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Research Paper

COMPARATIVE EFFICACY AND SAFETY OF INHALED INDACATEROL AND TIOTROPIUM IN GOLD STAGE-2 PATIENTS OF COPD

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Background:Current treatment guidelines, such as those from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) describe bronchodilators as the first-line therapy for patients with moderate to very severe COPD (stage 2-4 of GOLD Spirometric Criteria for COPD Severity). Indacaterol is a new once daily inhaled bronchodilator, recently approved for the treatment of COPD. Once daily dosing is an important step to improve the adherence and compliance of the patients. Methods: In this prospective, parallel group and open labelled study we compared Efficacy and Safety of Indacaerol and Tiotropium in Patients of Satge-2 GOLD. Total 60 patients were finally evaluated in the study. They were divided in two groups, group-1 (Indacaterol group) and group-2 (Tiotropium group) receiving 150 mcg/daily of Indacaterol and 18 mcg/daily of Tiotropium in each group respectively. All patients were evaluated by measuring FEV1 at zero day (before therapeutic intervention), 2, 4, 6, 8, 10 and 12 weeks. Results: Patients in both group showed gradual improvement at 2, 4, 6, 8, 10 and 12 weeks, but there was better improvement in Tiotropium as compared to Indacaterol group in terms of FEV_1. Although this difference was not statistically significant. Conclusion: Indacaterol 150 mcg/day is equally effective as Tiotropium in dose of 18 mcg /day patients of moderate COPD (stage-2 GOLD criteria).

Keywords: COPD, Tiotropium, Indacaterol, GOLD

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of morbidity and mortality throughout the world (Hanania and ,Marciniuk, 2011). The COPD as estimated may affect 10% of the world's population after the age of 40 years and the prevalence is said to be rise in coming years (Buist *et al.,* 2007; Mannino *et al*., 2007). COPD is characterized by a progressive development of airflow obstruction that is not fully reversible (Halbert *et al*., 2006). Inhaled bronchodilators are the main therapeutic agents to manage the patients of COPD (O'Reilly *et al.,* 2010 and Buhl *et al*., 2011).

The long-acting β_2-agonists salmeterol and formoterol have been used but these agents have 12-h duration of action and so are used twice a day in COPD patients (Gustavo *et al*., 2012).

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Current management guidelines recommend the use of either long-acting inhaled muscarinic antagonists (Tiotropium) or ultra-long-acting inhaled β_2-agonists (Indacaterol) for patients with moderate or severe disease COPD (GOLD guidelines, 2010).

Tiotropium is being used widely and has shown to provide better bronchodilation and clinical outcomes than twice daily salmeterol and formoterol (Rodrigo *et al.,* 2007). Indacaterol mechanism involves relaxation of airway smooth muscle through β_2-adrenoceptors stimulation whereas Tiotropium induced bronchodilation is due to competitive antagonism on muscarinic receptors (Cazzola *et al.,* 2012).

In important step to maintain the disease control is to improve the adherence and compliance with prescribed medicines. The once daily dosing is preferred regime because it enhances the compliance. Indacaterol is used worldwide in once daily dose in patients of COPD for maintenance therapy (Stephanie Korn *et al.,* 2011) and found to be at least as effective as Tiotropium once daily (Vogelmeier *et al.,* 2010; Buhl *et al.,* 2011). Indacaterol plus Tiotropium in patients with COPD have shown superior bronchodilation compared with tiotropium alone (Donald A Mahler *et al.,* 2010).

Inhaled beta-2 agonists (formoterol and salmeterol can have systemic effects particularly important in the cardiovascular system but Indacaterol has a good cardiovascular safety profile from available studies (Pascoe *et al*., 2011).

In this study we compared efficacy and safety of indacaterol and tiotropium.

MATERIALS AND METHODS

This was a randomized, prospective, open labelled and parallel group study conducted from April 2014 to January 2015 in the Department of Pharmacology and Department of Tuberculosis and Respiratory diseases, J.N. Medical College & Hospital, A.M.U. Aligarh, 202002 U.P.

The study was approved by IEC of JN Medical College & Hospital AMU Aligarh and also registered in Clinical Trials Registry-India (CTRI). All participants provided informed and written consent prior to taking part in the study.

Inclusion and Exclusion Criteria

This study includes male and female patients aged 18 to 70 years. The patients of forced expiratory volume in one second (FEV_1) between 30% and 80% of predicted normal value and an FEV_1/FVC) ratios of less than 0.7 (measured after puffs of Salbutamol) were included in study. The patients with a history of asthma or concomitant other pulmonary diseases; respiratory tract infection within 6 weeks prior to screening, Type-I diabetes or uncontrolled Type-II diabetes; Coronary artery disease and cancer patients were excluded from the study.

The patients were randomized according to the table generated by random allocation software). The total 73 patients were randomized and 60 patients completed the study for 12 weeks. Adverse events were also recorded in relationship to study drugs.

The total numbers of male and female patients were 46 and 14 respectively. The history of smoking was present in 81.7% patients (Table 1).

Table 1: Demographic Parameters			
		Number	Percentage
Male		46	76.7 %
Female		14	23.3 %
Age (18-70) in years	18-38	9	15%
	39-58	29	48.3 %
	>58	22	36.7 %
Smoker		49	81.7 %

Group-I patients received inhaled Indacaterol in the dose of 150 mcg once daily and Group II-patients received inhaled Tiotropium 18 mcg once daily for 12 weeks. The patients were evaluated by measuring FEV_1 at zero, two, four, six, eight, ten and 12 weeks.

STATISTICAL ANALYSIS

The observations FEV_1 in the study were evaluated by using students t-test and also by Repeated measures ANOVA that provides greater power to study the effects. The P values less than <0.001 were considered significant. The base line values of FEV1 of Indacaterol and Tiotropium group were compared by using Student 't' test.

RESULTS

The observed FEV_1 baseline mean values of Indacaterol and Tiotropium groups were 1.636L and 1.704 L respectively and the difference between two group was statistically insignificant (P>0.001). The FEV_1 values observed were higher in Tiotropium group as compared to Indacaterol group at 2, 4, 6, 8, 10 and 12 weeks of treatment although this difference was not statistically significant. One patient of each group complained of cough which appeared after inhalation of Indacaterol and Tiotropium. One patient of group-1 presented with headache within two weeks of Indacaterol inhalation and two patients in group-2 (Tiotropium) within four weeks of treatment reported headache for 2-3 days. However, no intervention was required for above complaints (Table 2).

Table 2: Comparison of FEV_1 (in Litre) in Indacaterol and Tiotropium Group upto 12 Weeks of Follow up			
	FEV_1 (Mean and SEM)		P-Value
	INDACATEROL (N=30)	TIOTROPIUM (N=30)	
Baseline	1.6367 (.10383)	1.7042 (.07532)	>0.001
2weeks	1.7125 (.10649)	1.844 (.06763)	>0.001
4weeks	1.737 (.10845)	1.8742 (.06889)	>0.001
6weeks	1.756 (.11007)	1.8975 (.06962)	>0.001
8weeks	1.7708 (.11170)	1.9200 (.07095)	>0.001
10weeks	1.7833 (.11241)	1.9392 (.07165)	>0.001
12weeks	1.7967 (.11219)	1.956 (.07210)	>0.001

Note: FEV_1: Forced expiratory volume in one second; SEM: Standard error of mean.

DISCUSSION

Many controlled studies have shown the efficacy of Indacaterol in patients with moderate to severe COPD (Dahl, 2010, Kornmann, 2011, Donohue *et al.,* 2010). Indacaterol was also found to improve clinical outcomes greater extent than Tiotropium (Buhl *et al.,* 2011).

In our study, inhaled Tiotropium 18 mcg once daily for 12 weeks provides better bronchodilation as compared to inhaled Indacaterol in the dose of 150 mcg once daily, although the improvement in FEV_1 between two groups was not statistically significant (P 0.001). In study conducted by Claus Vogelmeier *et al.* (2010) demonstrated that Indacaterol provided a 30-50 mL higher bronchodilator effect than tiotropium in terms of FEV_1 after 14 days of treatment. Our findings are consistent with Claus Vogelmeier *et al*. (2010) as far as doses are concerned, i.e., Indacaterol 150 mcg/day. The side effects observed in our study with Indacaterol and Tiotropium did not cause safety concern. These finding are close to the observation of Dahl *et al.* (2010), Kornmann *et al.* (2011), Donohue *et al.* (2010). One patient from Indacaterol group within two weeks of treatment and two patients in Tiotropium group within four weeks of treatment reported headache for 2-3 days. However no intervention was required for above complaints. None of patient of either group presented with tremor or palpitation as reported in some studies with $®_2$- agonist drugs.

The combination of Indacaterol and Tiotropium has also been recommended GOLD recommendations (Tashkin *et al.,* 2008). Overall, all treatments both the group had good safety and tolerability profiles.

CONCLUSION

Indacaterol at dose 150 mcg and tiotropium 18 mcg given once daily, resulted in bronchodilation in stage-2 COPD patients but Tiotropium provided better improvement in FEV_1 although difference between two groups in terms of mean FEV_1 was not statistically significant. Both the drug Indacaterol at doses 150 mcg and tiotropium 18 mcg once daily have demonstrated a good overall safety and tolerability profile. The bronchodilator efficacy of Indacaterol appears to be comparable with that of Tiotropium.

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