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A PHARMACOVIGILANCE STUDY ON EVALUATION OF CORRELATION BETWEEN DIFFERENT THERAPY OPTIONS, INHALATION-DEVICES, METHODS OF DEVICES AND SAFETY OUTCOME IN COPD PATIENTS

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ABSTRACT
This MAIDEN study is an effort to observe multiple factors simultaneously with number of interesting findings. Study data were first analyzed with the help of PIVOT TABLE to see the correlation between any two or three factors and then statistical tests were applied. Patients with confirm diagnosis of COPD from 30 year to 90 year from both gender were enrolled and observed for four months with recording of all inputs (i.e. drug combination, device and compliance to device) and outputs (i.e. improvement in FEV1, category of disease stage, side effect, infection rate, blood pressure etc). All labeled side effects, including cardiac events were observed in each category and prevalence matched with earlier studies. However, there were patients who did not had any side effect in each drug combination, therefore an appropriate combination can be selected which does not affect quality of life adversely due to side effects and reduce burden of co-prescription. Vertigo and rise in blood pressure were found in significant percentage, which suggests conducting a long-term study to further confirm the causality of ADRs with COPD treatment. Patients receiving Theophylline should be monitored more closely for increase in ADR. 62% patients were not able to comply well with devices specially inhalers, suggesting spacer as better choice followed by Rotacap (DPI). A meticulous follow-up for 6 months after initiating COPD treatment is advised to select the best drug combination for optimum safety and correct use of device.

KEYWORDS: COPD, Inhalation Devices, Safety, Therapy Options, ADR, Side-Effects.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is a progressively irreversible disease; recognized in 4 -10 per cent of adult male population of India and several other Asian countries. The severity of COPD depends on predicted FEV_1 %**;** ≥80 is mild, 50–79 is moderate, 30–49 is severe and <30 is very severe. Almost all forms of smoking products have been found to be significantly associated with COPD. In this disorder, oxidative stress is produced by the high concentrations of free radicals and cytokines are released due to inflammation as the body responds to irritant particles such as tobacco smoke in the airway. Tobacco smoke and free radicals impair the activity of antiprotease enzymes such as alpha 1-antitrypsin, allowing protease enzymes to damage the lung. Lung damage and inflammation result in chronic bronchitis, emphysema etc. Narrowing of the airways reduces the rate at which air can flow to and from the air sacs (alveoli) and limits the effectiveness of the lungs. There are multiple- individual and combined pharmacological treatment regimens, which include anticholinergic, β_2 agonists and steroids. Major dependence on these drugs is for symptomatic relief and to improve the quality of life. Proper follow-up and selection of best combination in optimum dosage and usage becomes secondary. However, none of them is known to reduce the mortality and decline in lung function, rather is associated with side effects (including increase in cardiac morbidity and mortality), which further affects the quality of life adversely.[1-5]

The drugs are given through different inhalation devices, like inhalers, rotacaps, turbohaler etc. Incorrect technique when taking inhaled medications frequently prevents patients from receiving the maximal benefit from their medications. The proper use and adherence to inhalation devices is of paramount importance to ensure better outcome.[6,7]

This study was designed to monitor factual clinical trends in the treatment of COPD and to evaluate the correlation between different therapy options, different inhalation-devices, methods of devices and different outcome related to safety.

MATERIAL AND METHODS

The study was conducted on 74 patients enrolled at Gyan Pushpa Research Centre, Indore and Bombay Hospital, Indore, out of which 2 dropped. Among the patients, 14 were females and 52 were males with diagnosis of COPD between 35 to 90 years of age, receiving inhaled corticosteroids (ICS) and / or $ß_2$ agonists with or without anticholinergic. When one patient was given another group of drugs during study then that was considered as new patient so after 64 patients due to change of therapy total number of patients came as 74. Subjects were screened for selection criteria. Screening assessments included complete medical and smoking history, clinical examination, ECG and Spirometry. After clinical examination, spirometric evaluation was done. Subjects were trained for the use of the Peak Flow Meter. Follow-up visits were scheduled every month till 16 weeks from baseline visit. Spirometry was performed at baseline, at every follow up and week 16 of treatment period. Patients who required more than eight puffs per day of levosalbutamol for >2 consecutive days were instructed to immediately contact their physician for assessment and initiation of appropriate therapy. Subjects with one episode of exacerbation were continued in the study after an OPD based treatment. In case of severe exacerbation, the subject was continued in the study on the physician discretion.

Endpoints

Primary safety parameter - Incidence of adverse events, Incidence of severe COPD exacerbations, requiring emergency attendance, hospitalization.

Secondary safety parameter - To record outcome with different inhalation devices and to record the compliance to uses of inhalation devices.

RESULTS

Occurrence of ADR (Group Wise)

Labeled side effects: ADRs are already known with the drug in use. Among the 12 groups of drugs, one or more side effects were noticed in the patients of all groups except "G" group (Table 1). Further, out of total 74 patients, 51 patients experienced side effects. 12 out of 14 females and 33 out of 51 males experienced side effects. Major side effects observed in the present study were acidity (21%), dry-mouth (16%), constipation (9.5%), loss of appetite (10%), leg cramps (9.5%) and tremors (9.5%).

Unlabeled side effects: Vertigo like symptoms were observed in four (3.4%) patients as confirmed by the treating physician, which are significantly high (although did not have significant correlation as per statistical analysis due to small sample).

Occurrence of side effects and Theophylline: Out of total 74 patients, 51 patients i.e. 69% had side effects and out of these, 29 patients (57%) were not on Theophylline (Table 2), although among rest of the 23 patients, some were on doxophylline. As per above data in this population of patients, there was no correlation between Theophylline and occurrence of side effects in COPD patients. Further, positive changes in ECG were noted in six patients, among which five patients received the medicine group with theophylline (Table 2A). No significant correlation was found between rise in blood pressure and presence of theophylline in medicine group (Table 2B).

Secondary objective: As per PFT results, patients were put in category of very severe (VS), severe (S), moderate (MD) and mild (M). If in last visit there was upward change of category, patient was taken in category- Improved (I) and if there was downward shift, then patient was taken in category- decline. If patient remained in same stage, patient was placed in 'Not Improved' (NI) category. Where PFT was not possible due to severity, for mean value calculation patients were assigned FEV1 = 20.

Compliance of inhalation devices: Out of 64 patients (who were examined throughout the study), 9 patients were on spacer, which is easy to use device, and out of remaining 55, only 21 i.e. 38.2% patients could use device in correct manner from the first visit and had maximum number of improved patients (82%) (Table 3). Seventeen patients were corrected in subsequent visits with 13 patients (76.5%) in improvement category, but 19 patients despite constant counseling could not use device correctly with no patient showing improvement (Table 3). The sum of corrected and incorrect patient's category is 36 i.e 65.45%. The chi square value of 36.13 is significant at 0.01 level with degree of freedom= 4, that means the responses are not distributed normally. This confirms that improvement largely depends upon appropriate use of inhalation device.

Impact of devices (Improvement in category and device): As per ANOVA, the F value of 4.36 is significant at 0.05 level with degree of freedom=2/62, it means there is a significant difference amongst the all three groups. Further, to test the significance difference between the groups Bonferroni Test was applied, which indicates that there is a significant difference between Inhaler-group and Spacer-group, whereas there is no significant difference between Rotacap-group v/s Inhaler-group and Rotacap- group v/s Spacer-group.

Following drug groups were made

Medicine Group	Combination of Drugs
A	Salbutamol + Ipratropium + Theophylline
B	Salbutamol + Ipratropium
C	Formoterol + Budesonide + Theophylline
D	Salbutamol + Ipratropium + Doxophylline
E	Formoterol + Budesonide + Ipratropium
F	Salbutamol + Ipratropium + Formoterol + Budesonide
G	Salmetrol + Fluticasone + Tiotropium + Doxophylline
H	Formoterol + Budesonide + Tiotropium + Doxophylline
I	Budesonide + Formoterol
J	Salbutamol + Ipratropium + Budesonide + Theophylline
K	Budesonide + Formoterol + Doxophylline
L	Formoterol + Fluticasone + Tiotropium

Table 1: Occurrence of ADR (Group Wise).

Medicine Group	Side-Effect		Grand Total
	No	Yes	
A	7	12	19
B	-	3	3
C	4	4	8
D	-	3	3
E	1	1	2
F	-	3	3
G	1	-	1
H	2	9	11
I	2	3	5
J	2	6	8
K	3	2	5
L	1	5	6
Grand Total	**23**	**51**	**74**

Table 2: Occurrence of side effects and Theophylline.

Side Effect	Patients On Theophylline		Grand Total
	No	Yes	
No	10	13	23
Yes	29	22	51
Grand Total	39	35	74

Table 2A: Occurrence of cardiac events and Theophylline.

Theophylline in medicine group	Cardiac Events		Grand total
	Normal	Positive	
No	34	1	35
Yes	24	5	29
Grand Total	58	6	64

Table 2B: Rise In blood pressure and Theophylline.

Theophylline	Change in Blood Pressure			
In medicine group	Decrease	Increase	Same	Grand Total
No	3	6	26	35
Yes	2	4	23	29
Grand Total	5	10	49	64

On further analysis of inhaler devices and improvement in stage of COPD, patients using spacer had highest (89%) in improvement category. In patients using Rotacap 69% patients were in improved category, followed by 44% patients in improvement category among using Inhalers. Similarly decline and not improved category was highest in inhaler group, followed by Rotacap group (Table 4).

Cardiovascular study

a) Cardiac Events: Out of 64 patients, 5 (7.8%) patients, whose baseline ECG was in normal limits showed different type of arrhythmic changes in last visit. One patient was already identified case of Angina and was on Amlodipin and Atenolol and did not improve with COPD therapy.

Table 3: Improvement with compliance of inhalation devices.

Method	Category			Grand Total	Spacer	Final
	Decline	Improved	Not Improved			
Correct	2	23	3	28	9	21
Corrected	1	13	3	17	-	17
Incorrect	5	-	14	19	-	19
Grand Total	8	36	20	64	-	55

Table 4: Improvement in category and device.

Device	Category			
	Decline	Improved	Normal	Grand total
Inhaler	9	19	15	43
Rota-Cap	-	9	4	13
Spacer	-	8	1	9
Grand Total	9	36	20	65

b) Impact on Blood Pressure: Out of 64 patients, 10 patients (15.63%) had increase in BP by > 10 mm Hg systolic in two subsequent visits, there was no statistically significant finding in different drug groups and increase in blood pressure. There was also decrease in Blood pressure in 5 pts (7.8%). In both cases Statistical Correlation was not there but Percentage Prevalence cannot be ignored.

DISCUSSION

Large number of landmark clinical trials has already documented the benefit and limitation of individual medicines or combinations extensively. Outcome of these clinical trials and their meta-analysis is not consistent with each other and no individual drug or combination is found to reduce mortality or morbidity. There is no definite relationship between side effects and different combinations of drugs and patient profile. Therefore, the basis of recommendation for COPD from all authorities was to- improve the quality of life and to slow down lung function decline with precision medicine.

This study is an effort to evaluate the correlation among different inputs (i.e. devices, medicine-groups, method of devices) and outputs (i.e. improvement in COPD, cardiac-events and side-effects etc.) simultaneously in one study. Different drug groups were considered in place of individual drugs where safety and efficacy were recorded along with impact of different inhalation devices and their methods.

This study was carried out from pharmacovigilance point of view to know what are the factors responsible for negative outcome. Although, all labeled side effects[8-28] were observed in clinically significant manner (in 69% patients), statistical correlation among different medicine groups and different side effects was not possible due to limitation of number of patients and duration of observation. Hyperacidity, dry mouth and other gastrointestinal problems were among most common SE which can be avoided with proper selection of drug- combination. Because as evident from the study that all drug groups had no side effects in certain set of patients which cannot be predicted.

Therefore, instead of co-prescription for symptomatic relief of side effects, a suitable combination should be selected for each patient through frequent follow- up visits by trying different combinations for safety. As co- prescription for these side-effects further increase the number of medicine and reduce the adherence, these follow ups will also help in timely diagnosis of cardiac events and monitoring of device usage. Tremors are already known with beta-agonist.[25] Similar observations were also noticed in study population. These were because of excessive use of rescue therapy of Salbutamol. Oral ulcers were also high in this study as patients were not doing gargles or rinsing after ICS.[27] Among other gastrointestinal side effects loss of appetite and constipation are due to multiple drug regimens and prevalence reported in this study matched with earlier studies.[20-25]

Among unlabeled side effects, vertigo was observed (5.4%) for which further study is required to evaluate causal relationship. Vertigo can be related to effect of drugs on CNS or Hemodynamic system. Although Theophylline is known for its side effects but in this study, there was no significance between occurrence of side effects and medicine-group with or without Theophylline. Since physicians use theophylline frequently, patients receiving theophylline should be monitored carefully for probable side-effects.[28] 7.5%

(5 patients) had changes in EGG, related to arrhythmia which matches with landmark clinical trials.[25-28] Theophylline along with LABA and anticholinergic. Therefore, a separate long-term study with a greater number of patients should be planned to evaluate if Theophylline increases the chance of arrhythmia when used with LABA/ anticholinergic which are already known for inducing arrhythmia. In practice physicians give combination of short acting beta blockers, LABA, anticholinergic, ICS, theophylline etc. and monitoring is mostly related to symptomatic relief of dyspnea, not related to minimize the side effects or to reduce the decline in lung function. Also, patient's compliance to therapy is not good due to side effects or lack of efficacy on account of incorrect use of devices.

Monitoring of correct use of Inhalers and Rotacap is also limited and has great impact on outcome.[14] In this study 55% patients were not using devices properly. There were patients using inhalation devices for months/years but not able to use properly on account of inadequate education. So, patient-counseling on use of device can help better results. Spacers are easy to use and study clearly establishes the advantages and superiority over other devices in terms of improvement in FEV1 as well as disease-category. Oro-pharyngeal deposition is lesser with spacers than other devices. Surprisingly physicians are little reluctant to put patient on spacers perhaps due to cost- considerations. Unlike other studies, in this study improvement was recorded quantitatively with the improvement in method of using devices.

In this study it was noticed that in 10 patients (15%) blood pressure was increased during therapy. Although there was no statistically significant correlation between therapy and rise in BP, still, 15% is considerably high. Therefore, patient should be monitored for the hypertension which can further add to risk of cardiovascular events.

Alternative therapy or medicine or changing physician for the search of cure is another reason which affects the follow-up. Incomplete records on past therapy are also a problem for new physician to select future course. Patient starts treatment at general physician level and mostly on SOS basis (for acute episodes) and disease being progressive, continues to increase the decline in lung- function which later becomes difficult to control.

CONCLUSION

- The results of the present study demonstrate that while initiating treatment for COPD, for first 4 to 6 months patient should be followed frequently to tailor right combination of medicine with least side effects. This right combination should be administered with right device in right manner.
- In these follow-ups, vitals of patients should be monitored to avoid occurrence of side effects including cardiac events and hypertension, specially those patients, who are on theophylline with LABA and anticholinergic.
- Spacer and inhaler require minimum efforts and counseling and give best of predictable results. In every visit patient should be asked to show the method of using given device and on each device, date of start of use should be put so that patient does not continue to use empty inhaler.
- After ICS, patient should rinse the mouth.

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