

The role of tiotropium in the management of asthma

Heung-Woo Park

Department of Internal Medicine, Seoul National University College of Medicine, Seoul 110-744, Korea

Asthma is a chronic respiratory disease characterized by reversible airway obstruction that is secondary to an allergic inflammation and excessive smooth muscle contraction. Cholinergic signals were known to contribute significantly to the pathophysiology of asthma. However, the use of anti-cholinergic agents in asthma has been justified only in acute asthma exacerbations, until tiotropium bromide, a long-acting anti-cholinergic agent was introduced. Recent reports showing a promising role of tiotropium in the treatment of asthma have aroused interest of the use of anti-cholinergic agent for the management of asthma. This report describes pharmacological characteristics, potential effects on inflammatory cells, and the current status of tiotropium in the treatment of asthma.

Key words: Anticholinergics; Asthma; Bronchodilators; Tiotropium

INTRODUCTION

Asthma is a chronic respiratory disease characterized by reversible airway obstruction that is secondary to an allergic inflammation and excessive smooth muscle contraction [1]. Currently, anti-inflammatory drugs (mainly inhaled corticosteroids) and bronchodilators (mainly inhaled β_2 agonists) are widely used in the treatment of asthma based on the understanding of asthma pathogenesis. Parasympathetic nervous system is the important neural pathway controlling airway smooth muscle. Stimulation of parasympathetic nerve results in bronchoconstriction, bronchial vasodilatation and mucus secretion via muscarinic receptors [2]. Moreover,

parasympathetic tone is known to be increased in asthma by several mechanisms; increased afferent stimulation caused by airway inflammation [3], abnormal muscarinic receptor expressions [4], an increased release of acetylcholine from parasympathetic nerve ending [5], and decreased levels of neuromodulators that attenuate parasympathetic tone [6]. Therefore it seems natural that we can expect a favorable outcome when we use anti-cholinergic agents that block parasympathetic tone in the treatment of asthma. However, early experiences with ipratropium bromide, a short-acting inhaled anti-cholinergic agent, in the treatment of asthma were disappointing [7-9]. The use of anti-cholinergic agents in asthma has been justified only in acute asthma exacerbations [10].

Correspondence: Heung-Woo Park
Department of Internal Medicine, Seoul National University
College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82-2-2072-0699
Fax: +82-2-742-3291
E-mail: guinea71@snu.ac.kr

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Anti-cholinergic agents had been left orphan in the field of asthma pharmacology until tiotropium bromide, a long-acting inhaled anti-cholinergic agent was introduced. During the last decade, tiotropium has been used widely in the treatment of patients with chronic obstructive pulmonary disease (COPD) and is indicated for once-daily maintenance treatment in the current COPD treatment guideline [11]. Recent reports showing a promising role of tiotropium in the treatment of asthma have aroused interest of the use of anti-cholinergic agent for the management of asthma [12-15]. This report describes pharmacological characteristics, potential effects on inflammatory cells, and the current status of tiotropium in the treatment of asthma.

Role of cholinergic signaling in the pathophysiology of asthma

So far, 5 muscarinic receptors (M1-M5 subtype) mediating cholinergic signal has been identified. However, only M1, M2 and M3 receptors have been convincingly demonstrated to exist in human airways. Among them, the M3 receptor in the airway smooth muscle is known to play an important role in the pathophysiology of asthma by inducing bronchoconstriction and mucus secretion [16, 17]. Whereas, the pre-junctional M2 receptor provides a negative feedback to attenuate further release of acetylcholine [18]. An increased release of acetylcholine from cholinergic nerve endings [19] and an abnormal muscarinic receptor expression (either an increase in M1 and M3 receptors or disruption of the M2 receptors) [20] have been proposed to explain an excessive bronchoconstriction found in asthmatics. Afferent sensory nerve endings exposed to the airway lumen by mediator-induced epithelial damage (e.g., eosinophil-derived major basic protein [21]) is thought to be an important mechanism for vagally mediated airway hyperresponsiveness [22]. Mucus hypersecretion is one of the cardinal features found in asthma contributing to an airway obstruction. Submucosal glands are innervated and express M1 and M3 receptors [23]. M3 receptor is thought to be the predominant receptor that mediates mucus secretion [24, 25] and muscarinic receptor stimulation transactivates the epidermal growth factor receptor [26] which is known to regulate goblet cell hyperplasia [27]. Along with this, it is reported that repeated administration of the cholinergic agonists promoted goblet cell hyperplasia and mucus gland hypertrophy in experimental animal models [22]. Interestingly, recent investigations have revealed that most inflammatory cells including T lymphocyte [28, 29], B

lymphocyte [28, 29], mast cell [28, 30] and eosinophils [31, 32] express functional muscarinic receptors. Those findings suggest that cholinergic signals can modulate inflammatory processes by paracrine and/or autocrine mechanisms [29, 33]. Moreover, there may be a distinct regulatory role for endogenous acetylcholine in promoting airway remodeling induced by allergen [34, 35]. Taken together, cholinergic signals contribute significantly to the pathophysiology of asthma.

Pharmacological characteristics of tiotropium

Tiotropium bromide monohydrate, chemically described as (1 α , 2 β , 4 β , 5 α , 7 β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane bromide monohydrate, is a second-generation inhaled anti-cholinergic agent and is sparingly soluble in water [36]. Compared with other anti-cholinergics, tiotropium shows peculiar selectivity and affinity for muscarinic receptor subtypes. It displays a 6-20-fold higher affinity for muscarinic receptors than does ipratropium [37]. Tiotropium is basically non-selective and thus binds to all three muscarinic receptors in the airway but it dissociates much faster from M2 receptors compared to M1 and M3 receptors [38, 39]. Therefore, it can be categorized as a more selective antagonist for M1 and M3 receptors. A prolonged pharmacologic activity is also attributed to its slow dissociation from M1 and M3 receptors. After an inhaled dose of tiotropium, about 20% is deposited in the lung [40]. Then, it rapidly absorbed into the systemic circulation and reaches the peak plasma concentration within 5 min [41]. The half-life of the tiotropium-M3 receptor complex is approximately 35 h, whereas 0.3 h for ipratropium [37, 39]. After the first dose, mean time to onset of effect is 30 min, mean time to peak effect is about 3 h and maximum effect is obtained after 1 week [37, 39, 42, 43]. It has been calculated that tiotropium at the steady-state concentration would occupy less than 5% of muscarinic receptors, which may explain the relatively low frequency of systemic adverse reactions [39]. There is no evidence for drug accumulation after repeated administration.

Effect of tiotropium on the asthma pathogenesis; results from experimental models of asthma

In both acute and chronic murine model of asthma, treatment with tiotropium significantly reduced airway inflammation and the Th2 cytokine production in bronchoalveolar lavage (BAL) fluid [44]. In this report, authors found that the levels of TGF- β 1 in BAL fluid were significantly suppressed after treatment and suggested that

the reduction of TGF- β 1 production might one of the underlying mechanism for their observations. Another interesting finding of this report was that authors verified that the M3 receptors were present on airway smooth muscle cells, inflammatory cells, goblet cells, and airway epithelium in lung section and on lymphocytes in the spleen section of mouse. As mentioned before, the non-neuronal cholinergic system is widely expressed in epithelial cells, submucosal glands, smooth muscle cells, and a variety of immune cells including lymphocytes, macrophages, and mast cells in the airway and choline acetyltransferase and/or acetylcholine and nicotinic and muscarinic receptors are found in these cells [28, 29]. This non-neuronal cholinergic system may account the reduction in Th2 cytokine production by the tiotropium treatment in murine model of asthma. In this sense, a recent report which evaluated the role of tiotropium on airway hyperreactivity using a vagotomized guinea-pig model of allergic asthma is worthy of being mentioned [45]. Authors focused on the non-neuronal cholinergic system and compared the effect of tiotropium on vagally mediated bronchoconstriction and bronchoconstriction induced by intravenous administration of acetylcholine. They found that tiotropium did not attenuate vagally-induced bronchoconstriction in sensitized controls, although it inhibited bronchoconstriction induced by intravenous administration of acetylcholine. Interestingly, tiotropium inhibited eosinophil accumulation in the lungs and around nerves. We can learn from those observations that tiotropium may inhibit airway hyperreactivity not only by blocking receptors for vagally released acetylcholine but also by working through an anti-inflammatory mechanism. Moreover, tiotropium was also found to decrease airways remodeling in animal models of ovalbumin-induced asthma and these effects were comparable to those of the corticosteroid [46, 47].

Efficacy of tiotropium on the asthma treatment; results from clinical trials

Consideration of tiotropium as a treatment option in asthma management has been provoked by the finding that a large proportion of asthmatics do not achieve control with current treatment options including the combination of long-acting β 2 agonist (LABA) and even high dose inhaled corticosteroids (ICSs) [48, 49]. Earlier studies in asthmatics demonstrated that inhaled tiotropium resulted in a rapid onset, sustained bronchodilation and reduced the airways hyperresponsiveness [50, 51]. And successive small-scale studies suggested factors capable of predicting good responses to tiotropium; asthmatics with COPD component [52],

severe asthmatics with non-eosinophilic phenotype [53], and severe asthmatics with Arg16Gly and Gly16Gly in *ADRB2* (coding β 2 adrenoreceptor) [12]. However, despite the early signals of efficacy, beneficial effects of tiotropium have not been fully evaluated in asthmatics. The tiotropium bromide as an alternative to increased inhaled glucocorticoid in patients inadequately controlled on a lower dose of inhaled corticosteroid study was the cornerstone of clinical use of tiotropium in asthma treatment [13]. This was a three-way, double-blind, triple-dummy, cross-over trial, which enrolled patients with milder asthma controlled inadequately by ICS. The purpose of this study was to assess whether the addition of inhaled tiotropium to ICS was superior in efficacy to the ICS double dose and noninferior to addition of the salmeterol (inhaled LABA) to beclomethasone (ICS). Tiotropium added to ICS showed a significantly improved morning peak expiratory flow rate (PEFR) compared to double the ICS dose. And a similar effect was observed by adding salmeterol. The tiotropium regimen also significantly improved the pre-bronchodilator forced expiratory volume in one second (FEV1) as compared to double ICS regimen and LABA regimen. Both the tiotropium and LABA regimens also significantly improved asthma symptoms, quality-of-life scores and lung function as compared to double ICS regimen. This study demonstrates that in partially controlled asthmatics with ICS, we can improve disease control not only by adding LABA but also by adding tiotropium. In addition, recently, well-designed studies showing a promising role of tiotropium in the treatment of moderate to severe asthmatics have been published [14, 15]. Kerstjens and colleagues [14] performed a study to compare the efficacy and safety of two doses of tiotropium (5 and 10 μ g daily) administered through the RespimatTM inhaler with placebo as an additive therapy in patients with uncontrolled severe asthma. They found that peak FEV1 was significantly higher with 5 μ g (difference, 139 mL; 95% CI, 96-181 mL) and 10 μ g (difference, 170 mL; 95% CI, 128-213 mL) of tiotropium than with placebo (both $p < 0.0001$). And trough FEV1 at the end of the dosing interval and daily home PEFR measurements were also higher with both tiotropium doses. In addition, they found that asthma-related health status or symptoms showed no significant difference between the tiotropium and placebo group. In addition, adverse events were similar across groups except for dry mouth which was more common on 10 μ g of tiotropium [14]. There has been concerns about the safety of regular use of LABAs in asthmatics [54, 55], especially regarding for asthmatics who are Arg16 homozygote in the coding region of the β 2 adrenergic receptor

Table 1. Summary of studies showing the clinical efficacy of tiotropium in the management of asthma

No.	Characteristics of enrolled asthmatics	Major findings	Reference
1.	138 severe asthmatics on conventional medications and with decreased lung function	I. As many as 30% of severe asthmatics responded to tiotropium treatment II. Arg16Gly in <i>ADRB2</i> may predict response to tiotropium.	[12]
2.	210 asthmatics whose symptoms are not adequately controlled on a lower dose of ICS	I. Tiotropium improved symptoms and lung function in patients with inadequately controlled asthma II. Its effects appeared to be equivalent to those with the addition of salmeterol	[13]
3.	107 asthmatics with a current diagnosis of severe persistent asthma	I. The addition of once-daily tiotropium to asthma treatment including a high-dose ICS plus a LABA significantly improves lung function over 24 h	[14]
4.	388 B16-Arg/Arg asthmatics whose symptoms were not controlled by ICSs alone (moderate persistent asthma)	I. Tiotropium was more effective than placebo and as effective as salmeterol in maintaining improved lung function II. Safety profiles were comparable	[15]

ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist

gene [56]. Bateman and colleagues tested the hypothesis that tiotropium might be an alternative (non- β_2 adrenergic agonist) bronchodilator in Arg16 homozygote asthmatics [15]. In this study, they found that tiotropium was superior to placebo and noninferior to salmeterol in maintaining improved lung function in moderate persistent Arg16 homozygote asthmatics [15]. And safety profiles were comparable [15].

CONCLUSION

There is increasing interest in using tiotropium for the treatment of asthma. Based on recent reports (Table 1), tiotropium may be a valuable alternative to LABA for patients whose symptoms are not controlled by ICSs alone and as an additive therapy in patients with severe asthma not controlled with available medications, including LABA. However, we need additional studies testing whether tiotropium reduces asthma exacerbations, an important marker of disease control [57] to the same extent as LABA [58]. In addition, safety issues related tiotropium should be cleared up so that we can determine whether tiotropium is an alternative to LABA for the long-term treatment of asthma. Because there is a concern for the possible association between tiotropium and cardiovascular events [59].

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