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EVALUATION OF ADVERSE DRUG REACTIONS IN A TERTIARY CARE CENTER IN SOUTH INDIA-A PROSPECTIVE OBSERVATIONAL STUDY

Pharmacology

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ABSTRACT

Aim: To Evaluate the Adverse Drug Reactions among patients attending a tertiary care centre.
Materials and Methods: A prospective spontaneous reporting method of Adverse Drug Reaction (ADR) in hospitalised setting was conducted for a period of six months.
Results: The study came across with the demography of patients, the most commonly involved classes of drugs and assessment of ADRs. The results showed that 136 adverse drug reactions were reported from a total of 11584 patients and the overall incidence of ADR calculated from patient population was 0.81%. No significant difference was seen in overall incidence of ADRs observed in males and females. Incidence of ADRs among adults (1.15%) was significantly higher than paediatrics and geriatrics. Antibiotics (39.71%) were the drug class most commonly associated with ADRs. Causality assessment states that majority of the reported ADRs were probable according to WHO-UMC criteria. According to the severity assessment majority of the ADRs were mild in nature. Most of the ADRs were not preventable (76.47%) according to Schumock and Thornton preventability scale.
Conclusion: ADR monitoring was found to be useful to measure the effectiveness and safe use of medication.

KEYWORDS

Adverse Drug Reactions, Spontaneous reporting, Causality assessment, Management.

INTRODUCTION

The development of highly effective drugs in the last decades has brought remarkable benefits for the patient community in the management of various diseases. The other side of the coin is that Adverse Drug Reactions (ADR) occur and it is universally accepted that "No drug absolutely free from side effects". ADRs are believed to constitute an important healthcare problem and they are a significant cause of morbidity and mortality[1]. World Health Organization (WHO) defines Adverse Drug Reaction (ADR) as the "any response to a drug which is noxious and unintended and which occurs at doses normally in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function" [2]. Karch and Lasagna define Adverse Drug Reaction (ADR) as "any response to a drug that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose[3].

Pharmacovigilance is the process of identifying and responding to risk-benefit issues arising with marketed medicines[4]. Pharmacovigilance is also known as Post Marketing Surveillance and it plays an important role in the study of safety and pharmaco-therapeutic decision making. Post-marketing surveillance for ADR is therefore a critical part of the process that decides whether the benefits of a drug outweigh its risk. WHO defines "Pharmacovigilance is the science and its activities relating to detection, assessment, understanding and prevention of adverse effect or any other drug related problem". Post-marketing surveillance programmes use the information generated from these reports to update drug labelling and on occasions, to revaluate the approval or marketing decision[5]. Even if the report does not warrant labelling changes, the information provided can signal potential problems with the use of certain drugs for whichrecommendations can be provided to decrease the risk, or be further investigated. Once the reports are studied and evaluated, the data generated can help to estimate the risk patterns such as identifying populations at risk of developing an ADR with certain medications, investigate the preventability of these ADRs to provide indicators for quality improvement or signpost for interventions[6]. The dissemination of this information is also a crucial aspect of pharmacovigilance, as it is needed for drug prescribing and regulation.

It has been estimated that approximately 2.9%–5.6% of all hospital admissions are caused by ADRs and as many as 35% of the hospitalized patients experience an ADR during their hospital stay. ADR in hospitalized patients can be divided into two broad categories: those that cause admission to hospital and those that occur in in-patients after hospital admission[7]. It has been found that the total cost of drug related morbidity and mortality exceeds the cost of medications themselves. The economic burden of the ADRs is considerable also: the estimated direct cost of ADR related hospital admissions in Germany are well above 1 billion German marks per years. For the United States, total costs of $ 47.7% billion drug related admission were reported. A South Indian study found out that majority (47%) of the reactions were moderate in severity and the total cost incurred in managing all reported ADRs was Rs 76,564 (US $ 1595) with an average cost of Rs 690 (US $ 15) per ADR[8].

Patients with multiple drug therapy are more prone to develop adverse drug reactions, either due to alteration of drug effect through an interaction mechanism or by synergistic effect. Drug-drug interactions contribute to a significant number of ADRs, especially in elderly patients and in patients that are under polymedication[9]. There is an exponential relationship between the number of drugs taken and the probability of an ADR, independent of the therapeutic class and the patient's underlying disease. Patients with multiple diseases are at an increased risk of developing ADR due to multiple drug administration for their multiple diseases[10]. Similarly, patient with impaired hepatic or renal status are also at high risk of developing ADR to drugs which are eliminated by liver or kidney[11]. The relatively high incidence of ADRs in elderly patients may be due to a number of factors including an increased incidence of diseases, altered pharmacokinetic and

pharmacodynamic properties of many drugs, multi-drug consumption associated with an increased risk of drug interactions[12]. Some drugs are highly toxic in nature and outpatients who are treated with these agents are at an increased risk of ADRs. Women are thought to be at greater risk of ADRs than men and females appear to have a 1.5 to 1.7 folder greater risk of developing an ADR[13]. Women are more susceptible to blood dyscrasias with phenyl butazone and chloramphenicol, histaminoid reaction to neuromuscular locking drugs and to drug induced prolongation of the QT interval on the electrocardiogram. It is evident that ADRs are more common in genetically predisposed individual[14]. For example patients who are genetically deficient of G6PD enzymes are higher risk of developing haemolysis due to Primaquine. It is evident that ADRs are more common in genetically predisposed individuals. For example patients who are genetically deficient of G6PD enzymes are higher risk of developing haemolysis due to Primaquine.

ADR spontaneous reporting systems are basic components for the comprehensive post marketing surveillance of the drug induced risks[15]. Clinicians, nurses, pharmacists, other healthcare professionals and patients as well are provided with forms upon which they can notify a central authority of any suspected ADRs that they detect. In the United Kingdom, the 'Yellow Card' has been used for this purpose since 1964. Similar forms are provided in the FP10 prescription pads, the British National Formulary and the other sources[16]. In the United States, the MedWatch form is used and is made available to health professionals to encourage reporting. This method led to the identification and verification of many unexpected and serious ADRs[17]. These finding have resulted in many marketed drugs being withdrawn or additional information being provided to guide the safer use of products[17]. The aim of this study was to assess the prevalence, severity and management of adverse drug reactions among patients attending a tertiary care centre.

MATERIALS AND METHODS

This prospective spontaneous reporting study was conducted in a Tertiary Care Hospital in South India for a period of 6 months after obtaining approval from the Institutional Human Ethics Committee (IEC). Adverse drug reactions reported from the inpatient department including medical ward, surgical ward, intensive care unit and outpatients were included in the study. Awareness about ADRs and spontaneous reporting to the health professionals such as doctors, nurses, pharmacist, laboratory technicians, nursing students and pharmacy students were given at the study site. Also an awareness programme conducted exclusively for nursing students about the importance of ADR reporting and its procedure. Proper information to the healthcare personnel about the ADR notification forms, their use and the reporting procedures and the ADR report box for their easy accessibility were given. Health care professionals were encouraged for ADR reporting through the email, telephonic messages and direct access during the ward rounds to the pharmacists. The ADR notification forms in the ADR boxes were kept all nursing stations and outpatient area for the easy accessibility of form.Data on that particular suspected drug and reaction were collected and documented in a suitably designed 'ADR Documentation Form'. After confirmation of the ADR, the relevant data including the details of all drugs the patient received prior to onset of reaction, their respective dosage, route of administration with frequency, date of onset of reaction and the patient's allergy status (to drugs and food) were noted. In addition, the patient's medication history was also taken and any co-morbidities were identified to assess the causality relationship between the suspected drug and reaction. From the day when the ADR was reported, the patient was interviewed daily throughout their hospital stay. The probability of ADR was assessed by using WHO-UMC Causality Assessment Scale. The preventability of ADR was categorized into Definitely Preventable, Probably Preventable and Not Preventable using the criteria of Schumock and Thornton. Depending upon the severity, ADR were classified into Mild, Moderate and Severe reactions using Modified Hartwig and Siegel Severity Scale. Drug Alert Cards were provided for the patients in case of high morbid and mortal ADRs to prevent the recurrence of a similar ADR in the same patient.

RESULT AND DISCUSSION

Among a total of 11584 patients sought medical treatment in the study centreduring the study period, 136 suspected adverse drug reactions (ADR) were reported from 94 patients. 109 adverse drug reactions were reported from 80 patients from the in-patient department; and 27 adverse drug reactions were reported in 14 out-patients. Among the 80 in-patients, 9 (11.25%) were admitted due to ADR and 71 (88.75%) patients developed ADR during the hospital stay. The age and gender wise distribution of ADRs are given in Table 1.

Table 1: Demographic characteristics of the patients – Gender, Age categorization, ADR reports and ADR incidence.

Characteristics	Number of ADRs (%)	ADR Incidence (%)	P Value
1. Gender			
Male	59 (43.38%)	46 in 5131 patients = 0.90%	0.4247
Female	77 (56.62%)	48 in 6453 patients = 0.74%	
Total	136 (100)	94 in 11584 patients = 0.81%	
2. Age Categorization			
Paediatrics (≤ 18)	8 (5.88%)	6 in 1497 patients = 0.40%	0.00006
Adult (19 – 60)	103 (74.74%)	72 in 6245 patients = 1.15%	
Geriatrics (> 60)	25 (18.38%)	16 in 3842 patients = 0.42%	
Total	136 (100%)	94 in 11584 patients = 0.811 %	

Therapeutic group of the drugs associated with the adverse drug reactions is shown in Table 2. The results shows that antibiotics, 54 (39.24 %) were the drug class mostly reported for adverse drug reactions followed by antihypertensive agents 18 (13.24%) and antiulcer agents, 12 (8.82%).

Table 2: Number of ADRs reported among the drug classes

Drug Class	Number of ADRs (%)
Antibiotics	54 (39.71%)
Antihypertensive	18 (13.24)
Antiulcer	12 (8.82%)
Antiretroviral	9 (6.62%)
NSAIDs	8 (5.88%)
Antihyperlipidaemic	6 (4.41%)
Antiplatelet	5 (3.68 %)
Antianginal	4 (2.94%)
Anticoagulant	3 (2.21%)
Antidiabetic	3 (2.21%)
Antivenom	1 (0.74%)
Haematinic	1 (0.74%)
Inotropic	1 (0.74%)
Antipsychotic	1 (0.74%)

The adverse drug reactions reported was classified based on Wills and Brown Classification. Results shows that Type A (53.68%) reactions were common compared to the Type H reactions (31.62%). The results showed that Type A reaction more common in females (34.56%) than male (19.12%) and Type H reactions were more common males (16.91%) than females (14.71%). The suspected adverse drug reactions were assessed to establish the extent of relationship between the suspected drug using WHO-UMC criteria. According to the WHO - UMC criteria, most (71.32%) of the reactions were probable or likely reaction. The majority of the reactions were not re-challenged, as it was unethical; and the serum concentration of the drug was not taken during the treatment. Severities of the reported adverse drug reaction were assessed using Modified Hartwig and Siegel. Most of the reported ADRs were under the mild level (82.35%). Severity of the reaction was compared in both genders. The results showed that mild and moderate reactions were more common in females (47.06% and 8.09%) when compared to the males (35.29% and 6.62%). Preventability of a suspected drug was assessed by using Schumock Thornton scale. The results showed that 76.47% of the reported adverse drug reaction was not preventable. The details regarding assessments of causality, Severity and Preventability are given in Table 3.

Table 3: Assessment of ADRs (Causality, Severity and Preventability)

Parameters	Number (Percentage) of ADRs
Causality (WHO-UMC Scale)	
Probable /Likely	97 (71.32%)
Possible	30 (22.06%)
Certain	9 (6.62%)
Unlikely	0
Conditional / Unclassified	0

Unassessible / Unclassifiable	0
Severity (Modified Hartwig and Siegel Scale)	
Mild – Level 1	28 (20.59%)
Mild– Level 2	84 (61.76%)
Moderate – Level 3	13(9.56%)
Moderate – Level 4(a)	0 (0%)
Moderate– Level 4 (b)	7 (5.15%)
Severe – Level 5	3 (2.21%)
Severe – Level 6	1 (0.74%)
Severe– Level 7	(0%)
Preventability (Schumock and Thornton Scale)	
Definitely preventable	18 (13.24 %)
Probably preventable	14 (10.29 %)
Not preventable	104 (76.47 %)

CONCLUSION

From this study, it was found that the incidence of ADRs in females were higher than that of the males and Incidence of ADRs among the adults were significantly higher when compared the geriatrics and paediatrics. Antibiotics were found to be the most common class of drugs associated with the ADRs. Causality of the ADRs were probable in most cases according to WHO-UMC criteria, majority of the ADRs were mild according to Hartwig Siegel severity assessment scale and majority of the ADRs were not preventable according to Schumock and Thornton scale. This study helped in a better monitoring of the therapy given to the patient who attended a tertiary care centre; also helped in the drug safety and efficacy.

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