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Adverse Drug Reactions with Drugs used in Pulmonary Medicine: A Pharmacovigilance Study

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ABSTRACT

World Health Organization defines Adverse Drug Reaction (ADR) as "Any response to a drug which is noxious and unintended, and which occurs at doses normally used in human beings for the prophylaxis, diagnosis or therapy for a disease, or for the modification of physiological functions".[1] ADR is considered to be responsible for 2.9 to 5.6% of all hospital admissions, either directly or due to ADR related events. It is associated with significant morbidity, disability and it may cause financial burden on patients due to prolonged hospitalization. A hospital based pharmacovigilance study on ADR with drugs used in the Pulmonary Medicine Department of Gauhati Medical College Hospital was undertaken over a period of six months. Criteria for identifying ADR were based on spontaneous reporting by physicians in Pulmonary Medicine department. Case records having incomplete patient information were excluded from this study. The causality of the reported ADRs was carried out using Naranjo's scale, and the severity of ADR was assessed with Hartwig's scale. Hospital records of 214 consecutive patients admitted to the Pulmonary Medicine department were analyzed for the reports of ADR. A total of 44 patients (20.56%) were found to have some type of ADR. The highest incidence of ADR was reported in the age group of 50 - 69 years. Hepatitis, nausea, vomiting, chest pain, loss of appetite, vertigo, dryness of mouth and sore throat were the prominent manifestations of ADR in this study. The drugs causing ADRs were classified as (a) First line of anti-tubercular drugs, (b) Corticosteroids, and (c) Other drugs used as supportive therapy. Out of the 44 patients with ADR, 5 patients improved with change of drugs, 24 patients improved without any change of drugs, and 15 patients improved with addition of other drugs. Analysis of the causality using Naranjo's scale showed that 20 (45.4%) ADRs were "Definite", 16(36.4%) were "Possible", and 8(18.2%) were "Probable". In analysis of the severity using Hartwig's scale, 32 (72.8%) of ADRs were mild, 7(15.9%) were moderate, and only 5(11.3%) were severe. There was no patient with ADR resulting permanent disability or death.

***Keywords:** Pharmacovigilance, Adverse Drug Reaction, ADR*

INTRODUCTION

Adverse drug reaction (ADR) has been defined by Edwards et al.[2] as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." Drugs, no matter how safe and efficacious, are always coupled with the inescapable risk of adverse reactions. Though modern medicine has changed the way in which diseases are managed and controlled, despite all their benefits evidence continues to mount that adverse reactions to medicines are common but preventable causes of morbidity and even death.[3] In some countries, ADR is recognized as among one of the top ten leading cause of hospital deaths.[4] ADR also adds to the already existing morbidity of the patient, prolongs the hospital stay and increases the healthcare cost.[5,6,7,8,9] Early detection, evaluation and monitoring of ADR are essential

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to reduce the increased morbidity of the patients, reduce treatment cost and hospital stay.

Although the concept of ADR monitoring and evaluation of data has been conducted for the last four decades in developed countries, the subject is still in its infancy in India. WHO started the programme of ADR monitoring in 1968 and India became a member of it in 1997.[10] With India becoming an attractive center for clinical trials and being one of the largest producers of pharmaceuticals in the world, it has become essential to set up a very strict pharmacovigilance system to prevent the population from potential harm that may be caused by ADRs.

ADR reporting is often delayed and inconsistent in format.[11] The incidence of ADR is likely to increase with advanced age and exposure of elderly patients to poly-pharmacy. This situation can be ideally studied in the Pulmonary Medicine department because of availability of case materials fulfilling both these criteria. Pharmacological therapy of asthma, chronic obstructive pulmonary disease (COPD) in the elderly patients can be potentially hazardous. Beta-2 agonists administered for asthma and COPD may cause adverse effects like hypokalemia. Diuretics and corticosteroids can cause electrolyte disturbances. Beta-2 agonists may also cause tremor and alteration in blood pressure. Long term treatment with oral or inhaled corticosteroids may cause suppressed adrenocortical functions. Theophylline may cause nausea and vomiting, sinus or supraventricular tachycardia. Anticholinergic drugs like ipratropium bromide can cause unpleasant taste and dryness of the mouth. Anti-tubercular drugs can cause a wide range of ADR, the most serious one being hepatitis.

The present study was undertaken to analyze the pattern of commonly encountered ADRs in the Pulmonary Medicine department, in relation to age and sex related variations, type and severity of ADR and the probable management strategy.

MATERIALS AND METHODS

This prospective observational study was carried out over a period of six months in the Pulmonary Medicine department of Gauhati Medical College Hospital. The aim of the study was to identify the reported incidence of ADR, type of drugs causing ADR, age and sex related distribution of ADR, determine the causality and severity of ADR. For detecting the incidence of ADR, an adverse drug event reporting form containing all possible aspects of adverse drug reaction was used. For assessing the causality, Naranjo's causality assessment scale was used. This scale classifies the ADR as (a) Definite/Highly probable, (b) Probable, (c) Possible and (d) Unlikely according to the score calculated for a particular drug reaction or combination of reactions. For assessing the severity of the ADR, the assessment scale proposed by Hartwig was used. This scale prescribes different levels of severity from level 1 to 7. For validation of ADR, all reactions were discussed and confirmed with the attending physicians. Prescribing indicators were: (1) Total number of drugs contributing to ADR, and (2) Most commonly implicated drug in the study. Statistical analysis was done for age and sex related variables, drugs most frequently implicated for ADR, causality and severity of ADR.

RESULTS

The result is based on screening of the records of 214 patients undergoing treatment in the Pulmonary Medicine department of Gauhati Medical College hospital during the study period. The age and gender distribution is shown in **table 1**. It is observed that the incidence of ADR was highest in the age group of 50 - 69 years.

Table 1 Showing age and sex distribution

Age group in years	Number of patients	Male	Female	Percentage distribution
≤ 19	2	0	2	0.93
20-29	25	11	14	11.68
30-39	28	10	18	13
40-49	29	16	13	13.55
50-59	56	39	17	23.33
60-69	42	24	18	19.62
≥70	32	19	13	14.95
Total	**214**	**119**	**95**	**100**

Out of 214 patients treated with various medications, 44 patients (20.56%) were reported to be having some kind of adverse drug reactions, which are shown in **table 2**. There were 24 males and 20 females in the effected group. Hepatitis, nausea and vomiting, chest pain, loss of appetite, vertigo, dryness of mouth and sore throat were the prominent symptoms of adverse drug reactions. The drugs responsible for causing ADR were the first line of anti-tubercular drugs (40.9%), corticosteroids (13.6%), and other drugs used in the department (45.4%).

Table 2 Showing list of ADR reported in 44 patients

Type of ADR	Number of patients	Male	Female	Percentage distribution
Hepatitis	5	3	2	11.3
Nausea	7	3	4	15.9
Vomiting	5	2	3	11.3
Chest pain	4	3	1	9
Loss of appetite	10	6	4	22.7
Vertigo	5	2	3	11.3
Dryness of mouth	3	2	1	6.8
Sore throat	5	3	2	11.3
Total	**44**	**24**	**20**	**100**

Majority of the patients with ADR belonged to the 50-69 years age group. The percentage of ADR in the age group of 50-59 years was 28.57% and in the age group of 60-69 years it was 23.81%, with the overall percentage of incidence being 20.56%. **Table 3** shows the age wise break up of patients with ADR.

Table 3 Age wise break up of patients with ADR

Age group in years	Number of patients with ADR	Total number of patients	Percentage distribution
≤ 19	0	2	0
20-29	3	25	12%
30-39	3	28	10.7%
40-49	5	29	17.24%
50-59	16	56	28.57%
60-69	10	42	23.81%
≥70	7	32	21.87%
Overall	44	214	20.56%

The adverse reaction due to the first line of anti-tubercular drugs was found in 18 patients (40.9% of total patients with ADR). It was found with corticosteroids in 6 patients (13.6%), and 20 patients with ADR (45.4%) were found to be due to drugs other than anti-tubercular drugs and corticosteroids. out of the total of 44 patients with ADR, 5 patients improved with change of drugs, 24 patients improved without any change in medication and 15 patients improved with other drugs added in the management of these patients.

The causality assessment was done using Naranjo's scale.[12] According to this score, 20 patients (45.4%) were classified as Definite/highly probable, 8 patients (18.2%) were probable, 16 patients (36%) were possible and there was no patient in the unlikely group.

The severity assessment was done using Hartwig's scale.[13] According to this scale, there were 32 mild adverse drug reactions (72%), 7 moderate reactions (15.9%), and 5 severe reactions (11.3%).

DISCUSSION

Adverse drug reactions are commonly encountered in clinical practice all over the world. Although many of these reactions are mild and disappear when the drug suspected to be causing it is withdrawn or the dose is regulated, some of the reactions are more serious and they last longer. In some cases they may be the causes of increased morbidity and prolonged hospital stay, and even may cause permanent disability or death.

Although all new drugs introduced into the market undergo clinical trials to demonstrate efficacy and detect adverse reactions, it is probable that only the most common ADRs are detected by the time the drug is marketed. Moreover clinical trials are unlikely to be carried out in some groups of individuals like elderly or pregnant women. Pharmaceutical products must therefore be continuously monitored in the clinical practice. Monitoring systems include manual methods and combined electronic and manual methods. The former may be voluntary reporting by service provider, which may again be incidental reporting or prompted spontaneous reporting. Methods of involuntary reporting include patients' record review, reporting by trained observers and by patient interviews. Combined methods use electronic data available from laboratory reports of patients likely to have ADR as screening criteria, which is manually confirmed. Other modalities for detection of ADR are individual case reports, prospective cohort studies, case control studies, patients record linkage studies and hospital based population studies. Besides these, WHO Collaborating center for International drug monitoring, established in 1968, collects ADR reports from participating countries.

In a meta-analysis study conducted by Lazarou et al.,[14] overall incidence of serious ADR was found to be 6.7% and fatal ADR was reported in 0.32% of hospitalized patients, making these reactions between the fourth and sixth leading cause of death. Several studies have been done for detection of ADR with drugs prescribed for respiratory diseases like COPD, Pulmonary tuberculosis, Asthma, Respiratory tract infections etc.[15,16,17] Besides the known adverse reactions reported with the use of common drugs prescribed for these conditions, there may be some uncommon or rare events which may be encountered with these drugs. The higher percentage of elderly patients admitted to the pulmonary medicine department is also another factor to be counted. It was observed in the present study that the proportion of patients belonging to the age group of 50 to 69 years was the highest, and consequently the percentage of ADR seen in this age group was also highest. There were fewer patients below the age of 40 years admitted in this department and the percentage of ADR seen in this age group was also less.

The purpose of the present study was to introduce an ADR monitoring programme in the Pulmonary Medicine department to identify and assess the nature, type and the drugs responsible for ADR, as well as to determine the causality and severity of ADR observed in this department. The physician prompted spontaneous reporting method was adopted. During the six month period of study a total of 214 patients were studied and 44 patients were reported to be showing adverse drug reactions. An interesting finding in this study was that out of 44 patients reported to be showing ADR, 20(45.4%) were classified as Definite in Naranjo's scale, majority of them being mild ADR (72%) by Hartwig's scale. No case was reported which may have been included as 'Unlikely' by Naranjo's scale. Another interesting finding in this study was that gastro-intestinal symptoms like nausea, vomiting and loss of appetite constituted a major proportion of the ADR, while 5 out of 44 ADR cases (11.3%) had signs of hepatitis. All cases recovered with adequate modification in the prescription of drugs like change of drug or addition of another drug, or with time and without any modification in drugs. There was, however no permanent disability to the effected patients, neither was there any death in this series.

CONCLUSION

This is a hospital based pharmacovigilance study carried out in 214 consecutive patients admitted to the Pulmonary Medicine department of Gauhati Medical College hospital. A total of 44 patients (20.56%) were found to have some type of ADR. The highest incidence of ADR was reported in the age group of 50 - 69 years. Hepatitis, Nausea, vomiting, chest pain, loss of appetite,

vertigo, dryness of mouth and sore throat were the prominent manifestations. The drugs causing ADRs were first line of anti-tubercular drugs, Corticosteroids and drugs used as supportive therapy. Out of the 44 patients with ADR, all improved with either change of drugs, addition of other drugs or with time without any change of drugs. Analysis of the causality using Naranjo scale showed that 20 (45.4%) ADRs were "Definite", 16(36.4%) were "Possible", and 8(18.2%) were "Probable". In analysis of the severity using Hartwig scale, 32 (72.8%) of ADRs were mild, 7(15.9%) were moderate, and only 5(11.3%) were severe. Although this is a small series, the significant observation was that there was no permanent disability or death.

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