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ORIGINAL ARTICLE

Investigation of the efficacy of generic and brand-name tiotropium bromide in the management of chronic obstructive pulmonary disease: A randomized comparative trial

Yunes Panahi [a], Mostafa Ghanei [a,*], Mohammad Behzadi [a], Maryam Salehi [a], Sara Saffar Soflaei [b], Amirhossein Sahebkar [c,d,*]

[a] *Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[b] *Neurogenic Inflammation Research Center, Department of Modern Sciences and Technologies, Mashhad University of Medical Sciences, Mashhad, Iran*
[c] *Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[d] *Cardiometabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia*

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Abstract *Introduction*: The beneficial effects of tiotropium bromide, a long acting anticholinergic bronchodilator, in the management of chronic obstructive pulmonary disease have been shown in previous studies. The present study aimed to compare the efficacy and safety of generic (Tiova®) and brand-name (Spiriva®) tiotropium preparations in patients with COPD. *Methods and materials*: In this randomized double-blind parallel-group trial, 79 patients with documented COPD were assigned to Tiova® or Spiriva® for a period of 4 weeks. Assessment of pulmonary function (using spirometry), quality-of-life (using St. George respiratory Questionnaire [SGRQ]) and severity of

* Corresponding authors at: Biotechnology Research Center, Department of Medical Biochemistry, Mashhad, Iran, P.O. Box 91779-48564, Iran. Tel.: +98 5118002288; fax: +98 5118002287 (A. Sahebkar). Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Molla-Sadra Street, Tehran, P.O. Box 19945-581, Iran. (M. Ghanei).
E-mail addresses: mghaneister@gmail.com (M. Ghanei), sahebkara@mums.ac.ir, amir_saheb2000@yahoo.com, amirhossein.sahebkar@uwa.edu.au (A. Sahebkar).

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respiratory symptoms (using breathlessness, cough and sputum scale [BCSS]) was performed at baseline and at the end of treatment period. *Results*: There were significant increases in FEV_1 and reductions in FVC by the end of study in both Tiova® and Spiriva® groups. FEV_1/FVC ratio did not change significantly neither in the Tiova® nor in Spiriva® group. Overall SGRQ score as well as subscale scores of symptoms, activity and impacts were improved by both drugs. In the BCSS scale, the frequency and severity of three main symptoms (dyspnea, cough and sputum) was decreased by both drugs. Baseline as well as post-treatment values of spirometric parameters, SGRQ and BCSS scores was comparable between the groups, apart from a lower post-treatment frequency of cough and sputum in the Spiriva® versus Tiova® group. There was no report of adverse events in either of the study groups. *Conclusion*: The findings of this comparative trial showed equivalent efficacy and safety of Spiriva® and Tiova® in lessening the symptoms as well as improving the quality of life in patients with COPD. This finding has an important translational value given the significantly lower costs of generic versus brand-name products.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a pathologic state which is characterized by chronic, progressive and irreversible airflow obstruction, leading to impaired pulmonary function. Smoking is the major risk factor for COPD (Currie, 2010). According to WHO estimates, 65 million people had COPD in 2005 and more than 3 million people died because of COPD in this year, amounting to 5% of all deaths globally. COPD was the 5th cause of death in 2002 all over the world and currently it is the third cause of death, preceded by ischemic heart disease and stroke. Moreover, 90% COPD-associated deaths occur in low- and middle-income countries. In Iran, COPD was among the four main non-communicable diseases which led to death in 2012 (Semba et al., 2014).

COPD is a chronic state that is accompanied by symptoms such as productive coughs and dyspnea. By progression of COPD, exacerbations become more frequent and are often triggered by respiratory bacterial infections, predisposing to several life-threatening conditions such as left ventricular failure, cardiac arrhythmia, pneumothorax, pneumonia and pulmonary thromboembolism (Longo et al., 2011). Although complete control of COPD is difficult, pharmacotherapy can alleviate the symptoms, slow the disease progression, reduce the frequency and severity of exacerbations and also prevent mortality. Bronchodilators and inhaled corticosteroids are routinely administered medications for COPD management (Hanania and Sharafkhaneh, 2010). Bronchodilators have also been shown to be helpful in patients with increased airway hypersensitivity. Combination of a β_2-agonist (e.g. salbutamol) and an anticholinergic (e.g. ipratropium bromide) has been found to be more effective than any of the other bronchodilators used alone (Balali-Mood and Hefazi, 2005).

Anticholinergic bronchodilators are widely used as standard treatments of COPD. Anticholinergics are indicated in all stages of COPD and are available in two forms: short-acting (ipratropium bromide) and long-acting (tiotropium bromide) (Vestbo et al., 2013). These bronchodilators block muscarinic receptors, resulting in relaxation and dilatation of airways and attenuation of mucus secretion (Kato et al., 2006). Tiotropium bromide is preferred over ipratropium bromide because of its specific inhibition of M3 receptors and longer duration of action (Vestbo et al., 2013). Tiotropium bromide is marketed under two trade names Spiriva® (manufactured by Boehringer-Ingelheim, Germany) and Tiova® (manufactured by Cipla, India). Tiova® is a generic product that is less expensive than the brand-name product (Spiriva®) (Tan and de Haan, 2014). Hitherto, only Spiriva® has been available and prescribed in Iran.

The present study aimed to compare the efficacy and safety of brand and generic products of tiotropium bromide in patients suffering from COPD.

2. Material and methods

This study was designed as a randomized double-blind clinical trial. Subjects were recruited from those referring to the Respiratory Clinic of the Baqiyatallah Hospital (Tehran, Iran). Inclusion criteria were documented history of COPD, age between 30 and 60 years, absence of spirometry contraindication, and a negative history of coagulopathy, prostate hypertrophy and glaucoma. Subjects with a history of hypersensitivity to tiotropium bromide, cigarette smoking, occupational exposure to toxic chemicals, allergic rhinitis or any other type of allergy, asthma, tuberculosis, lung cancer, systemic diseases with pulmonary complications (e.g. heart failure, renal dysfunction, hepatitis, cirrhosis and connective tissue disorders), anemia or polycythemia, and acute respiratory infection were excluded from the study.

2.1. Treatment

Eligible subjects were randomized to receive either Spiriva® ($n = 33$) or Tiova® ($n = 46$). Patients were instructed to take one capsule of either of the drugs daily at 12:00 a.m. Each capsule contained 18 μg of tiotropium bromide dry powder. Both study drugs were inhaled by the aid of appropriate apparatus i.e. Revolizer® (made by Cipla Ltd. For the use of Tiova®) and Handihaler® (made by Boehringer-Ingelheimmade Ltd. for the use of Spiriva®). During the study, all patients continued their standard COPD treatment regimen including Seretide® inhaler (containing Fluticasone and Salmeterol; one puff every 12 h), and N-acetylcysteine (600 mg every 12 h).

2.2. Assessments

Spirometric assessments were performed on a HI-801 Chest M.I. Spirometer (Tokyo, Japan), calibrated according to the manufacturer's instructions. Pulmonary function was assessed by measuring forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio at baseline and at the end of trial.

Breathlessness, cough and sputum scale (BCSS) was used to assess the severity of three main symptoms of COPD that are most likely affected by standard COPD treatment. BCSS is a reliable and easy-to-use medical tool to explore the severity of respiratory symptoms and efficacy of treatment in clinical trials of COPD. Each item in BCSS is answered on a 5-point likert scale, representing the severity of symptoms (Leidy et al., 2003).

Evaluation of quality of life was performed using St. George's Respiratory Questionnaire (SGRQ) at baseline and at the end of treatment. After receiving instructions about how to fill the questionnaire, subjects were asked to answer SGRQ in a calm place independently, in the presence of an observer. SGRQ contains 76 items categorized in three subscales: "Symptoms" which asks about respiratory symptoms, their frequency and severity; "Activity" which asks about activities that cause or are limited by dyspnea; and "Impacts" which asks about social functioning and psychosocial disorders due to lung disease. The overall score ranges between 0 and 100, and higher scores indicate more severe impairment. SGRQ has been reported to be a sensitive, repeatable and numerical tool for evaluating a range of disorders affecting quality of life in patients with airway diseases (Jones et al., 1991).

The results of SGRQ and BCSS were analyzed by an internist or a lung subspecialist. The study protocol was approved by the institutional Ethics Committee and written informed consent was obtained from all participants.

2.3. Statistical analysis

Data were analyzed using SPSS software, version 16.0. Within-group comparisons were made using paired samples *t*-test (for normally distributed data) or Wilcoxon signed-ranks test (for non-normally distributed data). Comparisons of baseline and post-treatment values between the study groups was carried out using independent samples *t*-test (for normally distributed data) or Mann–Whitney U test (for non-normally distributed data). Categorical variables were compared using McNemar's (within-group) or Fisher's exact (between-group) test. A two-sided p-value of <0.05 was considered as statistically significant.

3. Results

Out of the 79 eligible COPD patients (46 patients in the Tiova® and 33 patients in the Spiriva® group) who were initially recruited to the trial, 71 completed the study ($n = 38$ and 24 in the Tiova® and Spiriva® group, respectively). The reason for dropping from trial was not taking study medications due to personal reasons. Drop-out rate was not significantly different between the study groups ($p > 0.05$). The groups were comparable regarding age (48.78 ± 16.89 yrs and 46.69 ± 15.62 yrs in the Tiova® and Spiriva® group, respectively), gender (% males = 92.7% and 80% in the Tiova® and Spiriva® group, respectively) and BMI (24.12 ± 6.12 kg/m^2 and 24.38 ± 5.49 kg/m^2 in the Tiova® and Spiriva® group, respectively) ($p > 0.05$).

3.1. Spirometric findings

Spirometric findings in the study groups before and after the treatment are shown in Table 2. There were significant increases in FEV_1 by the end of study in both Tiova® ($p = 0.048$) and Spiriva® ($p = 0.027$) groups. In contrast, FVC values were significantly decreased in both groups ($p < 0.001$ and $p < 0.05$ in the Tiova® and Spiriva® group, respectively). FEV_1/FVC ratio did not change significantly neither in the Tiova® nor Spiriva® group ($p > 0.05$). The impact of studied drugs on the spirometric parameters was comparable since baseline as well as post-treatment values for FEV_1, FVC and FEV_1/FVC was not significantly different between the groups ($p > 0.05$). Spirometric findings in the Tiova® and Spiriva® group are shown in Table 1.

3.2. SGRQ

In this study, the impact of administered medications on the quality of life was evaluated using SGRQ. Overall SGRQ score was significantly reduced after 4 weeks of treatment with either Tiova® ($p = 0.002$) or Spiriva® ($p < 0.01$). Subscale analysis revealed that both drugs improved activities ($p < 0.001$ in the Tiova® group and $p < 0.01$ in the Spiriva® group) and impacts ($p = 0.002$ in the Tiova® group and $p < 0.001$ in the Spiriva® group) scores, whilst the symptoms subscale score remained statistically unaltered in both groups ($p > 0.05$). Between-group comparisons indicated that total as well as subscale SGRQ scores did not significantly differ between the

Table 1 Spirometric findings in the study groups at baseline and after treatment.

	Tiova®			Spiriva®			*p*-Value[a]	*p*-Value[b]
	Pre-treatment	Post-treatment	*p*-Value	Pre-treatment	Post-treatment	*p*-Value		
FEV_1	77.00 ± 34.20	81.38 ± 32.15	0.048	64.07 ± 28.32	84.61 ± 34.38	0.027	0.673	0.461
FVC	208.41 ± 132.70	80.58 ± 24.24	<0.001	179.41 ± 87.67	94.36 ± 31.24	<0.05	0.09	0.09
FEV_1/FVC	95.66 ± 37.25	94.84 ± 31.52	0.671	98.56 ± 35.40	102.72 ± 41.39	0.572	0.07	0.08

Values are mean ± SD. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.
[a] Comparison of pre-treatment values between the groups.
[b] Comparison of post-treatment values between the groups.

study groups, neither at baseline nor at the end of follow-up ($p > 0.05$). The effects of studied medications on the quality of life are summarized in Table 2.

3.3. BCSS

The severity of respiratory symptoms was evaluated using BCSS. The frequencies of cough, dyspnea, morning dyspnea and sputum were significantly reduced in both Tiova® and Spiriva® groups by the end of trial ($p < 0.05$). The frequency of none of the BCSS items (cough, dyspnea, morning dyspnea, sputum and hemoptysis) did significantly differ between the study groups at baseline ($p > 0.05$). However, a lower frequency of cough ($p = 0.028$) and sputum ($p = 0.003$) was observed with Spiriva® compared with Tiova® at the end of trial (Table 3).

3.4. Adverse events

Throughout the trial, both drugs were well tolerated and there was no report of typical anticholinergic side effects such as dry mouth, urinary retention and constipation in either of the groups.

Table 2 Comparison of quality of life indices between the study groups according to SGRQ.

	Tiova®			Spiriva®			*p*-Value[a]	*p*-Value[b]
	Pre-treatment	Post-treatment	*p*-Value	Pre-treatment	Post-treatment	*p*-Value		
Physical functioning	55.73 ± 36.22	64.31 ± 30.44	0.001	63.23 ± 28.12	68.24 ± 31.24	0.001	0.228	0.461
Role limitation health	76.88 ± 41.37	79.17 ± 40.31	0.495	74.14 ± 39.27	79.27 ± 38.41	0.362	0.921	0.09
Role limitation emotion	78.70 ± 41.37	77.78 ± 42.16	0.160	74.29 ± 37.50	76.18 ± 38.26	0.128	0.783	0.08
Energy fatigue	48.74 ± 22.39	48.11 ± 23.43	0.285	49.84 ± 18.29	47.24 ± 31.13	0.147	0.897	0.214
Emotional well	50.34 ± 22.69	49.62 ± 22.77	0.180	48.24 ± 25.39	46.12 ± 23.17	0.241	0.245	0.841
Social functioning	83.33 ± 22.95	84.72 ± 21.36	0.257	74.26 ± 26.31	77.12 ± 19.26	0.358	0.138	0.822
Pain	93.13 ± 15.46	93.43 ± 14.78	0.180	84.42 ± 21.34	78.37 ± 17.18	0.112	0.085	0.812
General health	39.51 ± 12.64	42.86 ± 15.78	0.843	36.41 ± 14.74	45.16 ± 18.21	0.163	0.167	0.217
Symptom score	49.31 ± 21.67	46.26 ± 21.07	>0.999	44.17 ± 19.53	49.36 ± 21.71	0.712	0.158	0.114
Activity score	47.59 ± 33.97	32.39 ± 21.81	<0.001	43.19 ± 27.71	31.23 ± 18.60	<0.01	0.389	0.09
Impact score	23.22 ± 23.27	9.02 ± 12.05	0.002	19.27 ± 13.17	7.69 ± 4.32	<0.001	0.115	0.148
Total score	66.83 ± 189.58	20.40 ± 11.52	<0.01	87.83 ± 47.58	29.43 ± 19.62	<0.01	0.713	0.132

Values are mean ± SD. SGRQ: St. George respiratory Questionnaire.
[a] Comparison of pre-treatment values between the groups.
[b] Comparison of post-treatment values between the groups.

Table 3 Comparison of BCSS indices between the study groups.

Parameter	Frequency	Tiova®			Spiriva®			*p*-Value[a]	*p*-Value[b]
		Pre-treatment (%)	Post-treatment (%)	*p*-Value	Pre-treatment (%)	Post-treatment (%)	*p*-Value		
Cough	Seldom	41.5	44.7	0.36	46.6	50.0	<0.05	0.568	0.028
	Little	26.8	31.6		30.0	36.6			
	Average	2.4	13.2		3.3	3.3			
	High	22.0	2.6		13.3	6.6			
	Very high	7.3	7.9		6.6	3.3			
Dyspnea	Seldom	26.8	32.5	0.018	33.3	43.3	<0.05	0.107	0.070
	Little	29.5	35.0		24.2	30.0			
	Average	17.1	20.0		16.6	23.3			
	High	29.3	5.1		13.3	3.3			
	Very high	7.3	2.6		10.0	0			
Morning dyspnea	Seldom	48.8	48.7	0.015	56.6	63.3	<0.05	0.681	0.167
	Little	12.2	23.1		10.0	20.0			
	Average	12.2	20.5		13.3	10.0			
	High	19.5	5.1		13.3	3.3			
	Very high	7.3	2.6		6.6	3.3			
Sputum	No	19.5	26.3	0.046	24.2	46.6	<0.05	0.494	0.003
	Yes	80.5	73.7		73.3	53.3			
Bloody sputum	No	87.8	96.9	0.317	90.0	100	0.112	0.822	0.246
	Yes	12.2	3.1		10.0	0			

BCSS: breathlessness, cough and sputum scale.
[a] Comparison of pre-treatment values between the groups.
[b] Comparison of post-treatment values between the groups.

4. Discussion

In pharmaceutical industry, generics are comparable with brand-name products in terms of safety and therapeutic efficacy, while they are significantly cheaper (~20–90%) (Dunne et al., 2013; Keith et al., 1998). Because of cost-efficiency and wider availability, the policy of prescription of generic products instead of brand-name products has been accepted in many countries including Iran (since 1980) (Nelson et al., 2006; Zargarzadeh et al., 2007; Dupont and Heller, 2009). However, before a generic product could be regarded as a substitute for the original drug, its efficacy and safety are required to be demonstrated by bioequivalence (non-inferiority) trials (Heshmat et al., 2007; Aleyasin et al., 2012; Hadjibabaie et al., 2013; Beiraghdar et al., 2012a,b). With respect to COPD, the importance of developing generic drugs is more important, given the high burden of mortality that occurs in low- and middle-income countries, where access to brand-name medications may not be easy and affordable (Semba et al., 2014). Hence, decreasing treatment-associated costs should be considered as an important and determining factor in the pharmacotherapy of COPD.

Tiotropium bromide is an inhaled long-acting anticholinergic bronchodilator which benefits patient with COPD including those with chronic bronchitis or emphysema. Long-term treatment with tiotropium bromide has been reported to improve exercise tolerance, health-related quality of life, and decrease dyspnea exacerbations and mortality (Tashkin et al., 2008; Balali-Mood and Hefazi, 2005). An important finding arising from the present study was the equivalent efficacy and safety of Tiova®, as a generic drug, compared with Spiriva®, as a brand name product. In spirometry, both Tiova® and Spiriva® improved FEV_1 significantly that is consistent with a meta-analysis of 22 randomized controlled trials on the efficacy of tiotropium bromide in the treatment of COPD (Karner et al., 2012). FEV_1 is a widely used measure for the assessment of the degree of airflow limitation, and its increase was comparable between Spiriva® and Tiova®. Our spirometric evaluations were complimented by assessment of quality of life and the frequency of symptoms. SGRQ is a reliable measure of health status in patients with COPD, and reflects the frequency of symptoms and the influence of breathlessness on daily activities as well as social functioning and psychological wellness. Our findings indicated that all three subscales of SGRQ (symptoms, activity and impacts) were significantly improved by both drugs, and that these improvements were equivalent between both groups. These findings are compliant with the results of two meta-analyses, including a Cochrane review, on the quality of life (assessed using SGRQ) in subjects receiving tiotropium bromide versus placebo. These studies indicated that tiotropium bromide improves quality of life in COPD patients (Karner et al., 2012; Yohannes et al., 2011). The positive effects of tiotropium bromide on quality of life were further confirmed by the results of BCSS, in which both studied drugs were found to reduce the severity of main COPD symptoms i.e. breathlessness, cough and sputum.

In summary, our comparative trial, being the first of its kind, showed comparable efficacy and safety of Spiriva® and Tiova® in lessening the symptoms as well as improving the quality of life in patients suffering from COPD. This finding has an important translational value for patients with COPD because of the lower cost of Tiova® versus Spiriva® (Spiriva® costs about three times as much as Tiova®), and the long-term nature of pharmacotherapy in COPD. In light of the present findings, Tiova® can be suggested as an effective and safe replacement for Spiriva®. However, since duration of follow-up in this pilot trial was relatively short, future large-scale studies are still required to compare the safety profile and quality of life-improving effects of Tiova® versus Spiriva® over longer-term periods.

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