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Adverse Drug Reaction Monitoring in Chronic Obstructive Pulmonary Disease Patients in a Tertiary Care Centre

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ABSTRACT
Polypharmacy and comorbidities makes the patients with Chronic Obstructive Pulmonary Disease (COPD) highly susceptible to adverse drug reactions (ADRs). ADRs are associated with considerable morbidity, mortality, high direct and indirect medical costs. This study was undertaken to map out the ADR profile of COPD patients in the inpatient setting. The pattern, frequency, risk factors and causality of ADRs were assessed. The study was a cross sectional survey conducted among inpatients with COPD in a tertiary care hospital in Kerala. ADRs were monitored based on daily questioning for symptoms. Descriptive statistics was used for data analysis. 71% of the patients developed ADRs. Theophylline was the most frequently prescribed drug. Highest proportion of ADRs were due to Systemic Corticosteroids. Overall, the commonest ADR was dyspepsia, however Causality assessment showed that hyperglycemia due to systemic steroids was the most frequent ADR for which a causality could be suggested. Physicians should be especially vigilant about hyperglycemia associated with systemic use of steroids. Presence of comorbidities were not associated with increased prevalence of ADRs; but there was a higher prevalence among males which was statistically significant.
Keywords-*ADR, ADR monitoring, COPD, Pharmacovigilance, Polypharmacy.*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1].

According to WHO estimates, 65 million people have moderate to severe chronic obstructive

pulmonary disease (COPD). In 2005- COPD caused 5% of all deaths globally. By 2030, it is predicted to be the third leading cause of death worldwide [2]. As per 2016 Global Burden of Disease (GBD) estimates, COPD is the second leading cause of mortality in India [3].

The treatment in COPD is life long -polypharmacy is the norm. In addition, COPD often coexists with other diseases. Cardiovascular diseases, osteoporosis, depression, anxiety, skeletal muscle dysfunction and metabolic syndrome occur frequently in COPD patients -Use of multiple drugs & presence of comorbidities are two of the most important risk factors for development of adverse drug reactions -(ADRs). Thus COPD patients are highly susceptible to ADRs [4].

Adverse drug reactions can cause poor adherence and subsequent treatment failure. ADRs occurring among inpatients will prolong the recovery and increase the overall hospitalization costs. Additional indirect costs incurred by ADRs include anxiety or depression and missed days of work for the patient and/or caregiver. Thus, ADRs are associated with considerable morbidity, mortality, high direct and indirect medical costs.

Though pharmacovigilance is an integral part of drug therapy, it is not widely practiced in Indian hospitals. Poor awareness and non-availability of a central co-ordinating body resulted in gross under reporting- The National Pharmacovigilance Programme of India (PVPI)- was initiated to address these issues.

Hospital-based ADR monitoring and reporting programmes are highly effective in identifying and quantifying the risks associated with the use of drugs. This information may be useful in identifying and minimizing preventable ADRs while generally enhancing the knowledge of the prescribers to deal with ADRs more efficiently [5].

There are few studies on ADRs in inpatients with COPD. Hence this study is done to assess the pattern & frequency of ADRs in COPD patients admitted in a tertiary care centre in Kerala.

The causality of ADRs were also assessed. Although several methods for assigning ADR causality have been developed, no system has been able to produce a definitive estimation of relationship likelihood. Regardless, causality assessment is a routine practice in pharmacovigilance. In this study, causality is assessed using World Health Organization-Uppsala Monitoring Centre (WHO-UMC)- causality assessment scale[6]

Materials and Methods

Ethical clearance was obtained from the Institutional Ethics Committee prior to the study. Informed written consent was obtained from all participants. This study was conducted in the Department of Pulmonary Medicine in a tertiary care teaching hospital in Kerala. The study was a cross sectional survey carried out over a period of six months (October 2011-March 2012) - 150 in patients were included. Inpatients of either sex who were diagnosed as COPD by the physician and confirmed by spirometry were included in the study. Pregnant or lactating females, Patients with active pulmonary tuberculosis and patients with liver / kidney disease were excluded.

The WHO definition of an ADR was adopted [7]. The ADRs were monitored based on daily questioning for symptoms and reviewing of routine laboratory investigation reports - All the relevant data including all drugs the patient had received before the onset of reaction, their respective dosages, their routes of administration with frequency, laboratory data results present in the medical records, clinical details and treatments received were recorded in a structured profoma. The study was focused on known ADRs to the commonly used drugs in COPD. No invasive investigations were undertaken as part of the study. The drug effects which were described by the patients and effects which were detected and reported by the physician were documented. Dechallenge and rechallenge were not done.

The possible risk factors for development of ADRs were sought – Sex, presence of comorbid illness etc. The causality relationship between the ADR and the suspected drug therapy was assessed using- World

Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment scale.

WHO-UMC scaleassess the causality based on some preformed description of the adverse reactions. According to that ADRs were classified into certain, probable, possible, unlikely, unclassified and unclassifiable.

The data from 150 inpatients were sorted, coded and entered into Ms Excel and subsequently analysed using Epi Info version 7. Descriptive statistics was used for data analysis. Data were expressed as mean ± standard deviations and percentages. Proportions were compared with the chi-square test and was considered to be statistically significant at the p-value < 0.05.

Results

Prospective evaluation of 150 patients who were receiving treatment for COPD in Dept. of Pulmonary Medicine at a tertiary care centre from October 2011 - March 2012 was carried out and the data was analyzed. The demographic features were as follows (Table 1).

Table 1: Demographic features of patients with COPD

Parameter	Value
Age (Years) Mean ± SD	64 ± 9
Duration of disease (Years) Mean ± SD	7 ± 5.5
Mean % predicted FEV1	55%
Males	140 (93%)
Females	10 (7%)

SD: Standard Deviation, PFT: Pulmonary Function Test,FEV1: Forced Expiratory Volume in one second

Pattern of utilization of drugs in COPD patients

Among the 150 patients observed, Theophylline (79%) was the most frequently prescribed drug followed by Inhaled beta2 agonists (77%), Systemic steroids (65%), Inhaled anticholinergics (51%), Oral beta2 agonists (55%) and Inhaled steroids (47%). The percentage of patients who developed ADRs to each group of drug is given in table 2.

Table 2: General profile of drug treatments and ADRs in COPD [8]-[9].

Drugs given	No. of patients receiving the drug.	No of patients with ADR	Percent age*
Systemic steroids	97	67	69%
Oral salbutamol	56	36	64%
Theophylline	119	52	47%
Levosalbutamol	27	11	41%
Inhaled steroids	39	6	15%
Inhaled beta2 agonists	61	8	13%
Inhaled anticholinergics	76	2	2%

*Total percentage exceeds 100 since patients were on more than one drug and/ or were having more than one ADR.

Prevalence of ADRs

Among the 150 patients observed, 107 patients (71%) developed adverse reactions to COPD drugs. Among the patients who developed ADR, 24% had only one ADR and 47% had more than one ADR. 43 patients (29%) did not develop any ADRs.

The commonest ADR was dyspepsia- reported variably as epigastric pain, abdominal discomfort, bloating, regurgitation etc. Such symptoms were reported by 77 patients (51%). Other common ADRs were insomnia (48%), palpitation (46%) & muscle cramps (40%). Hyperglycaemia, tremor and elevated blood pressure levels were noted in 35%, 34% and31% respectively.

Details of causality assessment of ADRs are shown in tables 3, 4 and 5.

Table 3: Causality assessment of individual ADR to theophylline by WHO Causality Assessment Scale [8]-[9]

ADR	Probable *	Possible *	Unlikely *	Total *
Dyspepsia	14	40	12	66
Insomnia	13	31	14	57
Restlessness	1	21	6	28
Dizziness	2	13	2	16
Total	30	105	34	169

Among 169 cases assessed, 30 had a “Probable” score. Dyspepsia was the commonest ADR. There

were no 'certain' or 'unclassified' or 'unclassifiable' reactions.

Table 4: Causality assessment of individual ADR to Systemic steroids by WHO Causality assessment scale [8]-[9]

ADR	Probable	Possible	Unlikely	Total
Dyspepsia	11	27	13	51
Insomnia	2	36	11	49
Hyperglycaemia	28	20	-	48
Hypertension	15	21	-	36
Restlessness	1	17	5	23
Cataracts	2	7	5	14
Myopathy	1	9	1	11
Total	60	137	35	232

The ADR with maximum "Probable" cases were 'Hyperglycaemia'. Among the 97 patients on systemic steroids, there were 28 probable& 20 possible cases of hyperglycaemia.

Table 5: Causality assessment of individual ADR to beta2agonists (Oral and inhaled Salbutamol, Levosalbutamol) by WHO Causality Assessment scale [8]-[9].

ADR	Probable			Possible			Unlikely	
	A	B	C	A	B	C	A	B
Palpitation	11	1	4	14	19	7	2	5
Tremor	12	1	4	8	13	3	2	2
Cramps	10	0	2	10	19	7	1	2
Total	33	2	10	32	51	17	5	9

A Oral Salbutamol, B- Inhaled Salbutamol, C- Levosalbutamol

There were 5 cases of dysphonia & one case of oral candidiasis associated with use of inhaled steroids. Causality assessment by WHO Causality Assessment Scale showed that all of them belong to the category "Possible". There were no certain/ unclassified/ unclassifiable reactions.

Among 150 patients, 2 cases of dryness of mouth due to inhaled ipratropium were seen - Causality assessment showed that both reactions were probable.

Risk factors for development of ADRs were also assessed (Table 6).

Table 6: Risk factors for development of ADRs in COPD patients

Risk factors		No. of patients	% of patients with ADR	% of patients without ADR	P value
Sex	Male	140	74%	26%	0.03
	Female	10	40%	60%	
CAD	Present	34	71%	29%	0.9
	Absent	116	72%	28%	
Diabetes	Present	52	73%	27%	0.7
	Absent	98	70%	30%	

CAD- Coronary Artery Disease

There was a statistically significant higher prevalence of ADRs among males (P value – 0.03). No significant association was found with presence of co morbidities like Diabetes mellitus or CAD.

Discussion

COPD is a disease that requires lifelong treatment with multiple drugs. The commonly used drugs are methyl xanthines, beta-2 agonists, anticholinergics, corticosteroids etc. Theophylline is known to cause dyspepsia, insomnia, restlessness, dizziness etc. Corticosteroids can cause glucose intolerance, hypertension, dyspepsia, insomnia, restlessness, proximal myopathy and cataract. Beta-2 agonists can cause tremor, palpitation and muscle cramps [8] [9].

In this study, among the 150 inpatients observed, 71% developed adverse reactions. In a similar study conducted among COPD outpatients, the prevalence of ADR was only 32%. The difference could be due to the fact that inpatients with COPD are generally hospitalised when they have an exacerbation and hence have a need to be treated with systemic drugs, including steroids, have more chance of co morbidities & polypharmacy [10].

Theophylline was the most frequently prescribed drug in the present study- used by 79% of the study population. The prevalence of theophylline use was comparable to that in the study by Tyagi et al. Use of Systemic steroids was higher in the present study (hospitalized COPD patients during exacerbations need prescription of steroids)& they were the

commonest cause of ADRs (69%). In the study by Tyagi et al, the common offending drug causing ADR was theophylline (47%), followed by systemic steroids (21%). The mean value of PFT (FEV1)in the study population was only 55%.

Among 169 cases of ADRs assessed for patients on theophylline, 30 were probable and 105 were possible. Dyspepsia was the commonest ADR. This is similar to the study by Tyagi et al. Other ADRs assessed were insomnia, restlessness & dizziness. Most of the case were "Possible" after causality assessment. Dyspnoea itself can cause insomnia & restlessness. Other COPD medications like systemic steroids are also known causes. This may be the reason why some cases had a low score in causality assessment.

Among the 56 patients on oral Salbutamol, probable cases of ADRs were observed as follows; 20% had tremor,21% had palpitation & 18% had muscle cramps. There were 27 patients on levosalbutamol. 15% of them developed tremor, 15% had palpitation & 7% had cramps. These values are higher than the known values given by FDA - Tremor due to oral salbutamol range from 10 – 20%, Palpitation (12%) and Cramps (11%). This high prevalence of ADRs due to oral Salbutamol and levosalbutamol may be due to over the counter use of these cheap and rapid acting drugs. In fact,patients admitted having self-medicated with these drugs. As expected, ADRs were negligible when inhaled Salbutamol was used.

The prevalence of ADRs to inhaled drugs was much lower in the present study (15% for inhaled steroids & 2% for inhaled anticholinergics); compared to 56% for inhaled steroids & 23 % for inhaled anticholinergics in the study by Tyagi et al.

The most common complaints of patients on systemic steroids was dyspepsia & insomnia. But after causality assessment, ADR with the maximum number of probable reactions were hyperglycaemia. Among the 97 patients on steroids, there were 28 probable cases (29%) and 20 possible cases. It is well established that corticosteroids may cause glucose intolerance. Conn & Poynard have reported that the prevalence of diabetes in corticosteroid treatment group was four times that of control subjects [11]. Lieberman et alreported prevalence of diabetes in the general population to be approximately 4 - 5% [12]. In Kerala, the prevalence of diabetes in the general population is reported to be higher than the national prevalence. A study conducted in Kerala by Ramankutty et alreported the prevalence in general population to be 16 % [13]. The high prevalence of hyperglycaemia in COPD patients on steroids may be explained by these observations.

Elevated blood pressure levels were seen in 36 patients; of which 15 were probable cases.

Although there were 23 cases of cataract and 14 patients had complaints related to proximal myopathy(difficulty in getting up from squatting), number of probable cases were very low as no formal assessment could be done.

When risk factors for development of ADRs were assessed, a statistically significant higher prevalence was seen among males (P value – 0.03). While the reason for adverse effects being more common in males was not clear from our study it could be due to the fact that addictions like smoking and alcoholism, current and past, were more prevalent in males whereas female COPD are more likely to be due to household indoor smoke exposure.

One of the major limitation of the study was the restricted period of monitoring of adverse drug reactions. Only known ADRs are assessed in this study. Administration of dechallenge and placebo could not be done.

Conclusions

Adverse drug reactions were very prevalent in inpatients with COPD; though in general they were non-serious nature not requiring withdrawal of the drug in any cases. Physicians should be especially vigilant about diabetes mellitus associated with systemic use of steroids. Treatment of ADRs like insomnia & peptic ulcers can improve quality of life. Encouraging patients to use inhaled medications as well as avoiding self-medication will prevent many ADRs.

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