



Anticholinergics for asthma: a long history

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Purpose of review

To provide a fast overview about the introduction and development of anticholinergic drugs in Western medicine to their current indications particularly in asthma.

Recent findings

Although short-acting muscarinic antagonists have been positioned in the last 15 years for the treatment of adults and children with moderate-to-severe acute asthma in the emergency setting (reducing the risk of hospital admissions and improving lung function), a growing body of evidence has recently emerged that positions the long-acting muscarinic anticholinergic tiotropium bromide as add-on therapy to at least inhaled corticosteroids (ICS) maintenance therapy in adults, adolescents, and children with symptomatic asthma. Thus, the addition of tiotropium bromide to ICS alone or ICS and another controller was associated with significant improvements in spirometric measures and asthma control, and a significantly decrease in the rate of asthma exacerbations.

Summary

Short-acting muscarinic antagonists and tiotropium bromide have a well established role in the treatment of different phases of asthma. Further data are needed to provide more evidence on other selective long-acting muscarinic antagonists in addition to tiotropium as potential treatment options.

Keywords

anticholinergics, asthma, ipratropium, tiotropium

INTRODUCTION

Two factors that have arisen in the past decades have revitalized the interest in anticholinergics bronchodilators. One was a better understanding of the cholinergic mechanisms that control airway caliber in healthy and disease states, and the second one was the development by pharmaceutical chemists of short and long-acting muscarinic antagonists (LAMAs), synthetic analogs of atropine that were not appreciably absorbed but retained the anticholinergic properties of the atropine. Today, physicians worldwide regularly prescribe different anticholinergic agents, and their role for the treatment of asthma exacerbations and moderate-to-severe asthma has been well established.

Brief history

The recreational and medicinal properties of atropine were well known to many cultures and for many centuries [1]. However, from the Western medicine perspective, atropine, in the form of the leaves and roots of *Datura stramonium*, was introduced in the early 1800s by British military officers from India (Fig. 1) [2,3]. Since then, stramonium, belladonna, and their alkaloid extract, atropine, had

their place in most pharmacopoeias in Europe, constituting the main bronchodilator for almost one century. Only the introduction of adrenaline in the 1900s displaced these agents as the first-line treatment for asthma and emphysema.

Undesirably, atropine (a tertiary ammonium compound) is well absorbed into the systemic circulation and penetrates the blood–brain barrier. As a result, it has multiple systemic side-effects that limit its clinical usefulness [4]. In the 1970s, there has been a renewed interest in the use of anticholinergic medications, given the need to develop alternatives to therapy with β -agonist agents. The development of less toxic alternatives to atropine led to their wider use in clinical practice. The newer anticholinergic agents are water soluble, quaternary ammonium compounds that are poorly absorbed, and

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KEY POINTS

- In the last 50 years, the development of synthetic analogues of atropine led to their wider use in clinical practice.
- Today, short-acting muscarinic antagonists and the long-acting tiotropium bromide, are used in different phases of asthma.
- Further data are needed to provide more evidence on other LAMAs in addition to tiotropium as potential treatment options.

when they are given by inhalation, they cause fewer systemic side-effects [5].

Mechanisms of action

To understand the rationale for the use of anticholinergic agents in patients with acute asthma, we must comprehend the mechanisms for bronchoconstriction and dilatation that are mediated by the autonomic nervous system. The majority of autonomic nerves in human airways are branches of the vagus nerve; the efferent preganglionic fibers of which enter the lung at the hilum and travel along the airways into the lung [6,7].

The efferent innervations derived from the postganglionic fibers end in the epithelium, submucosal glands, and smooth muscle of the airways as well as in the vascular structures (Fig. 2) [8]. Thus, the release of acetylcholine at these sites results in smooth muscle contraction and the release of secretions from submucosal glands stimulated by their

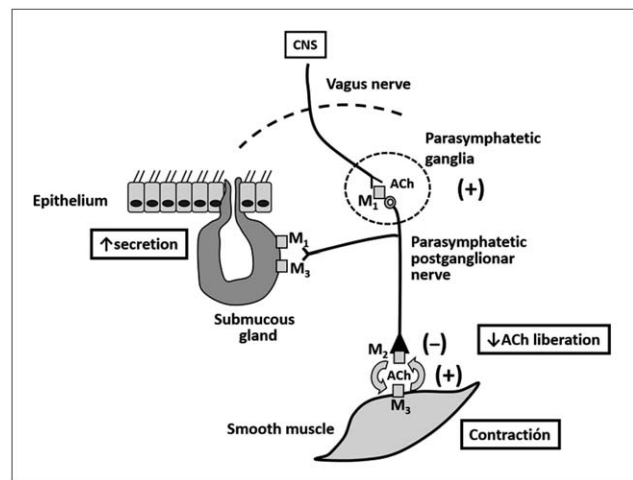


FIGURE 2. Neural regulation of respiratory airways. Ach, acetylcholine.

muscarinic receptors. Anticholinergic medications antagonize transmission at the muscarinic receptors. In humans, there are at least three pharmacologically distinct subtypes of muscarinic receptors within the airways, which are known as M1, M2, and M3 [9]. M1 receptors are present within the parasympathetic ganglion mediating cholinergic transmission. They may facilitate nicotinic transmission or be responsible for maintaining cholinergic tone. Inhibition would reduce cholinergic tone and, thus, would reduce bronchoconstriction. They are located particularly in peripheral lung tissue and in the alveolar wall. M2 and M3 represent the major population of cholinergic receptors. Prejunctional M2 receptors on the postganglionic nerves act as a negative feedback loop in neuronal transmission.

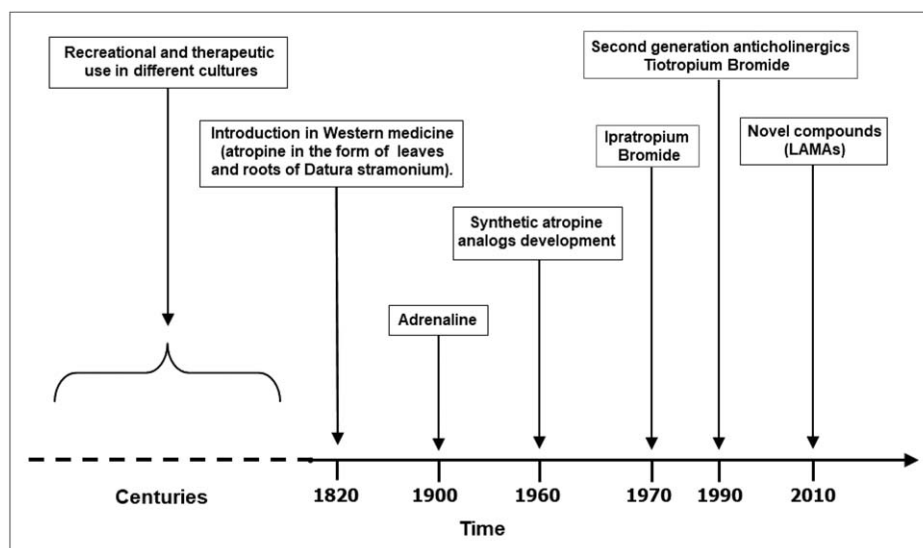


FIGURE 1. Landmarks in the development of anticholinergics in lung obstructive chronic diseases. LAMAs, long-acting muscarinic antagonists.

They are activated by the release of acetylcholine and promote its reuptake, thereby limiting the degree of bronchoconstriction produced. Under physiological conditions, the airway smooth muscle contraction induced by acetylcholine is mediated primarily via the M3 receptor (located on the airway smooth muscle). The receptor activation leads to a release of calcium ions from intracellular stores and a decrease in intracellular adenosine 3'/5'-cyclic monophosphate levels, resulting in the contraction of airway smooth muscle. M3 receptors also are located on submucosal glands mediating mucus secretion, and also mediate dilation of airway blood vessels [10].

ANTICHOLINERGIC AGENTS

Short-acting muscarinic anticholinergics

Nonselective anticholinergic agents such as atropine, ipratropium bromide, and oxitropium bromide block both the prejunctional M2 and postjunctional M3 receptors. In particular, the blockade of the prejunctional M2 receptors may increase the amount of acetylcholine that is released by cholinergic nerve stimulation [4]. Although extensively used in the past, the natural anticholinergic atropine is rarely used at the present time [11]. The fact that it is easily absorbed across the oral and respiratory mucosa and the high incidence of dry mouth, blurred vision, urinary retention, nausea, and tachycardia limits its utility.

Ipratropium bromide and oxitropium bromide are effective quaternary short-acting muscarinic anticholinergics (SAMAs) drugs that have been used in the treatment of respiratory diseases. Unlike atropine, they have low lipid solubility and do not pass the blood–brain barrier. Ipratropium bromide is poorly absorbed by the oral and nasal mucosa, and the swallowed drug is poorly absorbed from the gastrointestinal tract. Ipratropium starts to act within 15–30 min, but maximal bronchodilation may take up to 90 min [12]. The duration of action is approximately 6 h, but compared with short-acting beta-agonists (SABAs), they have a slower onset of action. When administered via inhalation at therapeutic doses ipratropium bromide is less effective than SABAs in patients with asthma [13].

Oxitropium bromide is another nonselective muscarinic antagonist but it is based on the scopolamine molecule instead of atropine. Its peak bronchodilation may take 60–90 min, and its duration is 5–8 h [14]. Its bronchodilator effect is similar to that of ipratropium bromide, but oxitropium bromide is longer lasting.

Long-acting muscarinic anticholinergics

Tiotropium bromide is a once-daily long-acting muscarinic anticholinergic (LAMA) with high potency and kinetic selectivity at the muscarinic receptors [15]. It displays a six to 20-fold higher affinity for muscarinic receptors than does ipratropium bromide. Although tiotropium bromide binds to all three muscarinic receptors, it dissociates much faster from the M2, which results in a more selective antagonist action for M1 and M3 subtypes. Its prolonged pharmacologic activity is the result of its slow dissociation from M1 to M3 receptors. The half-life of the tiotropium bromide M3 receptor is approximately 35 h, compared with 0.3 h for ipratropium bromide [14]. Tiotropium is rapidly absorbed into the circulation with a peak plasma concentration within 5 min followed by a rapid fall within an hour to a steady state and a terminal half-life of 5–6 days that is independent of dose. Tiotropium has been available since 2002 as a single-dose dry-powder formulation delivered via the HandiHaler (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) device, and since 2007 as an aqueous solution delivered via the multidose Respimat Soft Mist inhaler (Boehringer Ingelheim GmbH). Initially indicated for the treatment of chronic obstructive pulmonary disease (COPD) [16], from 2014 received approval for treatment of asthma [17]. In fact, tiotropium is the only LAMA that has been studied extensively in asthma, and is the first agent in the class to be indicated as add-on therapy for patients with asthma who are currently treated with maintenance ICS only or ICS and LABA therapy. Tiotropium HandiHaler and Respimat have similar efficacy, safety, and pharmacokinetic profiles [18–20].

The increasing evidence on the importance of tiotropium bromide for the treatment of chronic obstructive pulmonary diseases has encouraged the development of further research to identify new LAMAs that could be as successful as tiotropium bromide. Several novel inhaled LAMAs are available, including glycopyrronium bromide, aclidinium bromide, and umeclidinium bromide. However, these new LAMAs have been only approved for COPD.

ANTICHOLINERGICS FOR ASTHMA

Short-acting muscarinic anticholinergics for acute asthma treatment

The goals of acute asthma treatment are to maintain an adequate arterial oxygen saturation, to relieve airflow obstruction with repetitive administration of rapid-acting inhaled bronchodilators, to reduce airway inflammation, and to prevent future relapses

[21,22]. SABAs (mainly salbutamol) are the drugs of choice to treat acute asthma; their onset of action is rapid, and their side-effects are well tolerated. Because SAMAs are considered to be less effective than SABAs in achieving acute bronchodilation, they have been used in combination [23]. Three systematic reviews have analyzed the evidence from clinical studies comparing a combination of SABA and SAMA (mostly ipratropium bromide) vs. SABA alone in acute asthma patients in an emergency setting [24,25,26^{***}].

First, Rodrigo and Castro-Rodriguez [24] analyzed data from 32 randomized controlled trials (RCTs) including 3611 adults, adolescents, and children with moderate-to-severe acute asthma. The authors found significant reductions in hospital admissions in both children [risk ratio = 0.73; 95% confidence interval (CI): 0.63 to 0.85, number need to treat (NNT) = 13] and adults (risk ratio = 0.68; 95% CI: 0.53–0.86, NNT = 14) in those patients receiving combination inhaled treatment. Stratification of data suggested a trend toward a reduced risk of admission in children and adults with the most severe asthma attack and treated with multiple doses of anticholinergics. Combined treatment also produced a significant increase in spirometric parameters 60–120 min after the last treatment in children. In a similar way, adult patients treated with combined therapy had a significant mean difference in peak expiratory flow (PEF) of 44.1 l/min (95% CI: 57.5–30.8), in comparison with SABA alone. Again, the use of more than two doses of anticholinergics showed more benefit than lower doses. There was no apparent increase in the occurrence of side-effects such as tremor or heart rate among study participants treated with single or multiple-dose protocols.

More recently, Griffiths and Ducharme [25] assessed the efficacy and safety of the combination of inhaled SAMAs and SABAs in children with acute asthma exacerbations. Twenty RCTs met the review eligibility criteria (2697 children aged 1–18 years). The combination of SAMA and SABA significantly reduced the risk of hospital admission (risk ratio = 0.73; 95% CI: 0.63–0.85, NNT = 16). Statistically significant group differences favoring anticholinergic use were observed for lung function, clinical score at 120 min, oxygen saturation at 60 min, and the need for repeat use of bronchodilators prior to discharge from the emergency department. Trends toward a greater effect with increased treatment intensity and with increased asthma severity were observed.

Finally, Kirkland *et al.* [26^{***}] conducted an up-to-date systematic search and meta-analysis on the effectiveness of combined inhaled therapy (SAMAs

and SABAs agents) vs. SABAs alone to reduce hospitalizations in adult patients presenting to the emergency department with an exacerbation of asthma. In total, 23 RCTs (2725 patients) were included in the analysis. Overall, participants receiving combination inhaled therapy were less likely to be hospitalized (risk ratio = 0.72, 95% CI: 0.59–0.87). Although combination inhaled therapy was more effective than SABA treatment alone in reducing hospitalization in participants with severe asthma exacerbations, this was not found for participants with mild or moderate exacerbations (test for difference between subgroups $P = 0.02$). Participants receiving combination therapy were more likely to experience improved forced expiratory volume in 1 s (FEV₁); mean difference 0.25 l; 95% CI 0.02–0.48).

In summary, there is consistent evidence from clinical trials that combination inhaled therapy with SAMAs and SABAs reduced hospitalizations and improved pulmonary function in adults and children presenting to the emergency department with acute asthma. In particular, combination inhaled therapy was more effective in preventing hospitalization in asthmatics with moderate-to-severe asthma exacerbations, compared with those with mild exacerbations. This clinical evidence has been incorporated into the most relevant clinical guidelines for asthma management [22,27^{***},28^{***}].

Tiotropium bromide for moderate-to-severe symptomatic asthma

Tiotropium bromide is the only LAMA that has been studied extensively in asthma; Thus, it is the first agent in the class to be indicated as add-on therapy for patients with asthma [5,27^{***}]. A large clinical trial programme [29] that includes 18 RCTs with more than 6000 patients of all ages has demonstrated benefits of add-on treatment with tiotropium in patients with uncontrolled mild-to-moderate and severe asthma. These studies have been reviewed extensively and their findings supported in three systematic reviews.

In a meta-analysis of 13 studies (4966 adults and adolescents) [30], the addition of tiotropium bromide (delivered via Respimat inhaler) to ICS only, or ICS and LABA (salmeterol) demonstrated statistically and clinically significant improvements in lung function, clinically significant reductions in exacerbations and improved asthma control. Tiotropium as an add-on to ICSs showed statistically and clinically significant mean increases in PEF (22–24 l/min) and FEV₁ (140–150 ml). Additionally, the use of tiotropium as an add-on to ICS/salmeterol combination reduced asthma exacerbations (risk ratio = 0.70; 95% CI: 0.53–0.94; NNT = 17), and

improved asthma control compared with ICS/salmeterol. On the basis of improved lung function and increased time to severe exacerbation, both of which were shown to be independent of baseline characteristics (and across a variety of phenotypes) according to the different analyses of the tiotropium clinical programme [31]. Additionally, the use of tiotropium in patients poorly controlled despite of medium to high doses of ICS was not inferior to salmeterol. Finally, tiotropium was well tolerated, and no potential safety signals were observed.

Rodrigo and Castro-Rodriguez [32] assessed the efficacy and safety of inhaled tiotropium (Respimat) in adolescents with symptomatic asthma despite receiving moderate/high ICS dose alone or/and other controller. Three RCTs (approximately 1000 patients) were included. Tiotropium was associated with significant improvements in FEV₁ peak by 120 ml ($P < 0.001$) and trough by 100 ml ($P < 0.001$) compared with placebo. Also, tiotropium significantly reduced the percentage of patients who experienced a deterioration in asthma control, and the number of patients with at least one exacerbation (risk ratio = 0.74, 95% CI: 0.56–0.98, NNT = 16). Tiotropium in doses of 2.5 or 5.0 µg once daily resulted in equivalent effects.

Finally, a third meta-analysis analyzed data from three RCTs including more than 900 symptomatic school-age asthmatics receiving maintenance therapy with ICS alone or ICS and one or more controller medications [33]. Tiotropium was associated with significant improvements in FEV₁ peak by 102 ml ($P < 0.0001$) and trough by 82 ml ($P < 0.0001$) compared with placebo. Tiotropium 5 µg dose presented a trend (statistically nonsignificant) toward a greater bronchodilation in comparison with 2.5 µg dose. Also, tiotropium significantly increased asthma control and significantly decreased the number of patients with at least one exacerbation in comparison with placebo (risk ratio = 0.73; 95% CI: 0.60–0.89, NNT = 10). There were no significant differences in rescue medication use, withdrawals, and adverse events.

The present body of clinical evidence suggests that tiotropium provides an efficacious add-on to at least ICS maintenance therapy in patients with asthma, with balanced safety and tolerability compared with placebo. Accordingly, current guidelines have incorporated tiotropium bromide Respimat as an add-on option in symptomatic patients with moderate or severe asthma [27].

CONCLUSION

Anticholinergics have been used for centuries for their therapeutic properties. It is in the last 50 years

that the synthetic analogues of atropine were developed, and its therapeutic uses were determined with more accuracy. Today, SAMAs and tiotropium bromide, the first LAMAs developed, are used in different phases of asthma. Thus, as SAMAs are used in combination with SABAs in the treatment of acute asthma in the emergency setting, tiotropium bromide has been incorporated as an add-on treatment to at least ICS maintenance in moderate-to-severe asthma. Further data are needed to provide more evidence on other LAMAs in addition to tiotropium as potential treatment options.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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