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A COMPARITIVE STUDY OF TIOTROPIUM VS COMBINATION OF TIOTROPIUM AND FORMOTEROL IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Pharmacology

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. The goals of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) are to increase awareness of COPD and decrease morbidity and mortality from the disease. Many drugs are available for these diseases and aim of our study is to evaluate the bronchodilator efficacy of tiotropium versus a combination of tiotropium and formoterol both as dry powder inhalers in COPD.

Methodology: The study was conducted from May 2018 to April 2019 on an outpatient basis.Males and females aged 40 – 80 years., Diagnosis of COPD (moderate, severe or verysevere). Smokers or Ex-smokers with a history of 10 or more pack-years. Patients ready to give informed consent were included in the study. Only patients who were already on tiotropum or tiotropium with formoterol were included for screening to include in study.

Results and Discussion: Study group consisted of 150 outpatients clinically diagnosed with stable COPD.Results of our study showed a faster onset of action for the combination oftiotropium with formoterol than tiotropium alone. Both the treatments maintained sustained bronchodilation over a period of 24hours, though combination showed higher improvements in FEV1, FVC at 24hours.Both the treatments produced increase in 6-minute walk distance and Results of the present studysuggest that tiotropium has potential to produce relief of dyspnea. Addition of formoterol produced further improvement in all the pulmonaryfunctional parameters.Thus, combination of tiotropium with formoterol should be considered in patients with moderate to severe COPD when symptomrelief is inadequate with a single bronchodilator.

KEYWORDS

COPD, Tiotropium, formoterol, Combination.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from it or its complications. COPD is the fourth leading cause of death in the world, and further increases in its prevalence and mortality can be predicted in the coming decades[1].COPD is the only leading cause of death that continues to increase in prevalence; WHO (world health organization) is currently predicting that within 20 years COPD will be the third major cause of mortality worldwide[2].

The goals of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) are to increase awareness of COPD and decrease morbidity and mortality from the disease. GOLD aims to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy, and to encourage an expanded level of research interest in this highly prevalent disease. A nihilistic attitude towards COPD continues among some health care providers, due to the relatively limited success of primary and secondary prevention (i.e. avoidance of factors that cause COPD or its progression), the prevailing notion that COPD is largely a self-inflicted disease, and disappointment with available treatment options. Another important goal of the GOLD is to work toward combating this nihilistic attitude by disseminating information about available treatments (both pharmacologic and nonpharmacologic), and by working with a network of experts—the GOLD National Leaders—to implement effective COPD management programs developed in accordance with local health care practices[3].

At present treatment of COPD is mainly symptomatic and bronchodilators form the mainstay of treatment. Currently long-acting anticholinergic tiotropium and long acting β_2 agonists (LABAs) like salmeterol and formoterol are available for maintenance therapy of COPD[4]. Metered dose inhaler (MDI) is the most commonly used drug delivery device in COPD patients with or without spacers/holding chambers, as inspiratory flow is less in COPD patients especially thosewithsevereobstruction.Thereislackofpublishedinformationonco mbinationof long-acting bronchodilators and their effects on lung function parameters especially inspiratory capacity (IC) which correlates more with the sensation of dyspnea than forced expiratory volume in 1 second (FEV_1) especially when severity of obstruction increases[5]. There is wide interpatient variability in perceived symptoms of COPD, particularly sensation of dyspnea. Therefore, acute improvement in spirometric parameters such as, FEV_1may not always correlate with relief of symptoms and increased exercise tolerance;[6].

Based on this aim of our study is to evaluate the bronchodilator efficacy of tiotropium versus a combination of tiotropium and formoterol both as dry powder inhalers in COPD.Also to compare peak responses for FEV_1, FVC with tiotropium versus a combination of tiotropium and formoterol and to compare improvement in exercise tolerance as measured by 6 minute walk test [6 MWT] with tiotropium versus a combination of tiotropium and formoterol and finally to compare changes in oxygen saturation over 24 hours with tiotropium versus combination of tiotropium and formoterol.

MATERIALS AND METHODS

Patients with COPD as per GOLD guidelines were enrolled as the subjects for study after they fulfilled inclusion and exclusion criteria. The study protocol was approved by Institutional Ethics Committee. The study was conducted from May 2018 to April 2019 on an outpatient basis. The study was conducted in pulmonary function laboratory in the Department of Pulmonary Medicine. All the study subjects gave written informed consent before participating in the study. The study was carried out according to rules of Declaration of Helsinki.

All selected patients met the study criteria as per GOLD guidelines. Subjects were recruited from the outpatient department (OPD) of Pulmonary Medicine Coimbatore medical college. Males and females aged 40 – 80 years., Diagnosis of COPD (moderate, severe or very severe).Smokers or Ex-smokers with a history of 10 or morepack-years.Patients ready to give informed consent were included in the study. Only patients who were already on tiotropum or tiotropium with formoterol were included for screening to include in study. Whereas patients with history suggestive ofasthma., Any significant medical condition other than COPD which is not controlled. Exacerbation of COPD or respiratory tract infection 6 weeks before screening. Current oxygen therapy or within last 6 weeks before screening. Currently or within last 1 week on oral long acting β_2 agonist or theophylline. Pregnant or lactating females or females of childbearing age not using medically approved contraceptives were excluded from the study.A detailed clinical proforma of patient's history and physical examination was recorded in Case Report Form. A screening spirometry and 6 MWT (6-minute walk test) were performed.

All the measured parameters were normally distributed. We applied parametric tests for analysis. Comparison of baseline characteristics between two treatments was done by paired' test. Demographic data and pulmonary function characteristics of the study patients are presented as mean + standard deviation (SD). All the results are expressed as means with 95 percent confidence intervals (95% CI) in

parentheses or means ± standard error of mean (SEM). In all the figures in results the error bars represent SEM; only one-sided SEM is used to avoid overlapping of SEM bars on each other from the two groups of treatments. For analysis we used 21 patients who had completed both the treatmentperiods.We used SPSS 21.0 for data analysis. A probability level less than 0.05 ($p<0.05$) was considered as statistically significant.

RESULTS

In our study 450 patients were screened of which 150 were eligible to be included in the study, Study group consisted of 150 outpatients clinically diagnosed with stable COPD. Mean baseline forced expiratory volume in 1 second (FEV_1)was1.15 liters (95 % CI: 0.99-1.31 l) and mean forced vital capacity was 2.081(95 % CI: 1.84-2.321). 89 patients had moderate, 38 had severe and 23 had very severe COPD. 150 patients were separated into two study groups, of whom 75 patients received tiotropium and 75 patients received combination. There were no significant differences in baseline FEV_1, FVC between the two study arms (p=0.535, 0.991, 0.916respectively).

Onset of action was evaluated as mean FEV_1 at 15 minutes post inhalation The change in FEV_1 at 15 minutes over baseline after inhalation of tiotropium and formoterol combination [0.0921] was greater than for tiotropium alone [0.070l]. Mean difference in FEV_1 at 15 minutes was significant with combination compared to tiotropium (p=0.027). Mean time taken to achieve 12% improvement in FEV_1 above baseline was 35 minutes for combination and 60 minutes for tiotropium(p=0.035).

Similarly, we analysed Baseline mean FVC values were 1.861 for combination group and 1.86for tiotropium group. Combination produced a mean increase in FVC of 0.184 after 15 minutes over the baseline value, whereas tiotropium alone showed increase in mean FVC of 0.171 over the baseline. Difference between the two treatments was not statistically significant.Mean maximum increase in FVC was 0.460 for the combination and 0.469 for the tiotropium alone above the pre-dosing values. This was achieved for the combination at 154 minutes and for tiotropium at 162 minutes post dose. Difference in mean peak response was not significant between the two treatments (p=0.9).

Exercise tolerance (6 MWT)

Mean baseline 6-minute walk distance was 388.85 (±17.95) meters in combination group and was 386.21 (±17.21). With combination it was 416.60 (±16.06) meters and with tiotropium 396.20 (±17.45) meters. The difference between combination and baseline was statistically significant (p=0.047) and that between the tiotropium and baseline was not significant (p=0.175). Difference between the two treatments was also significant (p=0.018)

Table 1: Exercise tolerance – six-minute walk test

	Screening Day	After 24 hrs	P value
TIOTROPIUM + FORMOTEROL	388.85±17.95	416.60±16.06	0.047
TIOTROPIUM	386.21±17.21	396.20±17.45	0.123

Oxygen Saturation:

There was significant difference in oxygen saturation in both groups when compared to baseline. Mean baseline oxygen saturation for combination group was 98.43 (±0.36) % and this was maintained throughout the period of 24 hours. Mean Baseline oxygen saturation for tiotropium was 97.29(±0.36) % and this was also maintained throughout 24-hour observation period.

Table 2. Oxygen Saturation levels

	Screening Day	After 24 hrs	P value
TIOTROPIUM + FORMOTEROL	93.5±0.36 %	98.43±0.36%	0.012
TIOTROPIUM	94.4±0.36 %	97.29±0.36 %	0.045

DISCUSSION

Current medical therapy for COPD provides only symptomatic relief and improvement in quality of life with little or no effect on disease progression[7]. Bronchodilators are the mainstay of therapy in COPD. Current GOLD guidelines recommend regular treatment with long-acting bronchodilators since they are more effective and convenient than treatment with short-acting bronchodilators[4].

FEV_1 alone may not be an adequate measure of bronchodilator efficacy and hence bronchodilator studies should include parameters reflecting the dynamic hyperinflation such as IC[5]. Boni et al[6]suggested that changes in IC after bronchodilators in patients with COPD with expiratory flow limitation at rest may represent an objective tool for prescribing these drugs to attain symptomatic improvement and better quality of life, even in the absence of a significant increase inFEV_1.

Bronchodilator efficacy with tiotropium, as with other inhaled anticholinergic medications, is generally sustained with no evidence of tolerance. However, with salmeterol this effect declines over time[8]. There is no confirmative evidence on development of tolerance to formoterol. One study has shown that there is no tolerance to bronchodilating action of formoterol[9].

The present study has compared changes in FEV_1 along with those in FVC, to single doses of tiotropium and combination of tiotropium with formoterol in stable COPD patients. In the present study combination showed faster onset of action than tiotropium alone. The combination produced 12% increase in FEV_1 above baselinein 35 minutes whereas tiotropium took 60 minutes. It was earlier than the timings reported by Cazzola et al[10]. This was in coherence with the results in a study by Matera et al[11] where 12% increase in FEV_1 from baseline occurred in 66 minutes (95% CI: 45-87) fortiotropium.

The combination treatment produced sustained improvement in spirometric parameters consistently throughout the 24 hour period over predosing values. Mean FEV_1 at 24 hours was higher than the predosing value for the combination as well as tiotropium alone. Difference between the combination and tiotropium was significant at this time point.

There was a slight increase in the distance walked in 6MWT with both the treatments. Tiotropium was associated with statistically significant increase in distance walked when compared to the distance walked on screening day. Recently a single dose study of tiotropium compared to placebo showed increase in 6-minute walk distance. In this study tiotropium was associated with 15 meters increase in distance walked compared to placebo[12]. These results are coherent with the present study. There was significant change in oxygen saturation too.

There is need to conduct long term studies comparing long acting anticholinergic tiotropium with the combination of tiotropium with formoterol, in terms of changes in lung function (FEV_1, FVC), improvement in exercise tolerance. Also there is need to compare different formulations like MDI versus single dose or multidose DPI of these drugs.

CONCLUSION

FEV_1, FVC values were suggestive of sustained bronchodilation over a period of 24 hours for both the treatment groups, though combination produced greater response.The combination treatment was associated with rapid onset of action than tiotropium alone, though the difference in the time taken for onset of action was not statistically significant. There was marginal increase in the distance walked during 6 MWT after both the treatments. Thus we conclude from our study that combination of tiotropium with formoterol elicits faster onset of action, a trend for greater bronchodilation and sustained bronchodilation compared to tiotropium alone.

REFERENCES:

1. Lopez Ad, S. K., Rao C, Mathers Cd, Hansell Al, Held Ls, Schmid V, Buist S. (2006) Chronic Obstructive Pulmonary Disease: Current Burden And Future Projections. *Eur Respir J.,* 27,397-412.
2. Norman, P., Graul, A., Rabasseda, X., Castaner, J. (2000) Tiotropium Bromide. *Drugs Of The Future,* 25693-699
3. Global Initiative For Chronic Obstructive Lung Disease. November 2006 Ed., 2006 Mcr Vision, Inc. *Http//Www.Goldcopd.Org*(15 March 2007)
4. Rabe, K. F., Hurd, S., Anzueto, A., Barnes, P. J., Buist, S. A., Calverley, P., Fukuchi, Y., Jenkins, C., Rodriguez-Roisin, R., Van Weel, C. & Zielinski, J. (2007) Global Strategy For The Diagnosis, Management, And Prevention Of Copd - 2006 Update. *Am J Respir Crit Care Med*
5. O'donnell, D. E., Fluge, T., Gerken, F., Hamilton, A., Webb, K., Aguilaniu, B., Make, B. & Magnussen, H. (2004) Effects Of Tiotropium On Lung Hyperinflation, Dyspnoea And Exercise Tolerance In Copd. *Eur Respir J,* 23,832-40.
6. Boni, E., Corda, L., Franchini, D., Chiroli, P., Damiani, G. P., Pini, L., Grassi, V. & Tantucci, C. (2002) Volume Effect And Exertional Dyspnoea After Bronchodilator In Patients With Copd With And Without Expiratory Flow Limitation At Rest. *Thorax,* 57,528-32.
7. Belmonte, K. E. (2005) Cholinergic Pathways In The Lungs And Anticholinergic Therapy For Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc,* 2, 297- 304; Discussion311-2.
8. Donohue, J. F., Van Noord, J. A., Bateman, E. D., Langley, S. J., Lee, A., Witek, T. J., Jr., Kesten, S. & Towse, L. (2002) A 6-Month, Placebo-Controlled Study Comparing Lung Function And Health Status Changes In Copd Patients Treated With Tiotropium Or

Salmeterol. *Chest,* 122,47-55.
9. Barnes, P. J. (2000) The Pharmacological Properties Of Tiotropium. *Chest,* 117, 63s-6s.
10. Cazzola, M., Di Marco, F., Santus, P., Boveri, B., Verga, M., Matera, M. G. & Centanni, S. (2004) The Pharmacodynamic Effects Of Single Inhaled Doses Of Formoterol, Tiotropium And Their Combination In Patients With Copd. *Pulmpharmacolther,* 17,35-9.
11. Santus, P., Centanni, S., Verga, M., Di Marco, F., Matera, M. G. & Cazzola, M. (2006) Comparison Of The Acute Effect Of Tiotropium Versus A Combination Therapy With Single Inhaler Budesonide/Formoterol On The Degree Of Resting Pulmonary Hyperinflation. *Respir Med,* 100,1277-81.
12. Okudan, N., Gok, M., Gokbel, H. & Suerdem, M. (2006) Single Dose Of Tiotropium Improves The 6-Minute Walk Distance In Chronic Obstructive Pulmonary Disease. *Lung,* 184,201-4.