



Long-acting anticholinergics in the treatment of asthma

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Purpose of review

The use of anticholinergic medications is well established as maintenance therapy for chronic obstructive pulmonary disease (COPD). There is a growing interest in the use of anticholinergic medications in the treatment of moderate to severe asthma. The purpose of this review is to summarize the scientific evidence for the use of anticholinergic therapy in the management of asthma.

Recent findings

Early case reports and small studies evaluated the use of the anticholinergic agent, tiotropium bromide, as maintenance therapy in asthma. Included in this review are several recent clinical trials which provide additional evidence for the use of tiotropium as add-on therapy for asthma. The use of tiotropium was demonstrated to be superior to doubling the dose of an inhaled corticosteroid (ICS) and more effective than placebo based on change in morning peak expiratory flow (PEF). Two large multinational trials provide evidence for the use of tiotropium in a subset of asthmatic patients who have not achieved control using combination therapy with an ICS and a long-acting β_2 agonist (LABA).

Summary

The use of the long-acting anticholinergic agent, tiotropium, as maintenance of therapy in asthma, has been shown to be effective in some patients with moderate to severe asthma who are uncontrolled on combination therapy with ICS and LABA. Further studies are needed to better define which phenotypic subset of patients would benefit from the use of tiotropium.

Keywords

anticholinergics, asthma, ipratropium bromide, severe asthma, tiotropium bromide

INTRODUCTION

Asthma is a complex disease of the airways characterized by chronic inflammation, bronchial hyperresponsiveness, and both reversible and irreversible airway obstruction [1]. Approximately 300 million people have a diagnosis of asthma world-wide [2], and approximately 25.7 million people are affected in the United States, of which 18.7 million are adults 18 years of age or more. The overall estimated prevalence of asthma in the United States is 8.4% and these rates continue to increase annually [3]. In addition, it is estimated that up to 10% of patients with asthma have a severe phenotype that is unresponsive to standard medical therapy [4].

Well recognized is the concept of phenotype-driven treatment for asthma, given the heterogeneity of responses to guideline-specific treatment regimens. Much is known about the immunopathogenesis of asthma; however, recent therapeutic advances have been modest [5]. Most clinicians still utilize current asthma guidelines for the

management of asthma; however, prospective studies have demonstrated that up to 30% of patients do not achieve control on standard therapy [6].

Therapy for acute symptoms of asthma involves utilization of short-acting bronchodilators. The short-acting β_2 agonist, albuterol sulfate, is used routinely by inhaler or nebulized solution for quick relief of asthma symptoms. Ipratropium bromide is a short-acting anticholinergic bronchodilator that is routinely used in therapy for chronic obstructive pulmonary disease (COPD) and is less commonly used as first-line therapy to treat asthma. However, ipratropium is often used in combination with albuterol for the treatment of acute exacerbations of

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KEY POINTS

- Asthma is a complex disease of the airways characterized by chronic inflammation, bronchial hyper-responsiveness, and both reversible and irreversible airway obstruction, and up to 30% of patients do not achieve control on standard therapy.
- Long-acting anticholinergic agents like tiotropium may be beneficial for a subset of severe asthmatic patients who continue to have ongoing asthma symptoms and evidence of continued airway obstruction despite the use of combination therapy with moderate to high-dose ICS and a LABA.
- Continued research is needed to determine which phenotypes of asthma would benefit from therapy with long-acting anticholinergic agents.

asthma in emergency rooms [7]. Several previous publications have demonstrated the benefit of using combination therapy in acute asthma, leading to a decreased rate of hospital admission compared with albuterol alone [8,9].

Long-term management guidelines for asthma recommend a stepwise approach to medication usage beginning with the use of inhaled corticosteroid (ICS) leukotriene modifiers, or theophylline, as first-line controller therapy for all but the mildest asthmatic patients, that is those with intermittent asthma. For continued symptoms, step-up therapy focuses on the use of increased amounts of ICS or long-acting bronchodilators [long-acting β_2 agonists (LABAs)]. For those asthmatic patients who remain poorly controlled, LABAs in combination with high-dose ICS is recommended. There is still a subgroup or phenotype of severe asthmatic patients that continue to have poor asthma control despite treatment with high-dose ICS in combination with LABA. Step-up therapeutic options include oral glucocorticoid therapy and anti-IgE therapy. Although mentioned in the most recent Global Initiative for Asthma guidelines, long-acting anticholinergics, however, are not recommended as treatment options in recent asthma guidelines despite their availability since 2004 [1,10].

Long-acting anticholinergic agents have a well established role as maintenance therapy in moderate to severe COPD [11,12]. There was early evidence of the beneficial effects of long-acting anticholinergic therapy in asthma [13,14] and there is now growing evidence for the benefit of the long-acting anticholinergic, tiotropium, in the management of refractory or severe asthma phenotypes. One small study [15] observed a correlation between change in forced expiratory volume in 1 s (FEV_1) while taking

tiotropium and the degree of sputum neutrophilia together with an inverse relationship between percentages of eosinophils in induced sputum and FEV_1 change.

HISTORY/DEVELOPMENT

Inhaled muscarinic acetylcholine receptor antagonists, also known as anticholinergics, have been used as treatment for respiratory diseases for many centuries [16].

Smoking of plant alkaloids like *Atropa belladonna* and *Datura stramonium* (rich in anticholinergics) was routinely recommended as a traditional therapy for respiratory diseases by Ayurvedic medicine as early as the 17th Century [17].

In the early 19th Century, the use of these anticholinergic alkaloids was introduced to Great Britain by travelers from India. For the next 150 years, these anticholinergics were widely used throughout Europe and North America in the treatment of asthma, in the form of atropine and stramonium burning powders, cigarettes, and cigars.

Atropine is a tertiary ammonium compound that is well absorbed across the blood–brain barrier. Because of the side-effect profile of this agent (which will be discussed later), there was the creation of much safer quaternary anticholinergic compounds with similar pharmacologic effects.

PHARMACOLOGY

Short-acting muscarinic acetylcholine receptor antagonists include atropine methonitrate, ipratropium bromide, and oxitropium bromide (not available for use in the United States). The duration of action of these agents is approximately 6–8 h [7].

Long-acting muscarinic acetylcholine receptor antagonists include the agent tiotropium bromide which has been shown to inhibit smooth muscle contraction and mucus secretion. Additional supplementary benefits on inflammation and airway structure have also been suggested [18]. The chemical structure of these anticholinergic agents can be seen in Fig. 1 [19]. Tiotropium is available in two forms: a dry powder inhaler marketed in the United States as the Spiriva HandiHaler (18 mcg capsule given once daily by two inhalations to ensure maximum drug delivery), and a soft mist inhaler available in Europe as the Respimat device (two inhalations of 2.5 mcg representing a single dose) [20]. The onset of action is slower than ipratropium (34.8 min to achieve 50% maximum bronchodilation vs. 7.6 min for ipratropium); however, the duration of action is much longer,

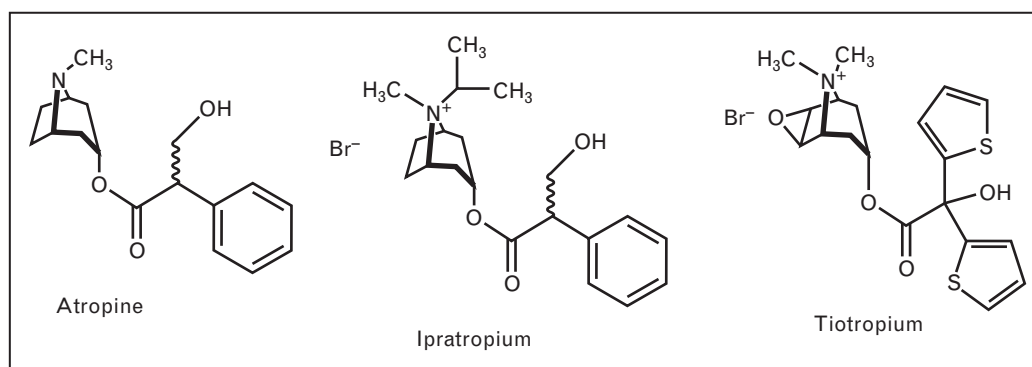


FIGURE 1. Chemical structure of anticholinergic agents. Source: [19].

approximately 24–48 h, due to its slow dissociation from muscarinic receptors [21].

STUDIES

Prior case reports and smaller studies [14,22–24] evaluated the efficacy of tiotropium as maintenance therapy for asthmatic patients, and provided the framework for larger, randomized trials. Heterogeneity in response to anticholinergic medications and asthma was observed. The study by Park *et al.* [23] included 138 severe asthmatic patients with decreased lung function who were taking conventional medications and to whose treatment 18 mcg of tiotropium once daily was added. A response was defined as improvement of more than 15% and 200 ml in FEV₁ maintained for at least 8 weeks and was observed in only 33.3% of patients [23].

Included in this review are recent clinical studies which provide additional evidence for the beneficial effects of tiotropium as maintenance therapy for a subset of asthmatic patients who have not achieved control using standard asthma therapies.

In 2010, Peters *et al.* [25] in the Asthma Clinical Research Network (ACRN), a nonpharmaceutical sponsored asthma research consortium, explored the use of tiotropium as step-up therapy for asthmatic patients and published the Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) trial.

Adult patients met initial inclusion criteria if they had a history of asthma which was confirmed by bronchodilator reversibility ($\geq 12\%$ reversibility to four puffs albuterol) or PC₂₀ 8 mg/ml or less to methacholine if not on ICS, or 16 mg/ml or less on ICS, FEV₁ of above 40% predicted and less than 10 pack-years' smoking history. After the 4-week run-in period, patients were eligible for assignment to the TALC study if they had no medical contraindication to tiotropium and poorly controlled

asthma (the FEV₁ was 70% or less of the predicted value or if during the final 2 weeks of the run-in period they had symptoms 6 or more days per week or used a rescue inhaler 6 or more days per week or were awakened by symptoms of asthma two nights or more per week). This was a double-blind, double-dummy, three-way crossover trial with an initial 4-week run-in period. Each treatment period lasted 14 weeks and was followed by a 2-week wash-out period. During the 4-week common run-in period and the 2-week washout periods, all patients received beclomethasone at a dose of 80 μ g (two puffs of 40 μ g) twice daily and all other asthma medications were discontinued. This study was designed to investigate whether adding once-daily tiotropium (at a dose of 18 μ g per day) to the ICS beclomethasone (two puffs of 40 μ g twice daily) was noninferior to adding salmeterol (dose of 50 μ g twice daily), and superior to doubling the dose of ICS (beclomethasone two puffs of 80 μ g twice daily). Medication adherence was measured by means of an electronic device for beclomethasone, a counter on the salmeterol inhaler, and assessment of used blister packs for tiotropium. The primary end-point was change in morning peak expiratory flow (PEF).

Results from 210 patients demonstrate that adding either tiotropium or salmeterol to beclomethasone was superior to doubling the dose of beclomethasone based on change in morning PEF. At the end of the study, there was no significant difference in lung function between the groups randomized to receive tiotropium or salmeterol. Asthma exacerbations occurred in 9 patients receiving tiotropium, 16 receiving double-dose ICS, and 5 receiving salmeterol. It is arguable that a short 14-week trial period is not sufficient to evaluate the frequency of asthma exacerbations which is an important outcome in evaluating long-term asthma control. What is interesting to note in this study is that patients were observed to have significant baseline bronchodilator responses to both albuterol and the anticholinergic agent ipratropium [mean

reversibility of 14.9 (± 9.8)% after four puffs of albuterol and mean reversibility of 12.4 (± 9.5)% after the administration of four puffs of ipratropium bromide]. Given the heterogeneity of responses to anticholinergic agents in asthma, the widespread applicability of the results to other asthma patients invited further investigation.

Two additional studies [26,27] demonstrate a role for tiotropium in the treatment of moderate to severe asthmatic patients. Bateman *et al.* [26] evaluated the efficacy and safety of tiotropium compared to salmeterol and placebo in patients with moderate to severe asthma who were uncontrolled with ICS alone. Enrollment was limited to asthma patients homozygous for arginine at the 16th amino acid position of the β_2 adrenergic receptor (B16-Arg/Arg). There was concern about the potential for worsening asthma after using inhaled LABAs in patients without this genotype. Data from prospective clinical trials have since confirmed that responses to salmeterol, when given in combination with ICS, are not different in patients with different genotypes at the B16 position of the β_2 adrenergic receptor [28,29].

This was a 16-week multinational, randomized, double-blind, placebo-controlled, parallel-group study, including adult patients on maintenance ICS (400–1000 μg of budesonide or equivalent per day). Patients were included if they had evidence of reversible airway obstruction, which included more than a 12% improvement in FEV₁ and 200 ml after inhalation of 80 μg of ipratropium bromide and 400 μg of salbutamol, and prebronchodilator FEV₁ of 90% or less of predicted value for patients previously receiving a daily dose of at least 100 μg of salmeterol or 18 μg of formoterol and ICS, or FEV₁ 80% or less of predicted for patients previously receiving ICS only.

During the 4-week run-in and 4-week follow-up periods, patients received open-label salmeterol, 50 μg twice daily. Participants were randomly assigned to tiotropium 5 μg once a day by Respimat inhaler, salmeterol 50 μg twice a day via metered dose inhaler, or placebo for 16 weeks. Use of ICS was continued at prestudy doses throughout the study. Adherence to treatment regimens and rescue medication use were assessed by monitoring entries in an electronic diary. The primary end-point was change in morning PEF.

Results from 388 patients with the B16-Arg/Arg genotype, who were identified as having significant bronchodilator response to ipratropium at baseline, demonstrated that tiotropium was more effective than placebo and not inferior to salmeterol in the primary outcome of changes in morning PEF. Similar observations were seen for some of the

patients reporting secondary outcomes, including activity limitation, daily asthma symptoms, and medication requirement. In this study, medication adherence was not strictly monitored.

In a subsequent double-blind, placebo-controlled, three-way crossover trial, the use of tiotropium as add-on therapy in patients with severe asthma, whose symptoms were not controlled despite high-dose ICS and LABA, was evaluated [27]. Patients were randomized to receive one of the two doses of tiotropium (5 or 10 μg via Respimat inhaler) once daily or placebo. All patients received each of the three treatments in a random sequence for 8 weeks in a crossover design.

Adults were included if they met the following criteria: Asthma Control Questionnaire (ACQ) of above 1.5, postbronchodilator FEV₁ of 80% or less of predicted value, forced vital capacity (FVC) 70% or less approximately 30 min after inhalation of four puffs of salbutamol 100 μg at screening, despite therapy with a high-dose ICS (≥ 800 μg of budesonide or equivalent) and a LABA. Concomitant medications including theophylline, leukotriene modifiers, and oral glucocorticoids were permitted in stable doses. The primary end-point was the peak FEV₁ (within 3 h after dosing) determined at the end of each 8-week treatment period by means of supervised spirometry.

Results from 107 patients with severe asthma on high-dose ICS and LABA demonstrated that the addition of tiotropium led to improvement in FEV₁ after 8 weeks of treatment and an overall reduction in the use of rescue medication. In addition, there was also a higher daily PEF home measurement in both tiotropium groups; however, there was no significant change in daily asthma symptoms. Dry mouth was more common with the higher dose of tiotropium. Response to ipratropium was not measured or required in this study, although interestingly 21 of 107 patients were taking ipratropium at baseline, but this was discontinued before patients were randomized into the study. This indicates that many of the patients included in this study were likely responders to the short-acting anticholinergic, ipratropium, so would be more likely to respond to the long-acting anticholinergic, tiotropium. These results suggest that tiotropium might be an alternative to LABA in asthma patients who are inadequately controlled on an ICS alone.

Two replicate, randomized, placebo-controlled multinational trials (PrimoTinA-asthma 1 and PrimoTinA-asthma 2 trials) in adult patients with poorly controlled asthma who were already on high-dose ICS (≥ 800 μg of budesonide or the equivalent) and a LABA evaluated the efficacy of the addition of

two puffs of tiotropium (total of 5 µg) using the soft mist inhaler Respimat or matching placebo for 48 weeks [30^{***}].

Adult patients were included if they demonstrated persistent airflow limitation (baseline FEV₁ after bronchodilator ≤80% than the predicted value and FVC ≤70% after the inhalation of four puffs of 100 µg of salbutamol or 90 µg of albuterol at the screening visit). In addition, patients were required to have had at least one asthma exacerbation that was treated with systemic glucocorticoids in the previous year, and to be either lifelong nonsmokers or to have a smoking history of fewer than 10 pack-years, with no smoking in the year before enrollment. Results from 912 patients demonstrated that tiotropium improved lung function. Airflow obstruction was significantly reduced with the addition of tiotropium, as compared with the addition of placebo.

At 24 weeks, the two tiotropium groups had a significant improvement in the adjusted peak FEV₁. The addition of tiotropium also increased the time to first severe exacerbation by 56 days (282 vs. 226 days in the placebo arm), corresponding to a reduction of 21% in risk [hazard ratio 0.79; 95% confidence interval (CI) 0.62–1.00; *P*=0.03]. In a post-hoc calculation, the number needed to treat in order to prevent one severe exacerbation during the 48-week treatment period was 15.

Adherence to study medications was not monitored in the study [31].

SAFETY PROFILE

All of the currently approved inhaled anticholinergic agents have a very wide therapeutic margin and are well tolerated due to poor absorption into the systemic circulation.

There are a number of side effects that have been reported to occur. Urinary retention has been reported and this medication should be used with caution in men who have benign prostatic hyperplasia [32]. Dilation of the pupils, blurred vision, and acute angle-closure glaucoma precipitated by ipratropium and tiotropium have been reported [33].

Perhaps the most concerning side effect was reported in a previous meta-analysis and demonstrated a 46% relative risk increase in death in COPD trials that used Respimat 5 µg mist inhaler [34] (not available in the United States), but this increase was not seen in trials using the HandiHaler dry powder inhaler (available in the United States only), a difference that has been attributed to deposition characteristics of the Respimat that increase systemic absorption. Despite the concerns that have been

raised regarding a potential increase in risk of death from cardiovascular causes, tiotropium did not increase cardiac events in the previous trials. It is important to remember that patients with serious comorbidity, including a history of cardiac disease, were excluded from these studies.

CONCLUSION

The current and previous evidence is summarized in Table 1 and suggests that long-acting anticholinergic agents may be beneficial for a subset of severe asthmatic patients who continue to have ongoing asthma symptoms and evidence of continued airway obstruction despite use of moderate to high-dose ICS with LABA.

Heterogeneity to asthma therapy has clearly been demonstrated as evidenced by the observation that noneosinophilic asthma is less responsive to ICS than classic eosinophilic asthma [35]. In one pediatric study [36], up to 55% of patients did not respond to standard asthma therapy, specifically to fluticasone and montelukast. This finding was broadened to evaluate the response to tiotropium in asthmatic patients and a previous study demonstrated an inverse relationship between sputum eosinophil counts and response to tiotropium in asthma patients. This small study [15] further brings to light the notion that there is likely a subset or specific phenotype of asthma, possibly those with noneosinophilic asthma, who will respond to this therapy. Future studies examining the use of tiotropium in specific phenotypes in asthma are needed.

Although there is some evidence that long-acting anticholinergic agents might be an alternative to LABAs and other controllers in patients whose condition is inadequately controlled on an ICS alone, most experts agree given the wealth of evidence that tiotropium provides additive benefits to combination ICS and LABA therapy [37]. Future studies will help to elucidate whether the use of tiotropium is more beneficial in lieu of certain therapies or as adjunctive therapy.

Future directions

Research is underway in identifying novel long-acting anticholinergic agents [16]. As we move towards more phenotype-driven asthma therapies and genetic profiling of asthmatic patients based on their clinical and pathophysiological presentations, we may continue to find evidence for the use of long-acting anticholinergic agents for maintenance of asthma control.

Table 1. Tiotropium in asthma

Study	Design	Size, duration of trial	Intervention	Outcomes	Comments
Iwamoto <i>et al.</i> [15]	Open label	N = 17	All patients were on ICS, many on additional controller medications. Addition of tiotropium	Improvement in FEV ₁ which correlated with percentage of neutrophils in induced sputum and inversely with percentage of eosinophils	Sputum neutrophilia correlated with improvement in lung function on tiotropium
Kapoor <i>et al.</i> [22]	Case report	N = 1	Addition of tiotropium to ICS/LABA	Successful reduction in requirement for oral steroids	
Park <i>et al.</i> [23]	Open label	N = 138, 8 weeks	All patients on ICS/LABA	33% patients responded with > 15% increase in FEV ₁ , sustained over 8 weeks. Arg 16Gly was positively associated with response	About one-third of patients on ICS/LABA can expect improved lung function with anticholinergics
Fardon <i>et al.</i> [24]	Double-blind, randomized, placebo-controlled, crossover study	N = 18, 4 weeks (for each of the two arms)	Addition of tiotropium 18 mcg Addition of salmeterol with placebo was compared to addition of salmeterol and tiotropium in patients whose ICS dose was halved	Tiotropium arm had greater improvements in lung function and decrease exhaled NO, but not QoL	Tiotropium might be associated with a steroid-sparing effect
Peters <i>et al.</i> [25]	Three-way, double-blind, triple-dummy crossover trial	N = 210, 14 weeks (for each of the three arms)	All on ICS. Compared tiotropium 5 mcg, salmeterol 50 mcg, and double-dose ICS	Tiotropium was superior to doubling the dose of ICS as assessed by improved morning PEF, evening PEF, FEV ₁ , asthma control days. Tiotropium was also noninferior to salmeterol	The addition of tiotropium was equivalent to salmeterol, and both were superior to doubling ICS, in terms of lung function and asthma control
Bateman <i>et al.</i> [26]	Double-blind, double-dummy, placebo-controlled trial	N = 388, 16 weeks	All patients had the B16 Arg/Arg genotype and were on ICS Compared tiotropium 5 mcg, salmeterol 50 mcg twice daily, and placebo	Tiotropium was noninferior to salmeterol based on change in PEF and both were superior to placebo	In patients with B16 Arg/Arg, on ICS alone, tiotropium and salmeterol equivalently improved lung function
Kerstjens <i>et al.</i> [27]	Double-blind, randomized, three-way crossover trial	N = 107, 8 weeks (for each of the three arms)	All on high dose ICS/LABA Compared tiotropium, 5 mcg, 10 mcg, and placebo	Both tiotropium groups had improved peak and trough FEV ₁ at the end of 8 weeks. Improved daily PEFR were higher in both tiotropium groups compared with placebo	Tiotropium improved lung function in patients already on ICS/LABA combination
Kerstjens <i>et al.</i> [30 ^{***}]	Replicate, randomized, placebo-controlled, multinational trial	N = 912, 48 weeks	All on high-dose ICS/LABA	Mean change in peak FEV ₁ from baseline was greater with tiotropium than with placebo. The addition of tiotropium increased time to 1st exacerbation, reduced severe exacerbations, provided sustained bronchodilation	Improved asthma outcomes with the addition of tiotropium in patients already on ICS/LABA combination
Compared the addition of tiotropium 5 mcg to placebo					

FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; NO, nitric oxide; PEF, peak expiratory flow; QoL, quality of life.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 454–455).

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