patients was 35% and 46% (with a range between 19% and 90% in individual studies.) The reasons for the wide range of preventability estimates in different studies may be attributable to different settings, assessment criteria etc. Many ADRs could be preventable by avoiding certain drug/drug combinations, hospitalization, dose-dependent side effects and appropriate individual dosing.

In our study, we found that antihypertensives, antibiotics, and anticoagulants were the drugs causing the majority of the preventable ADRs. Hospitalization due to ADRs could have been preventable if (a) Proper monitoring of cardiovascular drug monitoring (b) Avoiding the combination of antimicrobials with anticoagulants (c) Monitoring of electrolyte imbalance. Also in line with our data, the systemic review found drugs accountable for preventable drug-related hospital admissions to be Aspirin, Diuretics, NSAIDS & Anticoagulants.[16]

In a Swedish study on reported ADRs, a high number of preventable ADRs was found for the central nervous system, cardiovascular system and antithrombotic drugs.[17] The study by Lazarou et al suggested that 28.9% of ADR-related hospitalizations were considered preventable.[4]

In our study, 28% of the ADRs were considered "Non Preventable", because of the anti-infective class of drugs being most prescribed. Preventable ADRs mainly belonged to the antidiabetic group of drugs. This could be because of improper advice related to their usage, lack of knowledge of the patients, necessary laboratory tests not performed or preventive measures not prescribed when administering the drugs to the patients. Among the preventable ADRs (73%) only 11 % were preventable because of an inappropriate selection of drugs for the patient's condition and due to established available treatment for the ADRs. James BC and Raut et al. in their separate studies showed 60.5% and 55 % of the ADRs as preventable respectively.[18,19]

In the study regarding ADRs' outcome, the majority of the ADRs were recovering. This was because the action is taken immediately, the watchfulness of the clinicians, and awareness regarding reporting of the ADRs.

The common causality association with ADRs of the suspected drug was possible and probable). Similar observations were reported by Amin et al. in their study.[20]

In this study, most of the ADRs lead to hospitalization and they were severe. In India according to one meta-analysis, the occurrence of ADRs in hospitalized patients is around 6-7%, whereas admission to hospital due to ADRs is around 3-4%.[21]

In the multivariable regression model age and no. of drugs were significantly associated with the risk of presenting with ADRs ($P<0.01$ & $P<0.001$ respectively). Gender was not identified as a significant predictor of ADRs. ($P=0.03$). There are in line with the findings reported by Diana M R et al. [22]

Clinical Pharmacologists are encouraged to take responsibility for the development of Adverse Drug Reaction Monitoring and Reporting programs. This should lead to a heightened awareness of ADRs, increased reporting of ADRs, and increased opportunities for drug review, drug selection and prescribing practices affecting patient outcomes. [23]

Conclusion

Reporting ADRs systematically allows appropriate analysis and intervention which will improve the patient's safety. Many ADRs could be preventable by avoiding certain drug/drug combinations, hospitalization, dose-dependent side effects, appropriate individual dosing and applying for the Antimicrobial Stewardship Programme.

What new this study adds to existing Knowledge

Most of the studies regarding ADRs' monitoring and evaluation are conducted on the OPD based patients or general medicine inward patients, while we conducted on Emergency Medicine patients which presented with all the symptoms ranging from mild ADRs to severe ADRs, so that each and every drug related ADRs can be assessed.

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