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Incidence, Associated Factors and Pharmacoeconomic Impact of Adverse Drug Reactions at a South Indian Tertiary Care Hospital: Need for a Continuous Monitoring System

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ABSTRACT

The aim of the study was to analyze the incidence of adverse drug reactions (ADRs) at a tertiary care hospital and assess the functioning of the reporting system. The outcome of the study would provide information regarding associated factors and pharmacoeconomic impact of the ADRs. The causality assessment was determined by WHO UMC probability scale and Naranjo's algorithm. Outcomes of ADR, management and the pharmacoeconomic impact was assessed. Overall incidence of ADRs among the patients was 4.5%. A total of 61 ADRs were detected from 54 patients. As per the WHO UMC scale 44.3% of the ADRs were possible and as per the Naranjo's scale 53.1% of the ADRs were possible. Majority of the reactions were moderate in severity (47.6%). Most of the ADRs (73.8%) were predictable reactions and 39.3% were probably preventable. Multiple drug therapy (27.77%) was the most common associated factor. Withdrawal of the offending drug was the main line of management. Symptomatic treatment was required in majority of cases. The total direct cost involved in treatment of ADRs was INR 1, 10,284 (US$ 1730.22) at a rate of INR 2042.29 US$ 32.08 per patient. The direct cost per patient involved in ADR related hospital admissions (INR 2689 i.e US$ 42.30) was higher than ADR during hospitalization (INR 1769.60 i.e US $ 27.83).The ADRs were not recognized and recorded in majority of the cases. Patients on multiple drug therapy are more vulnerable to ADRs. The incidence and alarming pharmacoeconomic impact of the ADRs suggest that there is a need for a continuous monitoring system at tertiary care hospitals.

Keywords: Adverse drug reactions, Causality, Preventability, Management, treatment.

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INTRODUCTION

The World Health Organization (WHO) defines an ADR as "a response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis, therapy of the disease or for modification of physiological function" [1]. The monitoring of adverse drug reactions is a method of active pharmacovigilance surveillance. The spontaneous reporting of suspected ADRs helps in identifying the effects of the drug that was not found in the pre marketing trials. There have been many instances in the past where regulatory decisions have been made on the grounds of such spontaneous reports[2]. A good hospital based ADR reporting system can provide an insight into the potential problems related to drug usage in the hospital[3]. In this type of a system trained health care professionals monitor the patients admitted to the hospital by reviewing their treatment charts and conducting structured interviews with the patients and physicians. The various information like patient demographics, indication for treatment, duration of therapy, clinical symptoms, reasons for discontinuation of the drug are noted in the questionnaire[4, 5]. ADR is a major cause of morbidity and accounts for nearly 5% of hospitalization around the world[6]. Epidemiological studies claim that it is the fourth leading cause of death ahead of pulmonary disease, diabetes mellitus, AIDS, pneumonia and automobile deaths[7]. It is also an economic burden to the patients as they may lead to hospitalization or can occur during hospitalization and prolong the hospital stay[8]. Most of the times they are not recognized by the physicians as they mimic the disease conditions by acting through similar physiological and pathological pathway leading to inappropriate management of the ADR[9]. The present study was undertaken at a tertiary care teaching hospital to find out the incidence, associated factors, and pharmacoeconomic impact of ADRs among the hospitalized patients. We aimed to study the Management, treatment and outcomes of treatment of ADRs and assess the functioning of ADR reporting system.

MATERIALS AND METHOD

This prospective spontaneous reporting study was carried out over a period of 6 months from August 2014 to January 2015 at a Mangalore based 1200 bed private tertiary care teaching hospital. The study protocol was reviewed and approved by the central ethics committee. The study included all the patients admitted to the hospital primarily due to an ADR and those patients who developed an ADR during hospitalization. The intentional and accidental poisoning cases were excluded. All the in-patients were monitored and assessed routinely by the clinical pharmacists for any ADRs during their hospital stay and during ward rounds. All the health care

professionals were informed about the study taking place and were requested to report any adverse events to these pharmacists. Whenever an ADR was found it was discussed with the treating physicians and subjected to further evaluation. The age and gender of the patient was considered during evaluation. The patient's age were categorized into three groups according to previously published study [10] as children and teenagers (0-18 year old), adults (19-59 years old) and the elderly (above 60 years old). All the ADRs were classified according to the Wills & Browns classification. The causality relation between the ADRs and the suspected drug was determined by the WHO UMC probability scale[11]. The Naranjo's algorithm was also utilized for assessing the causality[12]. The severity of the ADRs was determined as per the Hartwig severity scale[13]. The assessment of Preventability was done by modified Schumock and Thornton scale[14]. ADRs were also assessed for its predictability, if literature incidence of any reported ADRs was 1 to 10% and more than 10% it was considered 'predictable'. The outcome of management and treatment was assessed. The pharmacoeconimic impact of the ADRs was calculated by finding the direct cost involved in both ADR related hospital admission and ADR during hospital admission. The direct cost included the hospital charges, bed chargers, medicine charges, nursing charges, laboratory investigation charges and charges involved in invasive and non-invasive procedures. The drugs involved in the ADRs were categorized into different classes as per the anatomical and therapeutic chemical classification (ATC) [15]. The age, gender, diseases, multiple drug therapy and previous exposure were considered for evaluating the associated factors. All the statistical analysis was performed using SPSS 16.0 version. After the evaluation of the incidence rate and economic impact of the ADRs it was clear that the system for monitoring and reporting the ADRs in the hospital should be strengthened. For this purpose a clinical lecture was organized with all the health care professionals in the hospital. The attendees were encouraged to report any ADRs through the ADR notification form. Provisions were made for reporting by telephone and direct reporting of the ADR to the pharmacist. An ADR notification form was designed that was a slightly modified form of the Central Drug Standard Control Organization (CDSCO) and included the details of the patient like the name, age, gender, diagnosis, the brand name and generic name of the suspected drug, dose and batch number, manufacturing date and expiry date, the reaction caused, date of onset of reaction, route of administration, date of withdrawal of drug. This form was made available at all the nursing counters and was collected by the pharmacy students on a daily basis. The ADR documentation and reporting form was also designed for the detailed analysis of the ADR. An alert card was designed in order to alert the patients, the treating physicians and also to prevent future occurrence of the same.

RESULTS AND DISCUSSION

During the study period a total of 1200 patients were followed among them 54 patients encountered 61 ADRs. The overall incidence of ADRs in the patients was 4.5%. The elderly age group was the most affected by the ADRs. In this study majority of the patients had multiple drug therapy as associated factor. The most commonly involved class of drugs were Antibiotics (27.9%) followed by anticancer drugs (24.6%). The organ system most commonly affected was the skin (45.9%) followed by the musculoskeletal system (13.1%). Majority of the ADRs accounted for type A-Augmented Reactions (55.7%) followed by type C- chemical reactions. Primaquine induced depression and suicidal attempt was classed under type U- Unclassified since there was not enough evidence to classify this ADR (refer table 1).

Table 1: Characteristics of ADRs

Characteristics	Frequency	Percentage
Gender		
male	20	37.03
female	34	62.9
Age group		
≤17	2	3.70
18-59	19	5.18
≥ 60	33	61.00
Associated factors		
Multiple drug therapy	15	27.77
Age	9	16.60
Previous exposure	7	12.96
Disease	7	12.96
Gender	-	-
Genetics	-	-
No factors	16	29.62
Classification of ADRs		
Type A (Augmented)	34	55.7
Type B (Bugs)	-	-
Type C (Chemical)	14	23.0
Type D (Delivery)	-	-
Type E (Exit)	-	-
Type F (Familial)	-	-
Type G (Genitotoxicity)	-	-
Type H (Hypersensitivity)	12	19.7
Type U (Unclassified)	1	1.6

As per the WHO UMC scale majority of the ADRs were possible (44.3%), according to Naranjo's scale majority of the ADRs were possible (53.1%). The severity of majority of reactions was assessed as moderate. About 73.8% of the reactions were predictable and 39.3% were probably

preventable. Withdrawal of the offending drug was the main line of management, symptomatic treatment was required in majority of the cases. (Refer table 2).

Table 2: Assessment of ADRs

Characteristics	Frequency	Percentage
1.Causality assessment		
a) WHO UMC Scale		
Certain	10	16.4
Probable	23	37.7
Possible	27	44.3
Unassessable/ Unclassifiable	1	1.6
b) Naranjo's Scale		
Definite	6	9.8
Probable	22	36.1
Possible	32	53.1
Doubtful	1	1.0
2. Severity assessment		
Level 1	22	36.1
Level 2	7	11.5
Level 3	18	29.5
Level 4 (a)	14	23.0
3. Preventability		
Definitely preventable	22	36.1
Probably preventable	24	39.3
Not preventable	15	24.6
4. Management of ADRs		
Drug withdrawn	27	44.3
Dose altered	7	11.5
No change	10	16.4
Added another drug	11	18.0
Substituted with another drug	6	9.8
5. Treatment of ADRs		
Specific	24	39.3
Symptomatic	28	45.9
Nil	10	13.0

The total direct cost involved in managing the ADRs was INR 1, 10,284 (US$ 1730.22). A sum of INR 2042.29 (US$ 32.08) was spent per patient. The direct cost was calculated in terms of ADR related hospital admission (16 patients) and ADR during hospitalization (38 patients). Total direct cost involved in managing ADR related hospital admissions was INR 43,039 and cost per patient was INR 2689.93 (US$ 42.30) whereas the total direct cost of ADR during hospitalization was INR 67,245 and cost per patient was INR 1769.60 (US$ 27.83). Some significant ADRs and manifestations found during the course of this study have been shown in table 3.

Table 3: Significant ADRs and manifestations

Drugs by class	Adverse Drug Reactions	ATC Code
Anti platelets drugs		
Aspirin + Clopidogrel	Acid peptic disease	B01AC04
Anticancer drugs		
Cyclophosphamide	Alopecia , vomiting, discoloration of limbs &finger nails	L01AA01
Paclitaxel	Sores in the mouth	L01CD01
NSAIDs		
Diclofenac	Breathlessness, Itching	M01AB05
Aceclofenac	Rectal bleeding	M01AB16
Opioid analgesics		
Tramadol + Paracetamol	Breathlessness & itching	N02AX52
Antibiotics		
Levofloxacin	Tendon rupture	J01MA12
Ciprofloxacin	Steven Johnsons Syndrome	J01MA02
Anti diabetic agents		
Insulin	Hypoglycaemia	A10AB01
Anticoagulants		
Enoxaparin	Bleeding under skin	B01AB05
Antipsychotics		
Olanzapine	Muscle stiffness	N05AH03
Diuretics		
Spironolactone	Gynaecomastia	C03DA01
Antitubercular drugs		
Pyrazinamide	Hyperuricaemia	J04AK01
Vasopressin receptor antagonist		
Tolvaptan	Stiffness & jerky movement of hand	C03XA01
Antimalarial drugs		
Primaquine	Depression, suicide attempt	P01BA03
Immunosuppressant		
Methotrexate	Anaemia	L01BA01

The incidence of ADRs among the hospitalized patients in our study is in agreement with the results of the study conducted by Hartwig SC et al. [13] but it is less compared with the results of a meta-analysis conducted by Lazarou et al. [16] who reported 15% of incidence among the hospitalized patients. The incidence in our study could have been greater if the hospital had an intensive monitoring system and online prescription monitoring to detect ADRs. Several other factors that may have contributed to this include under reporting, lack of knowledge on procedures for identifying and detecting an ADR. Under reporting was also reported in the study by Rao Padma et al.[3] In spite of the presence of many ADR monitoring centres under the pharmacovigilance programme of India (PvPI) very few reports are sent annually. Previous studies have reported the failure of the reporting systems to disseminate the knowledge of

pharmacovigilance to the individuals involved in prescribing the drugs which is the physicians as a contributing factor [27]. The approach towards reporting ADRs have been limited to theoretical rather than a practical approach. In a hospital set up there should be discussions between the physicians, clinical pharmacists and nurses during the ward rounds whenever a case of ADR is noted. On studying the overall statistics of the patients who encountered ADRs it was observed that there was female (n=34) predominance than male (n=20). In our study majority of the ADRs were reported in the elderly group this may be because of the changes in the pharmacokinetics and pharmacodynamics with advancing age that predispose them to ADRs. The other possible reason may be the multiple drug therapy in the elderly which is supported by the result of a previous study where in Poly pharmacy was identified as a risk factor in elderly patients for receiving inappropriate medications that can cause ADRs[17]. These results are contradictory to the findings of several other studies wherein a larger percentage of ADRs have been reported from adults to paediatric population[18, 19, 20]. The finding of multiple drug therapy and comorbidities as associated factors is consistent with the result of the previous studies[18,21]. The most common system associated with ADRs was the skin this finding is in agreement with the results of several other studies [10,22,23] .However it differs from the reports of another study where GI manifestations were highest[20]. In our study the most commonly implicated drug class with the ADR was antibiotics (27.9%). This result is consistent with the findings of other studies [3,21] whereas it differs from the finding of Bergman et al.[24] where cardiovascular drugs are most associated drug class and Davis et al.[25] where diuretics class was most associated with ADRs. The withdrawal of the suspected drug (44.3%) was the main line of management of the ADR. This result is consistent with findings of other studies.[22,26] Some intervention that have been suggested by previous studies for preventing ADRs include computerized prescribing and monitoring systems[28], the presence of a pharmacist in the ward rounds[29], enhanced education of prescribing leading to error reduction[30], systematic and periodic medical education of health care professionals[26]. The limitations of this study was the short time duration, a longer duration with more sample size can give a better insight on the types of ADRs and the classes of drugs which cause them. In this study the patients were manually followed and checked for ADRs. The results can be more accurate if a computerised monitoring system for monitoring ADRs had existed. An ADR monitoring system will provide information regarding the quality and safety of the drugs used in the hospital. The ADRs were not recognised and recorded in majority of the cases. Patients on multiple drug therapy are more prone to ADRs. The incidence and alarming pharmacoeconomic impact of the ADRs suggest that there is a need for a continuous monitoring system at tertiary care hospitals. The systematic monitoring of the

ADRs can prevent its economic and health related impact on the patients. The education of health care professionals in the hospital is necessary for the vibrant working of the monitoring system.

Author's contribution

This paper do not have any conflict of interest. This paper has not been submitted else were. All the authors have made significant contribution to the publication. NF contributed in designing the study and data collection, CSS analyzed the data and supervised all the stages of the study. RS critically reviewed the manuscript. All the authors were aware of the submission and had given their consent.

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