International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2022.215.220

Research Article
Effects of Tiotropium Bromide on Patients with Chronic Obstructive Pulmonary Disease

Zhiying Li, Lin Zhou, Hui Bi, Qiudi Zhang, Xiong Xu, Yuwen Liu and Hui Qiu

Department of Respiratory Medicine, The First People's Hospital of Changzhou, 185 Juqian Street, Changzhou 213000, Jiangsu Province, People's Republic of China

Abstract

Background and Objective: Chronic Obstructive Pulmonary Disease (COPD) is one of the common respiratory diseases that seriously endanger human health. This study aimed to evaluate the clinical effects of tiotropium bromide on the airway remodelling of patients with stable COPD. **Materials and Methods:** Sixty-eight patients with stable COPD treated in our hospital were randomly divided into a treatment group (n = 33) and a control group (n = 35). The treatment and control groups were given tiotropium bromide and placebo, respectively for 6 months. The changes of St. George's Respiratory Questionnaire (SGRQ) score, 6-min Walking Distance (6MWD), pulmonary function and plasma levels of Matrix Metalloproteinase-9 (MMP-9) and Tissue Inhibitor of Matrix Metalloproteinase-1 (TIMP-1) before and after treatment were recorded. **Results:** The two groups had similar SGRQ score, 6MWD, pulmonary function and levels of MMP-9 and TIMP-1 before treatment ($p>0.05$). After treatment, the SGRQ score and levels of MMP-9 and TIMP-1 of the treatment group significantly decreased ($p<0.05$ or $p<0.01$) and 6MWD and pulmonary function were significantly augmented ($p<0.05$). **Conclusion:** Tiotropium bromide has evident therapeutic effects on patients with stable COPD, probably by relieving the airway remodelling.

Key words: Tiotropium bromide, chronic obstructive pulmonary disease, airway remodelling

Citation: Li, Z., L. Zhou, H. Bi, Q. Zhang, X. Xu, Y. Liu and H. Qiu, 2022. Effects of tiotropium bromide on patients with chronic obstructive pulmonary disease. Int. J. Pharmacol., 18: 215-220.

Corresponding Author: Hui Qiu, Department of Respiratory Medicine, The First People's Hospital of Changzhou, 185 Juqian Street, Changzhou 213000, Jiangsu Province, People's Republic of China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease characterized by airflow limitation[1]. The clinical manifestations include dyspnea, cough, excessive sputum and decreased appetite, with recurring attacks. COPD is progressively aggravated and irreversible, which seriously affects the quality of life of patients and can induce chronic respiratory failure, sleep apnea-hypopnea syndrome, pulmonary heart disease and even death[2]. COPD is one of the common respiratory diseases that seriously endanger human health[3], with multiple complications[4]. At present, COPD is the fourth leading cause of death worldwide, which seriously affects the quality of life of patients and heavily burdens their families[5]. It is well-accepted that one of the main pathogenic mechanisms for COPD is based on proteases/antiproteases and the imbalance between plasma Matrix Metalloproteinase-9 (MMP-9)/Tissue Inhibitor of Matrix Metalloproteinase-1 (TIMP-1) plays an important role in its occurrence[6]. COPD is clinically treated by preventing its progression, relieving symptoms and improving pulmonary function conventionally through oxygen therapy, anti-inflammatory agents and theophylline but the outcomes are often unsatisfactory[7]. Anticholinergic drugs compete with acetylcholine for binding choline receptors on the smooth muscle surface, which can block smooth muscle contraction. Therefore, they have been widely applied to treat COPD[8]. Anticholinergic drugs are markedly superior to β2 receptor agonists in dilating the bronchus of COPD patients, accompanied by milder side effects[9]. Rice *et al.*[10] reported that tiotropium bromide provided many advantages for treating patients with stable COPD.

To assess the clinical effects of tiotropium bromide on the airway remodelling of patients with stable COPD, we herein recorded the changes of St. George's Respiratory Questionnaire (SGRQ) score, 6-Min Walking Distance (6MWD), pulmonary function and plasma MMP-9 and TIMP-1 levels before and after treatment.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Respiratory Medicine, The First People's Hospital of Changzhou, China October, 2013-2015.

Subjects: Sixty-eight patients with stable COPD treated in our hospital from October, 2013-2015 were included, who met the diagnostic criteria of the Guidelines for Diagnosis and Treatment of COPD established by the COPD Committee, Respiratory Society, Chinese Medical Association in 2013[11]. Exclusion criteria: 1) Complication with serious cardiovascular and cerebrovascular diseases, liver and kidney dysfunction and other systemic diseases, 2) history of other chronic lung diseases, 3) use of glucocorticoids, bronchodilators and other drugs within 24 hrs before this study, 4) history of smoking within 30 days, 5) history of respiratory tract infection within 30 days. All patients voluntarily received drug treatment and signed informed consent. By using a random number table, the 68 patients were divided into a treatment group (n = 33) and a control group (n = 35).

Methods: The treatment group inhaled one capsule of tiotropium bromide (Jiangsu Chia Tai Tianqing Pharmaceutical Group Co., Ltd., China) at (18 μg/10 sec)/time, once/day. The control group received a placebo, with the same dose and frequency as those of the treatment group. Both groups were treated for 6 months and Ventolin spray was used when necessary during treatment. The changes of SGRQ score, 6MWD, pulmonary function and plasma MMP-9 and TIMP-1 levels before and after treatment were recorded.

SGRQ scoring: Before and after treatment, the Chinese version of SGRQ[12] was used to assess the quality of life including symptoms, activity and impacts. The scores were preset. The questionnaire was explained to the patients before evaluation and they were required to complete the questions independently within 30 min. Afterwards, the scores of each part were recorded. A higher score meant worse health status.

Measurement of 6MWD: According to the Guidelines for the 6MWD test developed by the American Thoracic Society[13], the 6MWD values before and after treatment were measured. The patients were required to walk along a straight line on flat ground as fast as possible, without turning around quickly or taking a circular route. At the end of the test, the walking distance was measured. Heart rate, respiratory frequency and blood oxygen saturation were monitored before and after the test. In the case of dizziness, cold sweat, dyspnea and paleness, the test was stopped immediately and necessary measures were performed.

Detection of pulmonary function: The pulmonary functions before and after treatment were tested by Jaeger pulmonary function detector (Germany). Each patient was tested twice to record the best values. The difference between the two tests did not exceed 5%. The forced

expiratory volume in the first second (FEV1), Forced Vital Capacity (FVC) and forced expiratory volume in the first second/predicted value% (FEV1% pred) were used as the observation indices.

Measurement of plasma MMP-9 and TIMP-1 levels: Before and after treatment, the plasma MMP-9 and TIMP-1 levels were measured. In the morning, 2 mL of fasting venous blood was drawn, left still at room temperature for 1-2 hrs and centrifuged at 3000 rpm for 15 min to collect the serum that was then stored in a -70°C refrigerator. The plasma levels of MMP-9 and TIMP-1 were measured by ELISA and the MMP-9/TIMP-1 ratio was calculated. This procedure was carried out strictly according to the instructions of kits provided by Beijing Zhong Shan Golden Bridge Biological Technology Co., Ltd. (China).

Statistical analysis: All data were statistically analyzed by SPSS17.0 software and expressed as Mean±standard deviation ($\bar{x}\pm s$). The quantitative data were compared by the completely randomly designed t-test. Intragroup comparisons were conducted with the paired t-test. $p<0.05$ was considered statistically significant.

RESULTS

Baseline clinical data: Before this study, the two groups had similar gender ratios, age composition, disease course, smoking history and severity ($p>0.05$) (Table 1).

SGRQ scores before and after treatment: The two groups had similar SGRQ scores before treatment ($p>0.05$). After treatment, the SGRQ score of the treatment group significantly decreased ($p<0.05$) (Table 2).

6MWD values before and after treatment: The two groups had similar 6MWD values before treatment ($p>0.05$). After treatment, 6MWD of the treatment group was significantly augmented compared with that of the control group ($p<0.05$) (Table 3).

Pulmonary functions before and after treatment: Before treatment, FVC, FEV1 and FEV1%pred of the two groups were similar ($p>0.05$). After treatment, the values of the treatment group significantly exceeded those of the control group ($p<0.05$) (Table 4).

Plasma MMP-9 and TIMP-1 levels before and after treatment: Before treatment, the plasma MMP-9, TIMP-1 levels and MMP-9/TIMP-1 ratio of the two groups were similar ($p>0.05$). After treatment, the values of the treatment group were significantly lower than those of the control group ($p<0.05$) (Table 5).

Adverse reactions during treatment: During treatment, both groups had 1 case of dry mouth and 1 case of headache who underwent remission without special measures. There were no other adverse drug reactions.

Table 1: Baseline clinical data ($\bar{x}\pm s$)

Parameters	Treatment group (n = 33)	Control group (n = 35)	p-value
Gender (male/female)	22/11	25/10	>0.05
Age (year)	55.6±8.7	59.8±9.2	>0.05
Disease course (year)	12.0±7.7	13.7±8.6	>0.05
Smoking history (year)	18.9±10.4	15.8±12.4	>0.05
Severity (I/II/III)	12/14/7	12/15/8	>0.05

Table 2: SGRQ scores before and after treatment ($\bar{x}\pm s$, point)

Groups		Case no.	Symptom	Activity	Impact
Treatment	Before treatment	33	54.13±9.08	43.15±8.65	40.94±24.14
	After treatment		42.03±8.22$^{\Delta}$	31.68±7.46$^{\Delta}$	30.99±16.12$^{\Delta}$
Control	Before treatment	35	53.65±10.03	42.16±7.49	41.33±8.86
	After treatment		48.45±8.79$^{\#}$	40.42±5.57$^{\#}$	38.63±7.17$^{\#}$

Compared with scores of the same group before treatment, $^{\Delta}p<0.05$, intergroup comparison after treatment and $^{\#}p<0.05$

Table 3: 6MWD values before and after treatment ($\bar{x}\pm s$, m)

Groups	n	Before treatment	After treatment
Treatment	33	377.27±21.62$^{\Delta}$	390.93±22.38$^{\Delta}$
Control	35	376.49±21.81	377.19±21.74$^{\#}$

Compared with values of the same group before treatment, $^{\Delta}p<0.05$, intergroup comparison after treatment and $^{\#}p<0.05$

Table 4: Pulmonary functions before and after treatment ($\bar{x}\pm s$)

Groups		n	FVC/L	FEV1/L	FEV1(%) pred
Treatment	Before treatment	33	2.48±1.09	1.39±0.19	60.52±11.47
	After treatment		3.02±1.19$^{\Delta}$	1.54±0.23$^{\Delta}$	67.22±11.92$^{\Delta}$
Control	Before treatment	35	2.43±1.10	1.37±0.17	60.15±11.35
	After treatment		2.44±1.11$^{\#}$	1.38±0.15$^{\#}$	62.24±11.27$^{\#}$

Compared with values of the same group before treatment, $^{\Delta}p<0.05$, intergroup comparison after treatment and $^{\#}p<0.05$

Table 5: Plasma MMP-9, TIMP-1 levels and MMP-9/TIMP-1 ratio before and after treatment ($\bar{x}\pm s$, ng L^{-1})

Groups		n	MMP-9	TIMP-1	MMP-9/TIMP-1
Treatment	Before treatment	33	264.81±43.15	149.14±21.23	1.7±0.6
	After treatment		153.42±33.28$^{\Delta}$	111.61±14.92$^{\Delta}$	1.3±0.5$^{\Delta}$
Control	Before treatment	35	244.75±61.27	151.26±13.09	1.6±0.4
	After treatment		234.86±71.16$^{\#}$	149.54±14.97$^{\#}$	1.5±0.8$^{\#}$

Compared with values of the same group before treatment, $^{\Delta}p<0.05$, intergroup comparison after treatment and $^{\#}p<0.05$

DISCUSSION

COPD is characterized by continuous airflow restriction. Its airflow restriction develops progressively and its pulmonary function gradually reduces, mainly manifested as the progressive decline of FEV1, which seriously affects the quality of life of patients. Therefore, the focus of stable COPD treatment is to relieve dyspnea, improve lung function and the quality of life of patients. The condition of COPD patients can be evaluated by indicators such as SGRQ score, pulmonary function test and 6MWD. Based on these indices, the exercise endurance of COPD patients can be comprehensively evaluated[14]. Airway remodelling and emphysema are the main pathological changes during the development of COPD. MMP-9 is a widely existing gelatinase and TIMP-1 is an inhibitor of MMP-9. Studies have shown that MMP-9 and TIMP-1 are closely related to airway remodelling in COPD patients. When MMP-9 is over-expressed, TIMP-1 increases at the same time and MMP-9/TIMP-1 is unbalanced. Subsequently, the decomposition of elastin and collagen leads to lung tissue destruction and promotes the occurrence and development of airway remodelling.

Tiotropium bromide is a compound with a quaternary ammonium cationic structure, which is difficult to be absorbed when passing through cell membranes. There are three receptor subtypes in the human respiratory system, i.e. M1, M2 and M3 receptors[15]. M1 receptor exists in parasympathetic nerves and plays a role in promoting the transport of cholinergic neurotransmitters. M2 receptor is present in cholinergic postganglionic nerves, sympathetic nerves and airway smooth muscle and negative feedback regulation inhibits the further release of acetylcholine[16]. M3 receptor exists in airway smooth muscle, which is the main cause of airway contraction and also in submucosal glands, which can regulate the secretion of mucin[17]. Tiotropium bromide shows a unique kinetic selectivity for receptors, which can block the binding of acetylcholine to the M3 receptor, reduce the tension of airway smooth muscle and relax bronchial tubes. It can dissociate from the M2 receptor more quickly, reduce the release of acetylcholine and decrease the negative effect of receptor excitement on bronchodilation[18]. Due to the slow dissociation rate from the M3 receptor, tiotropium bromide has become a long-acting anticholinergic drug. One-time inhalation of tiotropium bromide has a continuous effect on bronchiectasis for 24 hrs[19] but the effect is slow.

Tiotropium bromide can reverse the airway smooth muscle remodelling induced by allergen, reduce the expression of smooth muscle myosin, decrease the number of smooth muscle cells and inhibit the thickening of airway smooth muscle and airway hyperresponsiveness, so it may also be one of the reasons for bronchiectasis[20]. *In vivo,* preclinical studies based on guinea pig asthma models have shown that tiotropium bromide can slow down airway inflammation and the remodelling process[21].

In this study, the SGRQ score of stable COPD patients treated with tiotropium bromide decreased significantly, the 6MWD and pulmonary function increased significantly, suggesting that after tiotropium bromide treatment, the symptoms of cough, expectoration and wheezing and the body hypoxia were relieved, the pulmonary function, the exercise capacity and the quality of life were improved and the development of COPD was delayed. The results may be attributed to the expectorant and antitussive effect of tiotropium bromide, which can reduce the sputum, relieve cough and partially alleviate respiratory muscle fatigue of COPD patients, conducive to the improvement of lung function[22]. Meanwhile, tiotropium bromide can dilate the bronchi, relieve the dyspnea of COPD patients and improve their clinical symptoms and exercise endurance.

This study also showed that there was no significant statistical difference in the serum levels of MMP-9, TIMP-1 and MMP-9/TIMP-1 between the two groups before treatment ($p>0.05$). After treatment with tiotropium bromide, the serum levels of MMP-9 and TIMP-1 in the treatment group significantly reduced, superior to those of the control group ($p<0.05$). At the same time, MMP-9/TIMP-1 in the treatment group significantly decreased ($p<0.05$), the balance of MMP-9/TIMP-1 in stable COPD patients was restored and the airway remodelling was improved, thereby fundamentally alleviating the dyspnea symptoms and improving exercise capacity and the quality of life. This suggests that tiotropium bromide has a significant effect on COPD, which may be related to the decrease of MMP-9 and TIMP-1 levels, the restoration of MMP-9/TIMP-1 balance and the improvement of airway remodelling. Tan *et al.*[23] reported that MMP-9 and FEV1% in patients with stable COPD were linearly and negatively correlated, which also confirmed that the lung function of patients in this study could be improved after treatment with tiotropium bromide.

CONCLUSION

In summary, tiotropium bromide can improve the dyspnea, exercise capacity and pulmonary function of COPD patients significantly. It has a good effect on stable COPD patients, in which the mechanism may be related to the improvement of airway remodelling, worthy of clinical promotion and application.

SIGNIFICANCE STATEMENT

This study discovers the clinical effects of tiotropium bromide on airway remodelling that can be beneficial for patients with stable COPD. This study will help the researcher to uncover the critical area of COPD treatment that many researchers were not able to explore. Thus, a new theory on the action mechanism for tiotropium bromide may be arrived at.

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