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Research Article

INCIDENCE, SEVERITY AND FINANCIAL BURDEN ASSOCIATED WITH ADVERSE DRUG REACTIONS IN MEDICINE INPATIENTS

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ABSTRACT

Aim: Present study was carried out to assess the incidence of adverse drug reactions (ADR) and assessment of causality, severity and additional financial burden associated with reported suspected ADRs.

Materials and Methods: A prospective spontaneous reporting study was conducted over a period of six months in inpatients of medicine wards and medical intensive care unit at Bharati Hospital, Pune. WHO Probability scale was used for causality assessment. Reported ADRs were classified according to Wills & Brown classification and assessed for severity using scale developed by Hartwig et al. Average cost incurred in treating an ADR was calculated.

Results: A total of 143 suspected ADRs were reported and evaluated from 58 patients showing an overall incidence of 4.75%. About 44 (3.60%) hospitalized patients experienced an ADR and 21 (1.72%) patients were hospitalized due to ADR. Gastrointestinal system (25.87%) was most commonly involved. Drug class most commonly associated was Antimicrobials (18.90%). 43.36% ADRs were classified as "Possible" in view of causality, while 62.24% were found to be "mild" in case of severity. Most patients (59.44%) recovered from the ADR. 68.53% ADRs were augmented or type A. Average cost incurred in treating an ADR was found to be Rs.412.79 (US$ 9.30) in India.

Conclusion: Awareness about ADR reporting is still poor amongst healthcare professionals in India. Incidence of ADRs was more in hospitalized patients compared to ADR induced hospital admission. Average cost incurred for treating ADR leading to hospital admission was higher.

Keywords: Adverse drug reaction, Prospective Spontaneous reporting, Causality, Severity, Cost.

INTRODUCTION

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems[1].

It has been estimated that approximately 2.9-5.6% of all hospital admissions are caused by ADRs and as many as 35% of hospitalized patients experience an ADR during their hospital stay[2]. An incidence of fatal ADRs is 0.23 - 0. 41%[3]. At least one ADR has been reported to occur in 10 to 20% of hospitalized patients[4].

Most of the advanced countries have set up an ADR reporting system at the national level. ADR reporting programs on an institutional basis can provide valuable information about potential problems in drug usage in that institution. Furthermore, reviewing pooled data from diverse geographic, social and medical population enhances the ability to identify rare events and to generate new signals and thus in setting up a sound Pharmacovigilance system in the country[5].

ADR in hospital patients are divided into two categories: those that cause admission to hospital and those that occur in hospital inpatients after admission. Hospital based ADR monitoring can provide valuable information on drug usage[6]. ADR add an unnecessary cost to an already burdened health care system and are usually preventable[7].

Membership of World Health Organization (WHO) for International Drug Monitoring is coordinated by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (UMC) [8]. UMC in Sweden is an international arm of WHO for monitoring ADRs. As per the Central Drugs Standard Control Organization (CDSCO) and the Ministry of Health and Family Welfare launched by Indian government 26 peripheral centers, 5 regional centers and 2 zonal centers were established. The Peripheral centers were to record the Adverse Events (AE) and send them to the Regional Centers[9].

In India, the concept of ADR reporting is still new although ADRs are of great concern to the general public, medical practitioners, pharmaceutical industries and the regulatory authorities[10]. Very little attention has been given so far and very few original studies have been done in this regard[11]. India rates below 1% in Pharmacovigilance as against the world rate of 5%[12] . We have very few ADR monitoring centers right now and lot of efforts is required in order to collect ADR data which may generate safety surveillance of billions of therapeutically active substances either alone or in combinations.

Reporting of ADRs is done by various methods but the most commonly used method is spontaneous reporting. Pharmacists have been encouraged to participate and contribute to the ADR reporting and monitoring program. This has considerably improved the rate of reporting[13]. It is the most likely method of detecting new, rare ADRs and frequently generates safety signals which need to be examined further. Spontaneous reports are a crucial element in the worldwide enterprise of Pharmacovigilance and form the core of the WHO Database[14].

The present study was carried out in Bharati Hospital and Research Centre, Pune which is 850 bedded multispecialty tertiary care teaching hospital providing healthcare services to the people in and around Pune city. The objective of this study was to assess incidence and characteristics of ADRs occurring in the medicine inpatients, causality of drug to these reactions and their severity. Also we tried to assess the impact of these ADRs on patient's hospitalization costs. The study was first of its kind in this hospital.

MATERIALS AND METHODS

Data Collection

A prospective spontaneous reporting study approved by the Institutional Ethics Committee (IEC) was conducted over a period of six months from October 2010 to March 2011. The study was coordinated by PharmD students. Patients of either sex above 18 years of age who developed an ADR admitted in medicine ward and medical ICU were included in the study. Patients with intentional or accidental poisoning, patients who developed an ADR during transfusion of blood or blood products and vaccines, patients treated

on Outpatient department (OPD) basis, patients with drug abuse and patients with non compliance were excluded from the study.

WHO definition of an ADR was adopted. Spontaneous reporting system was the method followed for monitoring ADRs. Medical staff, medical post graduates, nursing staff and patients were educated and encouraged to report ADRs by creating awareness through brief presentations and conducting clinical meetings. ADR notification forms were kept in the nursing stations of medicine wards and the ICU. PharmD students played a crucial role in monitoring through daily participation in ward rounds and encouraging the physicians to report. Any reaction noted by the student was brought into the notice of the physician, who if convinced enough of the drug cause of reaction filled the notification form. Informed consent was taken from the patient for suspected ADR before documentation. The demographic details of the patient were collected along with the current concern and drug therapy details in a systematically designed patient profile form. All relevant data including the drugs patient received prior to the onset of reaction, respective dose, and route of administration with frequency, date of onset of reaction and the patient's allergic status were noted. In addition to this patient's medication history and other co-morbidities were identified to assess causality relationship between the suspected drug and reaction. Patients were interviewed and the medication order and records were reviewed on daily basis throughout the stay of patient in the hospital. Any drug treatment and/or supportive therapy given for management of the reactions were also noted. The reported suspected ADRs were classified according to the Wills and Brown classification.

Causality assessment of ADR was carried out using WHO scale[15] which categorizes the causality relationship into certain, probable, possible, unassessable/unclassifiable, unlikely, conditional / unclassified. Severity of ADR was graded as per scale developed by Hartwig et al[16] as mild, moderate and severe. The most common class of drugs causing ADRs were identified and documented.

Average cost per patient was calculated by total amount spent on treating ADRs divided by the number of patients suspected with ADR. For analyzing the cost, ADR requiring specific drug and supportive therapy were considered. Drugs, laboratory investigation orders, syringes, applicants etc were all calculated per unit per patient. Reaction requiring a simple cessation of suspected drug, the cost was considered nil.

Statistical analysis

Incidence of ADR related admissions and ADR occurred during the hospital stay were calculated as percentage of inpatient population treated. Z-test was used to compare means. For other variables the chi-squared ($\chi 2$ test) was used. A two-tailed P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 143 suspected ADRs were reported and evaluated from 58 patients (30 males, 28 females- Fig 1) during the study period. Out of 58 patients, 32 (55.18%) patients developed more than one ADR. The overall incidence was 4.75%. Female experienced a significantly higher incidence of ADRs (5%) than male (4.55%). The overall incidence of ADRs found to be higher with geriatrics (6.10%) than adult patients (4.47%). This trend was observed in both ADR related admissions and ADRs occurring during the hospital stay [Table No. 1]. However statistical significance was not found.

Augmented Type A reactions were found to be 98 where as 32 were Type H hypersensitivity reactions [Table No. 2].

Assessment of ADRs is given in Table No. 3. Causality assessment of suspected ADRs shows out of 143 reported ADRs 62 (43.36%) were assessed to be "Possible", 38 (26.57%) as "Probable" and 37 (25.87%) as "Certain". Reported reactions were found to be "Mild" (89, 62.24%) followed by "Moderate" (48, 33.57%) and "Severe" (6, 4.20%).

In majority of ADRs (59.44%) "Complete recovery" was achieved, 18.88% ADRs were found to be "recovering" and 11.19% ADRs were of "unknown" outcomes in which the outcomes could not be assessed as the patients sought voluntary discharge from the hospital. Life threatening reactions were reported in three patients (2.10%) which were recovered later [Fig 2].

Table 1: Demography, Incidence and Age Wise Distribution Of ADRs

CHARACTERISTICS	NO. OF PATIENTS WITH ADR/ NO. OF PATIENTS HOSPITALIZED (%)	NO. (%) OF ADR RELATED ADMISSION	NO. (%) OF ADR OCCUR DURING HOSPITALIZATION
Male	30/660 (4.55%)	9/660 (1.36%)	23/660 (3.48%)
Female	28/561(5%)	12/561 (2.14%)	21/561 (3.74%)
Adult (19-60 yr)	45/1007 (4.47%)	15/1007 (1.49%)	34/1007 (3.37%)
Geriatric (>60 yr)	13/214 (6.10%)	6/214 (2.80%)	10/214 (4.67%)
Total	58/1221 (4.75%)	21/1221 (1.72%)	44/1221 (3.60%)

Table 2: Classification of ADRs According To Wills & Brown

TYPES OF ADR	NO. (%) OF ADRs REPORTED
Type A (Augmented)	98 (68.53%)
Type B (Bugs)	_
Type C (Chemical)	_
Type D (Delivery)	2 (1.40%)
Type E (Exit)	_
Type F (Familial)	_
Type G (Genetotoxicity)	_
Type H (Hypersensitivity)	32 (22.38%)
Type U (Unclassified)	11(7.67%)

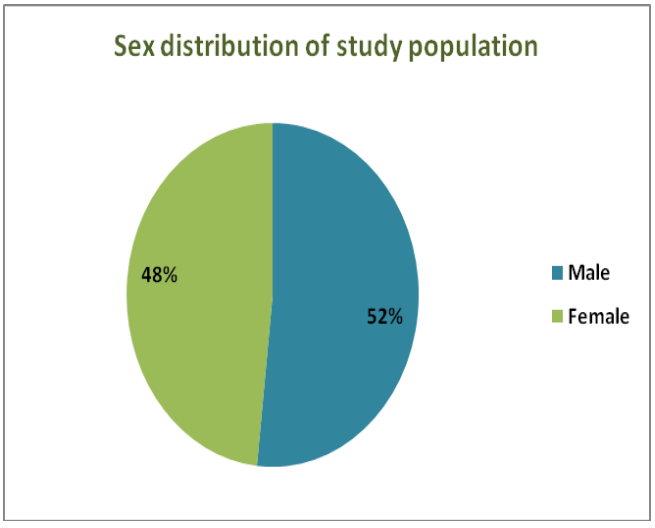

Fig 1: Sex Distribution of Study Population

The drug class most commonly associated with ADRs was Antimicrobials (37.38%) followed by cardiovascular agents (15.38%) while least affected class was found to be antianxiety drugs (0.70%) [Table No 4]. Accordingly, the organ systems most commonly affected by an ADR was the gastrointestinal system (25.87%) followed by the Skin (25.17%) and Endocrine/ Metabolic system (22.37%) [Fig 3].

Reporting of ADRs was dominated by the PharmD students [Fig 4] of Department of Clinical Pharmacy (41.96%). This was followed by medical post graduates who reported about 34.97% ADRs. Physician reporting was found to be 13.29% whereas patients were responsible for 7% reporting.

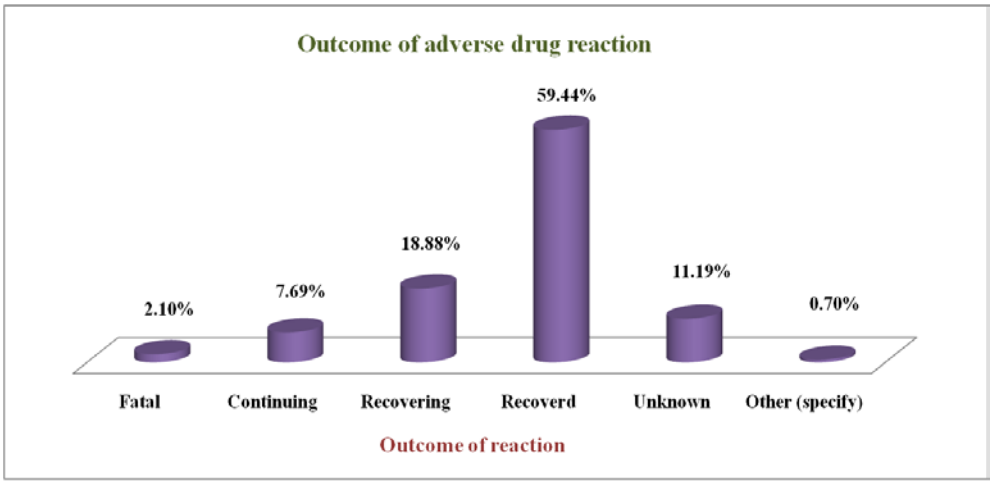

Fig 2: Outcome of Reactions

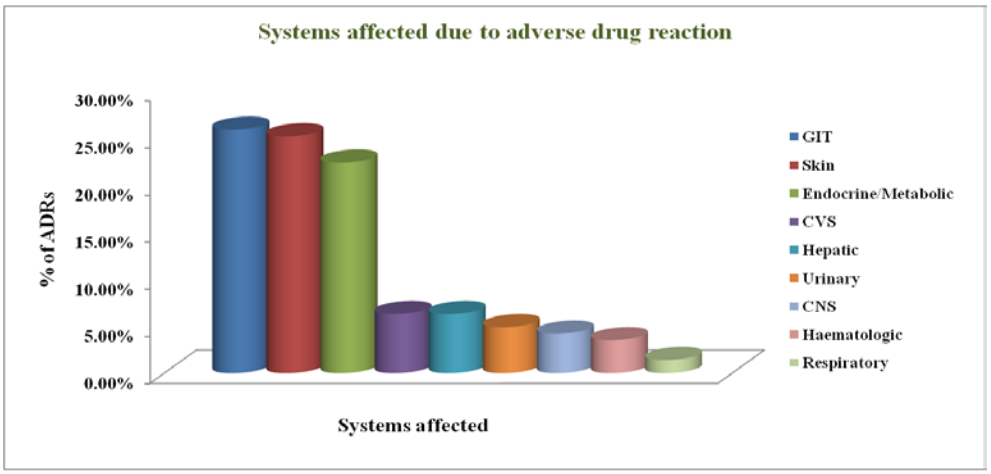

Fig 3: Organ Systems Most Commonly Associated With ADRs

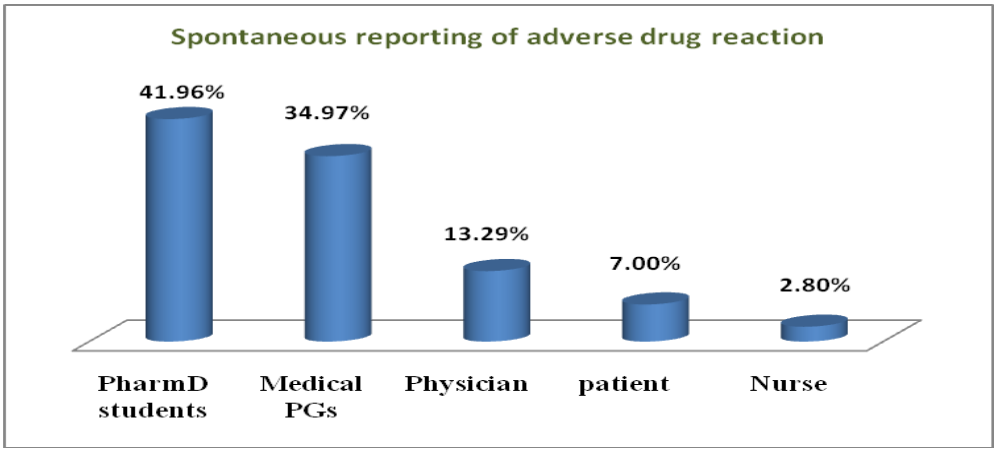

Fig 4: Spontaneous Reporting Of ADRs

Total cost incurred in managing all ADRs reported was Rs 23942.09 (US $ 539.37). The average cost incurred during "ADR related hospitalization" was found to be higher than "ADR occurred in hospitalized inpatient" i.e. Rs. 578.55 (US $ 13.03) and Rs. 441.86 (US $ 9.95) respectively. The average cost involved in treating ADR per patient was found to be Rs 412.79 (US$ 9.30) [Table No.5].

Table 3: Assessment of ADRs

CAUSALITY PARAMETERS (WHO SCALE)	NO. (%) OF ADRs REPORTED
Certain	37 (25.87%)
Probable	38 (26.57%)
Possible	62 (43.36%)
Unassessable/ Unclassifiable	3 (2.10%)
Unlikely	3 (2.10%)
Conditional/ Unclassified	0 (0.00%)
LEVEL OF SEVERITY (HARTWIG SCALE)	**NO. (%) OF ADRs REPORTED**
Mild	89 (62.24%)
Moderate	48 (33.57%)
Severe	6 (4.20%)

Table 4: Drug Class Most Commonly Associated With ADR

DRUG CLASS	NO. (%) OF ADRs REPORTED
Antimicrobials	54 (37.78%)
Cardiovascular agent	22 (15.38%)
Steroids	18 (12.59%)
NSAIDs	17 (11.90%)
Antidiabetic	8 (5.60%)
Laxatives	4 (2.80%)
PPI (Proton Pump Inhibitor)	3 (2.10%)
Anticonvulsants	2 (1.40%)
Antiemetic	2 (1.40%)
Antianxiety	1 (0.70%)
Others*	12 (8.39%)

*** = 4 (antiplatelet), 3 (anticoagulant), 2 (enzyme), 2 (vitamins), 1 (Calcium Carbonate)**

Table 5: Cost Incurred In Managing ADRs

CATEGORY OF ADR	TOTAL NO. OF PATIENTS	NO. OF PATIENT WHO INCURRED COST	TOTAL COST INCURRED IN Rs	AVG. COST PER PATIENT IN Rs (US $)
ADR in hospitalized inpatients	45	28	12372.09	441.86 (US $ 9.95)
ADR related Hospitalization	20	20	11570.98	578.55 (US $ 13.03)

US $ ≈ 45 Rs

DISCUSSION

Overall incidence of ADRs in our study was found to be 4.75% of which 3.60% patients experienced an ADR after hospitalization. This finding is similar to the reports generated from other Indian studies[17, 18] while slightly higher than reported by Vora M et al[6]. However ADR related hospital admission was 1.72% which is lower compared to previous studies[6, 17] while higher than reported by M Ramesh et al[18]. This can be attributed to the fact that the study was conducted over medicine inpatients excluding all other speciality departments of hospital. Also duration of the study was short of just six months.

Different epidemiological studies have indicated the female predominance in ADRs with no known underlying explanation for the occurrence. Our study results reveal similar higher prevalence in female gender (54.55%) compared to the male (45.45%) [4, 11, 17, 19].

Geriatric patients are more prone for ADRs as they are the major consumers of multiple numbers of drugs because of co-morbid conditions. Prevalence of ADRs in geriatrics was found to be 6.10% in comparison of 4.47% in adult patients. Previous studies also show the same pattern of incidence[5, 20].

Augmented reactions, also called Type A by Wills and Brown method of classification of ADRs were found to be 68.53%. These reactions are predicted by known pharmacology of the drug. This was followed by hypersensitivity, Type H reactions (22.38%), which are not preventable. This finding differs from study conducted by Arulmani et al which shows higher incidence of Type H reactions[17].

Causality assessment revealed 43.36% of the reactions as "Possible", 26.57% as "Probable" whereas 25.87% of the reactions were certainly related to drug. The findings were comparable with study results generated from other Indian studies[5, 6, 21].

The most common systems affected with ADR were found to be Gastrointestinal and Skin (25.87% and 25.17% respectively). Antimicrobial drugs are most commonly prescribed in hospitalized patients. Twenty to forty percent of patients treated in hospitals receive at least one antibiotic, and a significant proportion of them receive two or more. This practice leads to increased chances of ADR in patients. Antimicrobials were found to be more affecting class of drugs in this study inducing 54 ADRs. The study results correspond to similar studies on comparable population[4, 5, 11, 21, 22].

Severe reactions (4.20%) were those which required intensive medical care, permanent harm, or leading to death directly or indirectly, though no fatality was observed in the study. They required advanced treatment procedures and greater financial expenditure from the patients. Moderate reactions (33.57%) did require immediate cessation of the causative drug therapy, substitution with alternative drug and also treatment to the reaction. Mild reactions (62.24%) did not require any change in prescribed drugs, no extended hospitalization. Severity assessment was done according to Hartwig et.al criterion and study results were comparable with similar assessment in previous studies[10, 11, 13, 17, 19].

Outcome of the reaction showed 85 ADRs were "fully recovered" which shows better management of drug therapy. Serious ADRs

encountered in the study were Hepatitis and Erythmatuos and Purpuric rash (suspected for Steven Johnson Syndrome) which were recovered later. This outcome corresponds with two Indian studies[13, 17].

Spontaneous reporting was dominated by PharmD students. Although initial reporting by medical PGs was found to be lower but due to continuous clinical awareness and discussion spontaneous reporting was found to be improved with medical PGs reporting 34.97%. However clinician reporting was found to be still lower with 13.29%.

The average cost per patient incurred for managing each ADR was found to be Rs 412.79 (US$ 9.30) which resembles with the results of the other Indian studies[17, 18, and 21]. Average cost of hospitalized ADR per patient was found to be Rs. 441.86 (US $ 9.95) whereas for ADR related hospitalization per patient was Rs. 578.55 (US $ 13.03) which indicates that average cost for treating ADR leading to admission was higher.

CONCLUSION

Incidence of ADRs was more in hospitalized patients compared to ADR induced hospital admission. Geriatrics and females were most affected with ADRs. Antimicrobial drugs being mostly affecting class of drugs. Average cost incurred for treating ADR leading to admission was higher than treatment of ADR after hospital admission. There is need for establishing ADR monitoring centre at every multidisciplinary hospital. Also, more original studies need to be conducted in Indian population to know the exact prevalence of ADRs in Indian hospitals.

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