IAR Journal of Medicine and Surgery Research
ISSN Print: 2709-1899 | **ISSN Online:** 2709-1902
Frequency: Bi-Monthly
Language: English
Origin: KENYA
Website: https://jmsrp.or.ke/index.php/jmsrp

OPEN ACCESS JOURNALS

Research Article

A study to Monitor Adverse drug reactions in a patients of Chronic Obstructive pulmonary Disease

Article History

Received: 12.01.2024
Revision: 17.01.2024
Accepted: 05.02.2024
Published: 28.02.2024
Plagiarism check - Plagscan
DOI: 10.47310/iarjmsr.2024.V05i01.04

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How to Cite the Article:
Sangeetha M. A study to Monitor Adverse drug reactions in a patients of Chronic Obstructive pulmonary Disease *IAR J. Med & Surg Res. 2024;5(1):*16-20.

Abstract: ***Background:*** Inappropriate drug usage may preclude ideal benefit due to increased medical cost, adverse effects and mortality. Therefore drug utilization studies have become a plausible means in evaluating the healthcare systems. COPD management usually involves more than one drug which may escalate the risk of ADEs (adverse drug events). The present study aimed at assessing the current drug practice and ADEs in COPD management in ICU. ***Material and Methods***: A prospective, single centered, observational and open labeled study was carried out in Department of Pulmonary Medicine and Pharmacology, Tertiary Care Teaching Hospital. The patient population was broadly divided into four categories based on diagnosis - chronic obstructive pulmonary disease, Infections, Asthma and Others. Suspected ADRs were reported, analyzed, and causality assessment was carried out using Naranjo's algorithm scal0065. ***Results****:* In our study, most important causative drug was Budesonide (11.1%). Causality assessment of ADR by Naranjo's algorithm showed 11.9% probable and 88.1% possible reactions. According to WHO-UMC scale, 85.9% reactions are possible, 11.1% are probable, and 3% are unlikely. Among the 270 ADR reported, the most common ADR was oral thrush which accounted for 11.1% (n = 30) of the reported cases, followed by palpitation 11.1% (n = 30), sore throat 20 (7.4%), dizziness 17 (6.3%) cases, and headache 20 (7.4%) of reported ADR cases. ***Conclusion****:* Many research have been conducted separately on various respiratory diseases such as COPD, tuberculosis, asthma, respiratory tract infections (upper/lower), and so on. However, this study included some of the most common diseases in this field, such as COPD, tuberculosis, and respiratory tract infections. A routine patient follow-up is needed for the early detection and prevention of ADRs in order to improve patient adherence to drug therapy and provide improved drug therapy by avoiding associated morbidity and mortality.

Keywords: Adverse drug reactions, respiratory disorders, Pharmacovigilance

INTRODUCTION

Drug utilization studies, one of the most essential aspects of Pharmacoepidemiology, is defined as the marketing, distribution, prescription and use of drugs in a society, with distinct prominence to the resulting medical, social and economic outcomes. [1] Drug utilization audits ensure safe and correct usage of drugs, which can either be quantitative or qualitative or a combination of both. [2] Inappropriate usage of drugs may act as barrier in achieving ideal benefit as it may lead to sub-therapeutic effect, antimicrobial resistance, excess medical cost, adverse effects or mortality. Hence, drug utilization studies have become a plausible means in evaluating the health systems. [3]

Chronic Obstructive Pulmonary Disease (COPD), the fourth leading cause of death worldwide, is a common evitable, manageable and progressive disease characterized by sedulous airflow restriction. [4] Pharmacotherapy in COPD usually involves usage of numerous drugs, thereby increasing the risk of adverse drug events (ADEs) proportionally. Predominantly, no drug is absolutely innocuous and an ADE can eventuate when it is administered singly or in concoction. An ADE is "A response to a drug which is detrimental, unintended and which eventuate at doses commonly used in man for the prophylaxis, diagnosis or therapy for an illness". [5]

Most physicians fail to discern bacterial infections from viral infections and eventually end up prescribing antibiotics in viral infections. [6] Antibiotics serve the most frequent cause of ADEs in hospitalized patients, while bronchodilators are associated with approximately 20% of all ADEs in COPD, mostly fatal in severity. [7] Corticosteroids are also responsible for a number of potential ADEs. [8]

The prediction of a drug to develop an adverse event is assessed by clinical prudence. [9] Of late, there are various methods for assessing the causality, which include WHO probability scale, Naranjo's scale, Karch & Lasagna scale, European ABO system, to name a few. [10] Naranjo's scale is the easiest and most commonly preferred; involving a set of questionnaires, each attributed a certain score. Based on the total score, the drug-ADE association is termed definite, probable, possible or doubtful. [11]

Many studies have been conducted in the past on respiratory diseases, however to our knowledge published data particularly focused on COPD especially in India is limited. It was indeed necessary to assess the approach of Indian pulmonologists in treating COPD patients in order to refine the treatment practice. The present study aimed at assessing the current drug practice and ADEs in COPD management in ICU.

Material and Method

This study was single centered, prospective, observational and open labeled carried conducted at Department of Pulmonary Medicine and Pharmacology, Tertiary Care Teaching Hospital. The patient selection was random and the patient population was divided into four broad categories based on diagnosis as:

- Chronic obstructive pulmonary disease
- Infections (pneumonia, tuberculosis (TB), lower respiratory track infection)
- Asthma
- Others (pleural effusion, anti-tubercular drug induced hepatitis, obstructive sleep apnea, interstitial lung disease, pleurisy, obesity hypoventilation syndrome, corpulmonale).

Pediatrics and pregnant patients were excluded from the study.

Verbal Informed consent (in the vernacular language) was sought from the patients before their enrollment, on the basis of inclusion and exclusion criteria. Patients of either gender above 18 years admitted into (Pulmonology Department) were included in the study.

During the study, patients were monitored from the day of admission till the day of discharge. Sources of data were case sheets and verbal information while counseling the patients. The details were collected in patient profile form designed for the study purpose.

The details included: Demographics, medical history, medication history, laboratory data, history of drug allergy along with causative drug, current therapy, suspected ADR, description of ADR, date of onset, management and outcome aspects. Suspected ADRs were reported, analyzed and a causality assessment was carried out using Naranjo's algorithm scale.

Result

During the study period, a total of 90 patients were monitored, of which 42 patients were suffering from COPD (accounting 46.7%), 36 were those suffering from Asthma (40%), and 12 patients were suffering from bronchiectasis (13.3%). 459 ADRs were observed in total 90 observed patients Table 1.

Table 1: Type **of disease (COPD, asthma, bronchiectasis)**

Type of disease	No. of Patients (%)
COPD	42 (46.7)
Asthma	36 (40)
Bronchiectasis	12 (13.3)
Total	90

Table 2: Age and gender of the patients

Age group (Years)	Gender n (%) n=90		
	Male	Female	Total
01-10	-	-	
11-20	-	-	
21-30	8 (8.9)	8 (8.9)	16 (17.8)
31-40	5 (5.6)	9 (10)	14 (15.6)
41-50	10 (11.1)	12 (13.3)	22 (24.4)
51-60	13 (14.4)	15 (16.7)	28 (31.1)
61-70	6 (6.7)	4 (4.4)	10 (11.1)
71-80	-	-	-
Total	42 (46.7)	48 (53.3)	90 (100)

Demographic Characteristics

Age and gender of patients [Table 2]: Among 90 patients, ADRs reported was majority by female patients 53.3% (n = 48) in comparison to males, which was 46.7% (n = 42); however, there was not any significant difference in terms for ADR reported in both genders. About 31.1% of adults experienced ADRs were in the age group 51–60 years, which was closely followed by patients belonging to age group of 41–50 years. About 24.4% were of geriatric patient's age group. Least being in those between 31 and 40 years (15.6%).

Table 3: Marital status of patients

Marital status	Number	Percentage
Married	77	85.6
Unmarried	13	14.4

Table 4: Living status and religion of the patients

Living status	Religion n (%) n=90			
	Hindu	Muslim	Others	Total
Rural	25 (27.8)	10 (11.1)	5 (5.6)	40 (44.4)
Urban	35 (38.9)	15 (16.7)	-	50 (55.6)
Total	60 (66.7)	25 (27.7)	5 (5.6)	90 (100)

Living status and religion of the patients [Table 4]: In terms of living status it is seen majority 55.6% patients are from urban background whereas 44.4% patients belong to rural background. In the sample population the majority of patients were Hindus 66.7% (n = 60), followed by Muslims 27.7% (n=25) and just 5.6% were patients belonging to other religion.

Table 5: Type of ADR reported

ADR Reported	No. of Cases n (%) (n=270)		
	New	Follow up	Total
Oral thrush	16 (5.9)	14 (5.2)	30 (11.1)
Dysgeusia	4 (1.5)	2 (0.7)	6 (2.2)
Hoarseness of voice	3 (1.1)	2 (0.7)	5 (1.8)
Tremor	8 (2.9)	2 (0.7)	10 (3.7)
Tachycardia	5 (1.9)	3 (1.1)	8 (3)
Headache	12 (4.4)	8 (3)	20 (7.4)
Bitterness of tongue	1 (0.4)	-	1 (0.4)
Cough	7 (2.6)	4 (1.5)	11 (4.1)
Palpitation	20 (7.4)	10 (3.7)	30 (11.1)
Sore throat	15 (5.6)	5 (1.8)	20 (7.4)
Running Nose	10 (3.7)	-	10 (3.7)
Nervousness	-	2 (0.7)	2 (0.7)
Dry mouth	6 (2.2)	4 (1.5)	10 (3.7)
Diarrhea	8 (2.9)	-	8 (2.9)
Dyspepsia	5 (1.9)	2 (0.7)	07 (2.6)
Anxiety	6 (2.2)	5 (1.9)	11 (4.1)
Insomnia	3 (1.1)	2 (0.7)	5 (1.9)
Dizziness	10 (3.7)	7 (2.6)	17 (6.3)
Constipation	3 (1.1)	-	3 (1.1)
Abdominal pain	6 (2.2)	2 (0.7)	8 (2.9)
Hyperpigmentation of face	2 (0.7)	-	2 (0.7)
Weight gain	5 (1.9)	-	5 (1.9)
Restlessness	3 (1.1)	-	3 (1.1)
Altered taste	1 (0.4)	-	1 (0.4)
Nose Itching	2 (0.7)	-	2 (0.7)
Nausea	5 (1.9)	4 (1.4)	9 (3.3)
Thirst	4 (1.4)	-	4 (1.4)
Urinary difficulty	2 (0.7)	-	2 (0.7)
Glossitis	3 (1.1)	-	3 (1.1)
Voice change	2 (0.7)	-	2 (0.7)
Vomiting	1 (0.4)	-	1 (0.4)
Cramps	1 (0.4)	-	1 (0.4)
Paresthesia	2 (0.7)	-	2 (0.7)
Rash	1 (0.4)		1 (0.4)
Itching	1 (0.4)		1 (0.4)
Muscle pain	2 (0.7)	-	2 (0.7)
Anorexia	1 (0.4)		1 (0.4)
Gastric discomfort	1 (0.4)		1 (0.4)
Diuresis	1 (0.4)		1 (0.4)
Hepatitis	2 (0.7)	-	2 (0.7)
Mood change	1 (0.4)		1 (0.4)
Cold like symptoms	1 (0.4)		1 (0.4)
Total	192 (71.1)	78 (28.9)	270

Among the 270 ADR reported, the most common ADR was oral thrush which accounted for 11.1% (n = 30) of the reported cases, followed by palpitation 11.1% (n = 30), sore throat 20 (7.4%), dizziness 17 (6.3%) cases, and headache 20 (7.4%) of reported ADR cases. The other ADRs that were reported are listed in Table 5. Most of the ADR reported were non-fatal and treated with intervention. Patient with nausea and vomiting were given ondansetron as intervention. Diarrhea was treated primarily with symptomatic treated in form of fluid resuscitation and antibiotics. Hypersensitivity was treated with antihistaminic.

Table 6: Causative drug

Causative drug	No of cases n (%)
Budesonide	30 (11.1)
Formoterol	17 (6.3)
Ipratropium	4 (1.4)
Salbutamol	15 (5.6)
Salmeterol	20 (7.4)
Theophylline	42 (15.6)
Fluticasone	43 (15.9)
Indicaterol	6 (2.2)
Montelukast	28 (10.4)
Beclomethasone	1 (0.4)
Azithromycin	11 (4.1)
Albuterol	1 (0.4)
N-acetyl cysteine	1 (0.4)
Prednisolone	1 (0.4)
Derfylline	10 (3.7)
Levocetrizine	2 (0.7)
Doxycyline	1 (0.4)
Clarithromycin	5 (1.8)
Tiotropium	25 (9.3)
Cotrimoxazole	1 (0.4)
Guaifenesin	2 (0.7)
Carbocystein	2 (0.7)
Fexofenadine	2 (0.7)
Total	270

Drugs contributing majorly to ADRs were maximum number of ADR which were due to Budesonide (11.1%), followed by theophylline (15.6%), fluticasone (15.9%), and tiotropium (9.3%). The detailed drug versus prevalence rate of ADR is shown in Table 6.

Table 7: Causality assessment by WHO-UMC scale

Category	No. of ADR
Certain	0
Probable	30
Possible	232
Unlikely	8

Unclassified	0
Unclassifiable	0
Total	270

Causality Assessment of ADRs as Per WHO-UMC Scale
Of the total 459 ADR assessed, majority, 232 (85.9%) belonged to possible category, while 30 (11.1%) were probable and 8 (3%) were unlikely. No ADR were found belonging to certain, unclassified or unclassifiable categories [Table 7].

Table 8: Causality assessment by Naranjo scale

Category	No. of ADR
Definite	0
Probable	32
Possible	238
Doubtful	0
Total	270

Causality assessment of ADRs Naranjo algorithm was used to assess the causality which reve aled that ADRs can be categorized into 238 (88.1%) were found belonging to possible category, while 32 (11.9%) were probable. No ADR were found belonging to definite or doubtful [Table 8].

DISCUSSION

The physicians prompted spontaneous reporting method was used in this research. Adverse drug reaction reports were obtained from 60 patients (14.28 percent) of the 420 patients treated for different indications during the 8-month study period. The Naranjo scale revealed that out of 60 ADRs, 30 (50%) was listed as “Definite”, followed by 18 (30%) Likely, and 12 (20%) “Probable” adverse drug reactions. Hepatitis, loss of appetite, nausea, and vertigo were the most widely recorded ADRs in this study (Table 1.2). When the severity of ADRs was measured using Hartwig's severity scale, it was clear that the majority of the ADRs were mild (42 patients) to moderate (10 patients), with one serious (8 patients) reaction.

ADRs were often controlled by withdrawing the causative drug depending on the severity of the reaction. In the current research, 7 patients with drug-induced hepatitis were treated by switching medications, 18 patients were treated by adding other drugs to reduce the severity of ADRs, and 34 patients' prescriptions were not changed. There were no ADRs that caused permanent damage or resulted in the patient's death. The demographics of ADR patients were analyzed, and it was discovered that the prevalence of ADR was highest in the age group of 50-59 years (21 out of 60) and lowest in the age group of <=19 years.

The higher prevalence of ADRs in our study's extreme age groups (50-59 years) may be attributed to other co-morbidities or age-related disorders such as metabolic changes. The lower number of ADRs identified among those aged <=19 years could be due to a lower prevalence and occurrence of pulmonary disorders in this age group, as well as a lower number of patients attending the hospital. ADRs were found to be more common in males (32 patients) than females in this sample (28 patients). This may be due to the fact that there are more male patients in the ward than female patients. The therapeutic drug groups most often involved in ADRs were investigated. The most common culprits among the medications were found to be first-line TB drugs, which account for 21(35%) ADRs, corticosteroids, which account for 9(15%) ADRs, and other drugs used for different indications, such as ipratropium, furosemide, tramadol, and so on, which account for 30 (50%) ADRs.

This study's findings were close to those of several other studies that found these to be the most offending substances in their studies. [12] ADR research is also necessary to assess their prevalence in medical practice, estimate their contribution to hospital admissions, classify the types of ADRs seen, identify predisposing risk factors, and estimate the costs of ADRs in terms of ADR-related excess hospital stays. [13] One of the study's drawbacks is that we did not observe hospitalizations due to ADRs or collect information on their expense. [14]

One pathway for more actively monitoring Adverse Drug Reactions (ADRs) and, as a result, improving patient care safety is a structured Adverse Drug Reaction Surveillance network. Multiple methods for testing and recording the efficacy of drugs in clinical use are important for avoiding or reducing patient injury and strengthening public health. [15] This entails establishing a well-structured Pharmacovigilance programme in clinical practice. Once a prescription has been published into the "true world," pharmacovigilance is an important method of monitoring medication-related issues. [16] Pharmacovigilance and other drug-related problems should be familiar to those whose life is impacted by prescription procedures in some way. In recent years, pharmacovigilance has gained prominence as a technology critical to sound clinical practice and public health science. [17]

Since ADRs have such a detrimental influence on patients' wellbeing and inflict too much financial strain, it's critical to carefully monitor each medication for any potential adverse effects in animal models (preclinical studies) and clinical trials until releasing it. [18] Pharmacovigilance aims to play a key role in combating the dangers faced by an ever-growing number of drugs, each of which is vulnerable to unpredictably negative side effects. When adverse effects and toxicity occur, they must be recorded, analysed, and the importance of the results correctly communicated to those who may understand the evidence. By ensuring that prescription drugs of high consistency, purity, and effectiveness are used rationally, the risk of injury will be minimised. [19]

CONCLUSION

Many research have been conducted separately on various respiratory diseases such as COPD, tuberculosis, asthma, respiratory tract infections (upper/lower), and so on. However, this study included some of the most common diseases in this field, such as COPD, tuberculosis, and respiratory tract infections. A routine patient follow-up is needed for the early detection and prevention of ADRs in order to improve patient adherence to drug therapy and provide improved drug therapy by avoiding associated morbidity and mortality.

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