Safety and efficacy of Tiotropium bromide compared with placebo in COPD and Bronchial Asthma

Ahmed Abdul Bari Hazari

Assistant Professor, Dept. of Pharmacology, Ayaan Institute of Medical Sciences, Kanakamamidi, R.R District, Telangana, India

***Corresponding Author: Ahmed Abdul Bari Hazari**
Email: drfarhanhazari@gmail.com

Abstract

Introduction: Tiotropium is well tolerated, with a safety profile comparable with that of placebo.

Objective: To know the safety and efficacy of Tiotropium bromide compared with placebo.

Material and Methods: The present clinical study was conducted in patients with stable as well as exacerbated COPD and Br. Asthma at Shadan Hospital, Telengana State from May 2015 to Feb 2016.

Results: In case of Br. Asthma patient (n-10), the FEV_1 improved to 0.18 L (26.16%) with respect to baseline 0.15 L (P value < 0.01). FVC is 0.21L (22-34%) with respect to the baseline 0.17L (P value<0.01). The FEV_1/FVC ratio is improved by 65.10% (5.51%) with respect to the baseline 61.70% (P<0.01) during 14^{th} weeks of period. In case of COPD patients the FEV_1 is improved by 0.17 L (23.64%) with respect to baseline 0.14 L (P value < 0.05) after 14 weeks. The mean maximum response value of FVC is improved by 0.13 L (23.61%) with respect to baseline 0.10 L (P<0.01), the ratio of FEV_1/FVC value improved by 64.72% (7.11%) with respect to the baseline 60.42% (P value < 0.05).

Conclusion: In spirometric as well as clinically, placebo in COPD group patients (n-7) and Br. Asthma group patients (n-10) showed very less improvement, which is statistically not significant.

Keywords: Bronchial Asthama, COPD, Placebo**,** FEV_1, FEV_1/FVC, FVC.

Introduction

In the United States of America (USA), COPD affects more than 15 million people, with the majority of the patients being over the age of 50 years and current or past smokers. According to the World Health Organization (WHO) about 600 million people suffer from COPD although many are undiagnosed.

Currently, it is fifth leading cause of death and projected to become the world's third leading fatal disease by 2020. COPD exerts a huge socio economic burden with very high direct health costs, particularly due to hospitalization as a result of exacerbations in the disease, and has a major impact on the quality of life of the individual patient and their family. [1-5]

There is no cure for COPD, and treatment is aimed mainly at controlling symptoms. Inhaled Anti cholinergic bronchodilators are now considered to be the first line treatment for COPD and exert their pharmacologic action by blocking muscarinic receptors, particularly M_3 receptors.

Because Acetylcholine increases bronchial muscle tone, through vagal nerve stimulation and primarily M_3 receptors, acetylcholine blockade with Anti cholinergic medications may reduce brochoconstriction and improve airflow.

The primary studies available for Tiotropium bromide enrolled patients older than 40 years of age with a diagnosis of COPD, at least 10 packs/year of tobacco use and FEV1/FVC ratio <0.70 with FEV_1 <65% of predicted value

Br. Asthma prevalence in the USA is estimated at approximately 30 million, and COPD prevalence may be as high as 24 million based on the latest National Health and Nutrition Examination Survey III.

Br. Asthma and COPD are clinically defined airway disorders that individually have significant hetero genecity with regard to underlying pathogenesis and response to therapy. For both conditions, the chronic inflammation can lead to structural changes referred to as airway re modelling. These changes are believed to be irreversible and cause gradually worsening of airflow obstruction and reduced response to bronchodilators and glucocorticoids.[6] Bronchodilators play a central role in symptomatic relief of acute bronchoconstriction in both conditions and are the primary maintenance therapy for COPD patients. Asthmatics with any stage of this disease should be treated with inhaled glucocorticoids as their first line of control and maintenance.[7]

The present prospective study has been undertaken in Shadan Hospital, Hyderabad, with the following objectives to know the safety and efficacy of Tiotropium bromide compared with placebo.

Materials and Methods

The present clinical study was conducted in patients with stable as well as exacerbated COPD and Br. Asthma at Shadan Hospital, Telengana State from May 2015 to Feb 2016.

A total of 120 patients, out of which 50 patients with mild to moderate COPD, 50 Br. Asthma patients and another 20 patients, 10 each for COPD and Br. Asthma were taken for placebo study.

They were diagnosed based on the clinical findings and Pulmonary Function tests. The study was conducted for a period of 14 weeks.

Study design

This is an open label, randomized, parallel group study. The total number of patients in both COPD and Br. Asthma

categories were randomized into 3 groups; 50 patients of Br. Asthma, 50 patients of COPD and 20 patients each disease with placebo.
Group I received – 50 patients of COPD.
Treated with 18 mcg of Tiotropium. (2 puffs/day).
Group II received – 50 patients of Bronchial Asthma.
Treated with 18 mcg of Tiotropium inhaler (2 puffs/day)
Group III – Group III A, 10 patients of COPD and
Group-III B, 10 Br. Asthma patients.
Both groups received, inhalation with placebo, 2 puffs / day, every morning.
A detailed history, Clinical Examination, investigation (baseline, ECG, X-ray Chest PA view) was taken.

Pulmonary Function Test
Baseline, after drug administration, on the 1st day, 3rd day, 7th day and every 2nd week up to 3 1/2 months. A written Informed Consent was obtained from the patient.

Patient was given study number and included in one of the following groups
Group I: COPD patients – (50 cases).
Drug – Tiotropium bromide inhalation.
Dose – 18 mcg, once daily.
Duration – 14 weeks.
Group II: Br. Asthma patients (50 cases).
Drug – Tiotropium bromide inhalation.
Dose – 18 mcg. Once daily.
Duration – 14 weeks.

Group III: Group III A: COPD patients treated with placebo,
Group III B: Br. Asthma patients treated with placebo.
Either groups (10 each).
Drug – placebo.
Dose – 2 puffs / day.
Duration – 14 weeks.

All the patients were advised to take Salbutamol inhalation (100-150 mcg) as needed. All the drugs were given as metered dose inhalation. Patients were shown inhalation techniques with spacers. They were advised to rinse their mouth after each inhalation. They were followed up 3 times in the 1st week after each inhalation and after that every 2nd week till a period of 14 weeks. At each visit, they were clinically assessed and PFT was done.

Screening was done for the (cough, Wheeze, Breathlessness, severity of nocturnal symptoms, frequency of use of rescue medication) parameters before and after treatment.

Score for cough, wheeze, breathlessness and severity of nocturnal symptoms[8] for Br. Asthma:0 – No symptoms, 1 – Mild, 2 – Moderate, 3 – Severe

Score for frequency of use of rescue medication: [9]
O – < 2 puffs / week
1 – < 2 puffs day
2 – 2 to 4 puffs / day
3 – > 4 puff / day

At each visit, patients were assessed for any adverse effects.

Pulmonary Function Test
Evaluation of lung disease by SPIROMETRY is the most widely used Pulmonary Function Test. Spirometry is a measure of airflow and lung volumes during a forced expiratory maneuver from full inspiration

Pulmonary Function Test (PFT) is a powerful tool required in the assessment of respiratory conditions. In addition to helping with diagnosis, PFTs can help to make an objective assessment of severity and monitor the response to treatment.

Spirometry provides three basic measurements
1. Forced vital capacity (FVC).
2. Forced expiratory volume in one second (FEV_1).
3. Forced expiratory ratio (FEV_1/FVC).

Statistical analysis
Data is presented in mean + SEM and percentages as applicable. ANOVA was applied for comparison of the treatment group. Unpaired student's t-test was applied to test the level of significance.
$P < 0.05$ was considered as the level of significance.
Pulmonary Function Test: FEV_1, FVC, FEV_1/FVC%
1st Day:
Baseline, after 30 min; 60 min; 120 min; 180 min on 1st day, next 3 day, 7th day thereafter every 2nd week.

Results
A total of 120 patients selected from Outpatient Department of Shadan Hospital, Hyderabad and included in the study. Out of them, 60 patients were diagnosed with mild and moderate COPD and another 60 patients with mild intermittent and mild persistent Br. Asthma.

COPD and Br. Asthma patients treated with placebo
In these groups, 10 patients of mild and moderate COPD patients and 10 patients of Br. Asthma were taken to compare with the drug Tiotropium. Out of 10 patients of COPD, 3 patients were excluded from the study because of patients poor compliance. The remaining patients participated in the study till the last week. These patients were screened in the same way as in drug treatment groups. In these groups, patients showed less improvement compared to the treatment groups.

Clinical assessment
There was little improvement symptomatically in spite of rescue medication. In case of Br. Asthma, the clinical improvement is only 30-35% with respect to baseline (P value < 0.01). In case of mild COPD patients with placebo, 35-40% clinical improvement is observed with respect to baseline (P value<0.001). This is very low compared to the treatment group patients. (Table 1, 2)

Spirometric assessment

In case of Br. Asthma patient (n-10), the FEV_1 improved to 0.18 L (26.16%) with respect to baseline 0.15 L (P value < 0.01). FVC is 0.21L (22-34%) with respect to the baseline 0.17L (P value<0.01). The FEV_1/FVC ratio is improved by 65.10% (5.51%) with respect to the baseline 61.70% (P<0.01) during 14th weeks of period. In case of COPD patients the FEV_1 is improved by 0.17 L (23.64%) with respect to baseline 0.14 L (P value < 0.05) after 14 weeks. The mean maximum response value of FVC is improved by 0.13 L (23.61%) with respect to baseline 0.10 L (P<0.01), the ratio of FEV_1/FVC value improved by 64.72% (7.11%) with respect to the baseline 60.42% (P value < 0.05). No gross adverse effects were reported in both the treatment groups. Table 3-6

In our study the overall results showed that Tiotropium inhaler is significantly effective in COPD patients and it is more or less equally effective in case of Br. Asthma patients.

Table 1: Mean score improvement of COUGH in Bronchial Asthma and Placebo patients during 14 weeks

Time-period	Drug in Br. Asthma	Placebo in Br. Asthma
Baseline	1.68+0.121	1.321+0.202
1st week	0.946+324	0.745+531
6th week	0.628+0.153	0.612+0.241
14th week	0.46+0.136	0.950+0.336

Table 2: Mean score improvement of wheeze in COPD and Placebo patients during 14 weeks

Time-Period	Drug in COPD	Placebo in COPD
Baseline	1.861+100	1.32+0.155
1st week	1.62+0.43	1.21+0.024
6th week	1.14+0.028	0.982+0.086
14th week	0.104+0.065	0.714+0.111

Table 3: Mean max response in FEV_1 in COPD and placebo patients during 14 weeks

Time-Period	Drug in COPD	Placebo in COPD
Baseline	1.320+0.607	1.421+0.268
1st week	1.520+0.452	1.342+0.734
6th week	1.86+0.685	1.521+0.342
14th week	2.218+0.694	1.757+0.196

Table 4: Mean max response in FEV_1 in bronchial asthma and placebo patients during 14 weeks

Time-Period	Drug in Br. Asthma	Placebo in Br. Asthma
Baseline	1.421+0.796	1.402+0.352
1st week	1.58+0.458	1.342+0.656
6th week	1.742+0.384	1.62+0.561
14th week	2.131+0.734	1.895+0.303

Table 5: Mean max response in FVC in COPD and placebo patients during 14 weeks

Time-Period	Drug in COPD	Placebo in COPD
Baseline	1.65+0.709	1.067+0.376
1st week	1.832+0.21	1.24+0.863
6th week	2.21+0.642	1.28+0.524
14th week	3.112+0.715	1.319+0.278

Table 6: Mean max response in FVC in bronchial asthma and placebo patients during 14 weeks

Time-Period	Drug in Br. Asthma	Placebo in Br. Asthma
Baseline	2.148+0.834	1.754+0.365
1st week	2.24+0.126	1.824+0.343
6th week	2.64+0.312	1.98+0.421
14th week	3.134+0.854	2.146+0.336

Discussion

Moderate-to-severe COPD is frequently associated with significant hyperinflation that leads to stretch and compromise of the respiratory muscles and significantly increases the work of breathing. Reduction in hyperinflation frequently leads to reduced dyspnea and greater exercise tolerance. Bronchodilators can reduce hyperinflation by allowing for greater emptying and reductions in FRC or thoracic gas volume and increased inspiratory capacity. Celli et al[10] have shown that after 4 weeks of treatment, patients treated with Tiotropium had reductions in FRC and improved inspiratory capacity vs placebo.

O'Donnell and colleagues[11] demonstrated that compared with placebo, Tiotropium reduced hyperinflation and allowed for greater tidal volume recruitment during exercise on a constant work rate cycle ergometer, leading to a 21% improvement in endurance time and improved dyspnea index scores.

Casaburi et al[12] studied 921 patients to compare Tiotropium 18 mcg daily vs. placebo in a randomized controlled trial lasting 1 year and reported that Tiotropium could reduce exacerbations by 14-24% vs placebo, it was also demonstrated that with placebo, Tiotropium reduced Wheezing and SOB but not cough or chest tightness when using a severity score from 0 to 3.

Brusasco and colleagues[13] compared 1,207 patients receiving Tiotropium or Salmeterol or placebo in a randomized, double-blind, double-dummy trial for 6 months and when compared with Salmeterol, Tiotropium achieved a clinically relevant drop in SGRQ. (i.e., a > 4- point drop)

The spirometric response to drug administration has generally served as a useful initial standard to judge efficacy among bronchodilators. In addition to smoking cessation, bronchodilator therapy is the foundation of CODP medicated managements. Current guidelines recommended regular Anti cholinergic therapy once symptoms became persistent.

Ipratropium bromide has been used successfully for the past two decades and the early clinical development of the next generation Anti cholinergic drug, Tiotropium, has been reported recently.

A recent large trial by Rennard Si et al[14] comparing Ipratropium bromide to Salmeterol demonstrated that Ipratropium and Salmeterol had a similar AUC for both FEV_1 and FVC from 0-12 hour.

The spirometric improvements with the novel Anti cholinergic Tiotropium have now been evaluated in separate comparative trials with two common used maintenance inhaled bronchodilators prescribed for the treatment of COPD or Br. Asthma patients.

A 3-month trials with 288 COPD patients demonstrated that Tiotropium therapy was superior to Ipratropium in improving FEV_1 and FVC. Compare with Ipratropium, Tiotropium therapy produced higher pre dose through FEV_1 (130ml), peak FEV_1 (50ml) and average FEV_1 (80ml) over six serial measurement post dose.

In the present trial, Tiotropium was superior in all end points and is very effective in both the diseases i.e., Br. Asthma and COPD.

It shows more or less equal response in both the cases. Bronchodilator efficacy with Tiotropium, as with other inhaled Anti cholinergic medications, is generally sustained with no evidence of tolerance.

In addition to objective measures of airflow, patients receiving Tiotropium reported significantly less SOB and wheezing. The degree of bronchodilation observed in this trial is significantly effective in the both groups.

In our study, it was reported that Tiotropium is also effective in mild intermittent and persistent asthma patients in both aspects that is clinical as well as spirometric therefore, Tiotropium has the potential to provide superior bronchodilation with once daily dosing.

British Thoracic Society (BTS) and modified Indian guidelines reported that Tiotropium bromide is useful only in case of severe persistent Asthma.

No adverse effects were reported in any of the treatment groups, except in very few cases i.e., <10% dry mouth was seen. Local adverse effects like oral candidiasis was not observed in any of the treatment groups. This might be due to the use of spacer and thorough rinsing of mouth after each inhalation. Spacer decreases oropharyngeal deposition of drug and also minimized the risk of oral candidiasis. The dose used in the present study is well tolerated and no adverse effects reported in our study.

Conclusion

In spirometric as well as clinically, placebo in COPD group patients (n-7) and Br. Asthma group patients (n-10) showed very less improvement, which is statistically not significant. The improvement observed was superior to placebo 2puff/day with MDI.

Acknowledgment

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Conflict of interest

None.

Source of funding

None

Ethical Approval

Permission for the study was obtained from the College authorities prior to commencement.

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