Use of Inhaled Anticholinergic Agents in Obstructive Airway Disease

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In the last 2 decades, anticholinergic agents have been generally regarded as the first-choice bronchodilator therapy in the routine management of stable chronic obstructive pulmonary disease (COPD) and, to a lesser extent, asthma. Anticholinergics are particularly important bronchodilators in COPD, because the vagal tone appears to be the only reversible component of airflow limitation in COPD. The inhaled anticholinergics approved for clinical use are synthetic quaternary ammonium congeners of atropine, and include ipratropium bromide, oxitropium bromide, and tiotropium bromide. This article reviews the most current evidence for inhaled anticholinergics in obstructive airway disease and summarizes outcomes reported in randomized controlled trials. *Key words: anticholinergic, muscarinic receptor, antimuscarinic, chronic obstructive pulmonary disease, COPD, asthma, ipratropium, oxitropium, tiotropium.* [Respir Care 2007;52(7):833–851.

Introduction

Atropine and scopolamine are naturally occurring anticholinergic alkaloids that have been used in traditional medicine for centuries. It is believed that the alkaloid daturine, extracted from the *Datura stramonium* plant, was identified as atropine in 1833 and was the first pharmaco-

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logic agent used to treat asthma in the West.[1] However, it slowly lost popularity, due to its multiple systemic adverse effects from its absorption into the systemic circulation. With the discovery of ephedrine and adrenaline bronchodilator derivates in the 1920s, followed by the methylxanthines, atropine was displaced as a first choice in the management of obstructive airway disease.

A synthetic quaternary ammonium salt congener of atropine, SCH 1000, was discovered in the 1970s. In 1987, the compound coded SCH 1000 was released in the United States as ipratropium bromide. The fact that ipratropium was fully ionized, very poorly absorbed when given via inhalation, and did not distribute well across lipid membranes revived interest in the anticholinergics and enabled the development of newer agents, such as the oxitropium and tiotropium bromides.[2–5]

Although anticholinergic agents have been generally regarded as the first-choice bronchodilator therapy in the routine management of stable chronic obstructive pulmonary disease (COPD), a study by Taylor et al,[6] in the United States, reported that anticholinergics were prescribed for asthma in 8% of the patients 18–54 years old. Additionally, data from a United Kingdom general practice database on new use bronchodilators in severe asthma showed that, of 14,657 patients, 20% received ipratropium bromide.[7]

Ipratropium and oxitropium bromides have relatively short durations of action, which requires administration every 6–8 h; this regimen may affect patient adherence to therapy. They have been used alone and in combination with short-acting β_2 agents, for both maintenance therapy and exacerbations of airway obstruction. Tiotropium bromide has a duration of approximately 24 h, which makes it suitable for once-daily dosing. All of the currently available inhaled anticholinergics are very poorly absorbed; they have a wide therapeutic margin and are well tolerated by patients.

Boehringer Ingelheim announced the discontinuation of Atrovent Forte (ipratropium bromide), Atrovent Autohaler (ipratropium bromide), Oxivent Inhaler (oxitropium bromide), and Oxivent Autohaler (oxitropium bromide) as of May 31, 2004, anticipating that these agents would no longer be available for prescription. Patients who use those agents were expected to transition to newer formulations (eg, hydrofluoroalkane-propelled metered-dose inhaler [MDI]) or different agents (eg, tiotropium).[8]

Recent studies also suggest that the effects of inhaled anticholinergics probably extend beyond their well known bronchodilation. The newer agent tiotropium might inhibit the rate of decline of lung function in COPD patients.[9]

Acetylcholine, which acts through the muscarinic receptors, may play an essential regulating role in the pathological changes associated with airway remodeling.[10]

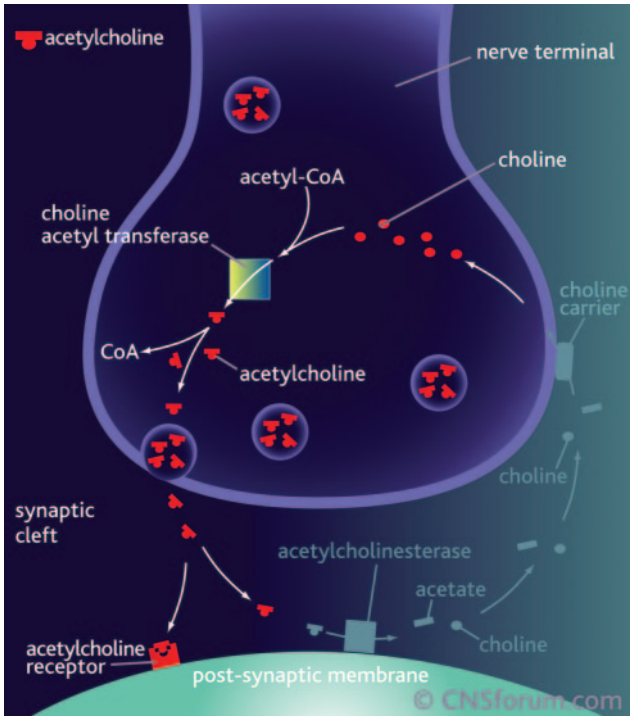

Fig. 1. Cholinergic nerve transmission mediated by acetylcholine. Acetyl-coA = acetyl-coenzyme A. (Courtesy of the CNS Forum at the Lundbeck Institute, Skodsborg, Denmark.)

Parasympathetic Regulation

Cholinergic Neurotransmitter Function

Acetylcholine is the primary parasympathetic neurotransmitter in the airways. It is synthesized from acetyl-coenzyme A (acetyl-coA) and choline in the cytoplasm of autonomic presynaptic nerve terminals after catalysis by the enzyme choline acetyltransferase. Once formed, acetylcholine is transported into and packaged into synaptic vesicles that contain between 1,000 and 50,000 molecules. When an action potential reaches the presynaptic neuron, an influx of calcium causes exocitosis of the vesicles, and the acetylcholine attaches to the various receptors on the postsynaptic membrane (Fig. 1).[9]

Muscarinic Effects

There are 2 types of acetylcholine receptor: nicotinic and muscarinic. In COPD, bronchoconstriction and mucus secretion are caused mostly by increased parasympathetic nerve activity mediated by muscarinic receptors. Muscarinic acetylcholine receptors belong to a class of metabotropic receptors that have 7 transmembrane segments, which use G proteins as their signaling mechanism. In this type of protein coupled receptor, the signaling molecule or ligand is the acetylcholine. The ligand binds to the musca-

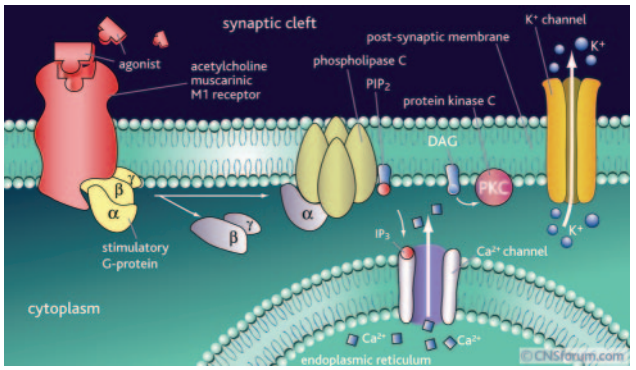

Fig. 2. Cholinergic muscarinic receptor subtype M_1, showing effects in the target cell mediated by the stimulatory G protein. PIP_2 = phosphatidylinositol bisphosphate. DAG = diacylglycerol. (Courtesy of the CNS Forum at the Lundbeck Institute, Skodsborg, Denmark.)

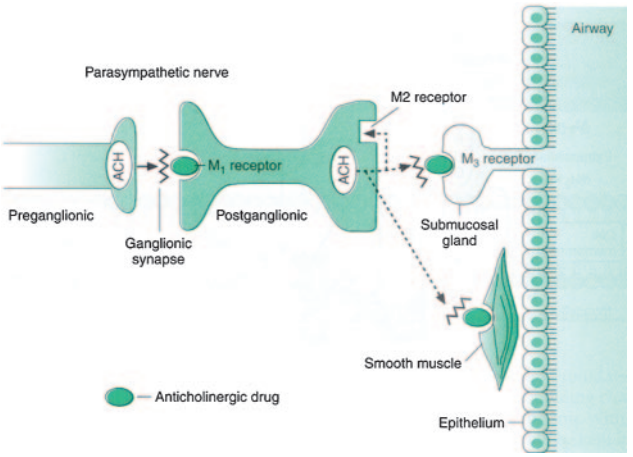

Fig. 3. Identification and location of muscarinic receptor subtypes M_1, M_2, and M_3 in the vagal nerve, submucosal gland, and bronchial smooth muscle in the airway, showing nonspecific blockade by anticholinergic drugs. Ach = acetylcholine. (From Reference 4, with permission.)

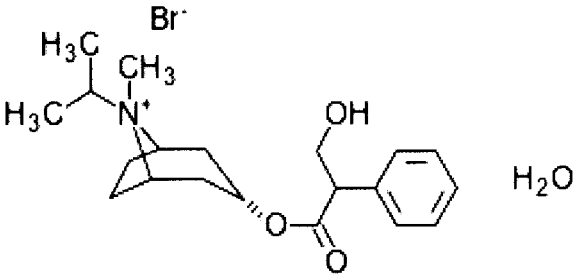

Fig. 4. Molecular structure of ipratropium bromide. 8-azoniabicyclo[3.2.1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo,syn)-.

rinic receptor and initiates the information cascade within the cell. Typical responses in the target tissue include inactivation of adenyl cyclase, activation of phospholipase C, and opening of the potassium channels (Fig. 2).[9,10]

The muscarinic receptors are classified into M_1–M_5 subtypes. The M_1 receptors are widely distributed throughout the parasympathic ganglia and exocrine glands and are responsible for cholinergic transmission. The prejunctional muscarinic M_2 autoreceptors are found in the smooth muscle and the myocardium, and they provide negative presynaptic feedback to reduce further release of acetylcholine.[11–15] The M_3 receptor subtypes in the airway smooth muscle mediate bronchoconstriction and mucus secretion.[2,3,16] When coupled to G proteins, M_1, M_3, and M_5 muscarinic acetylcholine receptors have a stimulatory effect on the target tissue, whereas the M_2 and M_4 subtypes are inhibitory (Fig. 3).[16]

An increased release of acetylcholine from cholinergic nerve terminals[17] and an abnormal muscarinic receptor expression, via either an increase in M_1 and M_3 receptors or disruption of the M_2 muscarinic receptors, have been postulated to explain the increased acetylcholine release and the potentiation of cholinergic-induced bronchoconstriction in asthmatic patients.[18] CD8+ T lymphocytes induced by viral infection are necessary for M_2 receptor dysfunction and result in cholinergic activation in asthmatic airways.[19–21] The ideal anticholinergic drug for obstructive airway disease should antagonize M_1 and M_3 receptors, with little affinity for the M_2 receptor.

Available Agents

Currently available anticholinergic agents compete with acetylcholine at muscarinic receptors on airway smooth muscle, which decreases the intracellular concentration of cyclic guanosine monophosphate and inhibits tonic cholinergic activity.[22,23] Bronchodilation following inhalation of anticholinergic agents is primarily a local, site-specific effect. Much of an administered dose is swallowed, as shown by fecal excretion studies.[23] All of these agents contain a quaternary ammonium, which is the reason these drugs do not penetrate the blood-brain barrier, have lower systemic absorption, and have a longer duration of action than their predecessor, atropine, which is a tertiary amine.[2,3]

Ipratropium Bromide

Ipratropium bromide (succinylcholine 1000, Atrovent) is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo[3.2.1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo,syn)-, (±), a synthetic quaternary ammonium compound chemically related to atropine (Fig. 4).[22]

Ipratropium bromide is a crystalline substance, freely soluble in water and lower alcohols but insoluble in lipophilic solvents such as ether, chloroform, and fluorocar-

bons.[10,15] The half-life of elimination of ipratropium bromide is about 1.6 h after inhalation. It is minimally bound (0–9% in vitro) to plasma albumin and α1-acid glycoprotein. Ipratropium is poorly absorbed into the circulation from either the nasal mucosa or from the airway, and it is partially metabolized by ester hydrolysis to inactive products. Autoradiographic data in rats showed that ipratropium bromide does not penetrate the blood-brain barrier.[16]

Ipratropium bromide is a nonselective antagonist of M_1, M_2, and M_3 receptors. The blockade of the M_2 receptor subtype allows further release of presynaptic acetylcholine and may antagonize the bronchodilatory effect of blocking the M_3 receptor.

Among the anticholinergic agents, ipratropium bromide is the most widely administered therapy for COPD, alone or in combination. In controlled 90-day studies in patients with bronchospasm associated with COPD, ipratropium was associated with significant improvement in pulmonary function ($\geq$15% increase in forced expiratory volume in the first second [FEV_1]) and forced expiratory flow in the middle half of the forced vital capacity) within 15 min. Its peak action is reached in 1–2 h, and it persists for 3–4 h in the majority of patients, both as monotherapy and in combination with short-acting β_2 adrenergic agents (SABAs), and up to 6 h in some patients.[23–25]

The ipratropium bromide aerosol formulation contains a microcrystalline suspension of ipratropium bromide in an MDI. Each MDI actuation emits 21 μg of ipratropium bromide from the valve and delivers 18 μg of ipratropium bromide from the mouthpiece. Ipratropium bromide is also available as a nebulizable solution of 0.02% concentration in a 2.5-mL vial, and as a nasal spray of 0.03% or 0.06% strength. A newer formulation, designed to decrease nebulization time, which contains 500 μg of ipratropium in 1 mL of solution, is available in Australia under the brand name Ipravent. The recommended dosage with the MDI is 36 μg 4 times a day. With the nebulizer formulations the dosage is 2.5 mL vial (500 μg) 3–4 times a day. Because the original dose of ipratropium, 40 μg, was found to be suboptimal for some patients with COPD,[26] a double-strength MDI formulation, Atrovent Forte, was made available outside the United States, until discontinued by the manufacturer in May 2004.[8] Combinations of ipratropium with albuterol are also available in an MDI form (Combivent) and in a nebulizer form (DuoNeb). MDI combinations of ipratropium and fenoterol are also available (DuoVent and Berodual) outside the United States.

Oxitropium Bromide

Oxitropium bromide (Ba 235 Oxivent) is a quaternary derivative of scopolamine. It is chemically described as 6,7-epoxy-8-ethyl-3-[(S)-tropoyloxy]tropanium bromide; (3s,6R,7S,8r -)-8-ethyl-3-[(S)-tropoyloxy]-6,7-epoxytropanium bromide (Fig. 5).

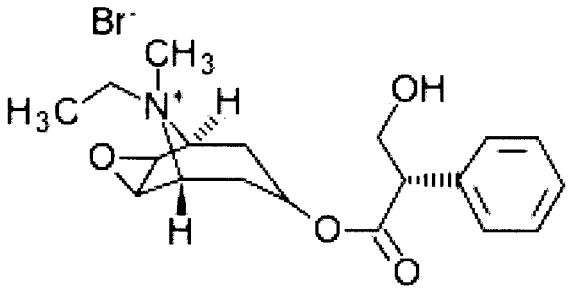

Fig. 5. Molecular structure of oxitropium bromide. 6,7-epoxy-8-ethyl-3-[(S)-tropoyloxy]tropanium bromide; (3s,6R,7S,8r-)-8-Ethyl-3-[(S)-tropoyloxy]-6,7-epoxytropanium bromide.

Oxitropium bromide's peak bronchodilation may take 60–90 min, and its duration is 5–8 h.[27–29] It has been available outside the United States as Oxivent, in an MDI that delivers 100 μg/puff. Oxitropium's bronchodilation effect is similar to that of ipratropium bromide, but oxitropium is longer-lasting.[27,28] The usual dose is 200 μg, 2–3 times daily. It is considered to have twice the strength of ipratropium per dose.[30,31] Although widely used for many years (alone or in combination with short-acting β agonists) for both maintenance treatment of stable disease and exacerbation of airway obstruction,[32] Boehringer Ingelheim announced the discontinuation of Oxivent formulations as of May 2004.[8]

Tiotropium Bromide

Tiotropium bromide monohydrate (Ba 679 Spiriva HandiHaler), which is structurally related to ipratropium bromide, is a second-generation anticholinergic agent introduced early in the present decade. It is chemically described as (1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4] nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. It is sparingly soluble in water and soluble in methanol (Fig. 6).

Tiotropium differs from other anticholinergics in its functional relative selectivity and higher affinity for muscarinic receptor subtypes. It displays a 6–20-fold higher affinity for muscarinic receptors than does ipratropium.[33] Although tiotropium binds to all 3 muscarinic receptors, it dissociates much faster from the M_2 receptors, which results in a more selective antagonist action for M_1 and M_3 muscarinic receptor subtypes.[34,35] Its prolonged pharmacologic activity is the result of its slow dissociation from M_1 and M_3 receptors. The half-life of the tiotropium M_3 receptor complex is approximately 35 h, compared with 0.3 h for ipratropium (Fig. 7).[2,33,35]

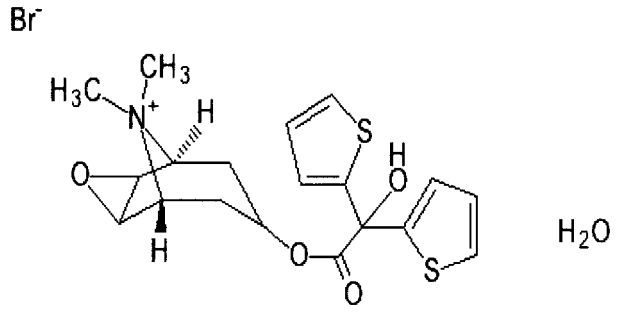

Fig. 6. Molecular structure of tiotropium bromide. 1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4]nonane bromide monohydrate.

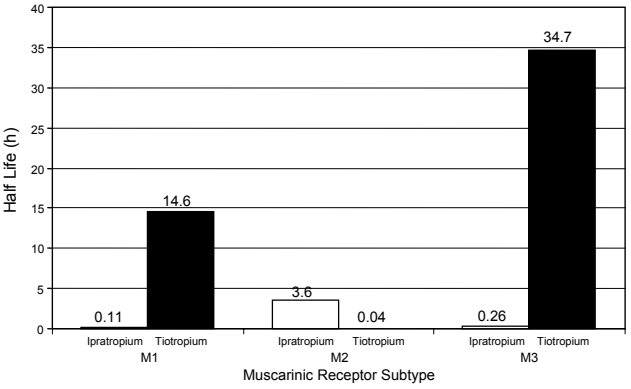

Fig. 7. Muscarinic receptor complex half-life of ipratropium bromide and tiotropium bromide. Although tiotropium binds to all 3 muscarinic receptors, it dissociates much faster from the M_2 receptors, resulting in a more selective antagonist action on the M_1 and M_3 receptors. (Data from References 2 and 4.)

After the first dose, mean time to onset of effect is 30 min, and the mean time to peak effect is about 3 h. Subsequent doses increase efficacy, until maximum effect is obtained after 1 week.[2,33,35–40] Since the M_2 receptor inhibits further release of acetylcholine, blocking of the receptor may increase acetylcholine release and offset the bronchodilatory effect known to ipratropium and oxitropium.[35] Tiotropium gives a prolonged, dose-dependent protection against inhaled methacholine challenge.[36]

Tiotropium is available in a powder form, in a capsule used with the Spiriva HandiHaler. The capsule contains 18 μg of tiotropium (equivalent to 22.5 μg of tiotropium bromide monohydrate). A "soft mist" form delivered by the Respimat device is also available in some countries. Combinations of tiotropium and other bronchodilator agents are not currently available. The recommended dose is 18 μg once daily. Following powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggested that the fraction that reaches the lung is highly bioavailable.[33] Since tiotropium has a duration of longer than 24 h, it can considerably improve drug adherence.[41,42]

Table 1 summarizes the doses and routes of the anticholinergic agents.

Clinical Use of Anticholinergics

Lung function has been the major outcome measure in most clinical trials of response to anticholinergic bronchodilators. Lung function variables include mean pre-dose FEV_1 and forced vital capacity (FVC), mean peak change in FEV_1, FVC from the test-day baseline, and mean area under the FEV_1 and FVC curves above test-day baseline FEV_1 and FVC. Other relevant outcomes include health-related quality of life scores (HRQL), dyspnea scores, exercise capacity, adverse effects, use of other medications, hospital admission rate, and exacerbations.

Stable COPD

Eleven randomized controlled trials, which included almost 4,000 patients with stable COPD, compared at least 4 weeks of treatment with ipratropium bromide alone or in combination with SABAs.[43–51] Ipratropium showed a small benefit over SABAs on lung function outcomes, improvement in HRQL, and reduction in the requirement for oral steroids.[52] There were no clinically important acute or long-term electrocardiographic changes and no significantly different changes in mean blood pressure and pulse rate during the first 3 h after treatment.[53] Similar data on hemodynamic effects were reported by 4 different trials in the analysis of combination therapy versus SABA therapy alone over 85 days of evaluation.[53]

Table 2 summarizes the results of clinical trials that compared ipratropium bromide to SABA agents, via nebulizer or MDI. Table 3 compares data on ipratropium plus SABA versus SABA monotherapy.

In a recent meta-analysis by Apleton et al,[54] a total of 7 studies, with 2,652 patients, compared ipratropium bromide monotherapy to salmeterol-plus-ipratropium to formoterol alone.[55–61] Although salmeterol[55–58] and formoterol[59,60] were associated with a significantly greater change of morning peak expiratory flow (PEF) (weighted mean difference [WMD] −10.96, 95% confidence interval [CI] 16.09 to 5.83) and FEV_1 (WMD −0.06, 95% CI −0.11 to 0.0), there were no significant differences in HRQL (WMD −0.58, 95% CI −3.50 to 2.35), odds ratio (OR) of exacerbations (OR 1.23, 95% CI 0.84 to 1.80), exercise capacity (WMD 10.47, 95% CI −1.24 to 22.19), rescue bronchodilator use (WMD 0.34, 95% CI −0.20 to 0.88), adverse effects (OR 1.08, 95% CI 0.75 to 1.57) or any of the symptom scores, compared to monotherapy with ipratropium bromide.

Compared to long-acting β_2 adrenergic agents (LABAs) alone, the combination of ipratropium bromide plus LABA significantly improved post-bronchodilator lung function

Table 1. Inhaled Anticholinergic Agents

Generic Name	Trade Name	Delivery Method and Dose	Onset (min)	Peak (h)	Duration (h)
Ipratropium bromide	Atrovent	MDI: 18 μg/puff, 36 μg 4 times a day SVN: 200 μg/mL, 500 μg 3 or 4 times a day	15	1–2	3–6
Oxitropium bromide	Oxivent*	MDI: 100 μg/puff, 200 μg 2 or 3 times a day	15	1–1.5	5–8
Tiotropium bromide	Spiriva	DPI: 18 μg/capsule, 18 μg/d	30	3	24

*Available outside the United States
MDI = metered dose inhaler
SVN = small-volume nebulizer
DPI = dry powder inhaler

Table 2. Summary of Outcomes With Ipratropium Bromide Versus SABA in Stable COPD

Outcome Measure	Number of Studies	Weighted Mean Difference	95% CI	P	References
Lung Function					
Mean test-day baseline FEV_1	6	0.03 L	0.00 to 0.06	< 0.05	43–47, 49
Mean test-day baseline FVC	6	0.07 L	0.01 to 0.14	< 0.05 > 0.05	43–47 51
Mean peak change from test-day baseline FEV_1 (at 12 weeks)	5	0 L	−0.02 to 0.01	> 0.05	43–47
Mean test-day peak change in FVC	5	−0.01 L	−0.06 to 0.03	> 0.05	43–47
Mean area under the FEV_1 curve above test-day baseline FEV_1	6	0.10 L	−0.02 to 0.22	> 0.05 < 0.05	43–47 51
Mean area under the FVC curve above test-day baseline FVC	5	0.28 L	0.01 to 0.55	> 0.05 < 0.05	44–46, 50 51
Health-Related Quality of Life					
Chronic Respiratory Questionnaire dyspnea score	5	0.16 units	0.09 to 0.23	< 0.05	43–47
Chronic Respiratory Questionnaire fatigue score	5	0.13 units	0.02 to 0.23	< 0.05	43–47
Chronic Respiratory Questionnaire emotion score	5	0.17 units	0.04 to 0.29	< 0.05	43–47
Chronic Respiratory Questionnaire mastery score	5	0.18 units	0.06 to 0.30	< 0.05	43–47
Dyspnea Scores					
Wheezing	5	−0.04	−0.13 to 0.04	< 0.05	43–47
Shortness of breath	5	0.00	−0.09 to 0.09	< 0.05	43–47
Tightness of chest	5	0.01	−0.06 to 0.09	< 0.05	43–47
Coughing	5	−0.08	−0.13 to −0.03	< 0.05 Favored SABA	43–47
Exercise Capacity					
6MWD	1	62.60	−15.85 to 140.85	< 0.05	49
Other Variables					
Medication-related adverse effect	5	OR 0.94	0.64 to 1.39	> 0.05 < 0.05	43, 45, 46, 51 47
Addition/increase systemic (oral) steroids	4	OR 0.52 NNT 15	0.37 to 0.74 12 to 28	< 0.05	43, 45–47

SABA = short-acting β_2 adrenergics
COPD = chronic obstructive pulmonary disease
CI = confidence interval
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
6MWD = 6-min walk distance
OR = odds ratio
NNT = number needed to treat.

Table 3. Summary of Outcomes With Ipratropium Bromide Plus SABA Versus SABA Alone in Stable COPD

Outcome Measure	Number of Studies	Weighted Mean Difference	95% CI	p	References
Lung Function					
Mean test-day baseline FEV_1	6	0.00 L	−0.03 to 0.03	< 0.05 > 0.05	44–46, 50, 51 52
Peak change from test-day baseline FEV_1 (3 months of therapy)	5	0.07 L	0.05 to 0.08	< 0.05	44–46, 50, 51
Area under the FEV_1 curve above test-day baseline	5	0.37 L/h	0.24 to 0.49	< 0.05	44–46, 50, 51
Mean test-day baseline FVC	5	0.05 L	−0.21 to 0.12	> 0.05	44–46, 50, 51
Mean area under the FVC curve above test-day baseline FVC	5	0.77 L/h	0.50 to 1.05	< 0.05	44–46, 50, 51
Mean test-day peak change in FVC	5	0.12 L	0.08 to 0.17	< 0.05	44–46, 50, 51
Health-Related Quality of Life					
Chronic Respiratory Questionnaire dyspnea score	4	0.01 units	−0.06 to 0.08	> 0.05	44–46, 50, 51
Chronic Respiratory Questionnaire fatigue score	4	0.02 units	−0.09 to 0.13	> 0.05	44–46, 50, 51
Chronic Respiratory Questionnaire emotion score	4	0.02 units	−0.12 to 0.16	> 0.05	44–46, 50, 51
Chronic Respiratory Questionnaire mastery score	4	0.03 units	−0.09 to 0.14	> 0.05	44–46, 50, 51
Dyspnea Scores					
Wheezing	6	0.01	−0.07 to 0.08	> 0.05 < 0.05	44–46, 50, 51, 52
Shortness of breath	6	0.04	−0.05 to 0.13	> 0.05 < 0.05	44–46, 50, 51, 52
Tightness of chest	5	−0.02	−0.09 to 0.6	> 0.05	44–46, 50, 51
Coughing	5	0.00	−0.05 to 0.05	> 0.05	44–46, 50, 51
Other Variables					
Medication-related adverse effect	5	OR 1.16	0.86 to 1.57	> 0.05	44–46, 50, 51
Number of subjects who experienced exacerbations	1	OR 0.42	0.18 to 0.96	< 0.05	52
Addition/increase systemic (oral) steroids	1	OR 0.42	0.18 to 0.96	< 0.05	54

SABA = short-acting β_2 adrenergics
COPD = chronic obstructive pulmonary disease
CI = confidence interval
FEV_1 = forced expiratory volume in the first second
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6 MWD = 6-min walk distance
OR = odds ratio.

(FEV_1 area-under-the-curve WMD 1.38 L, 95% CI 0.98 to 1.77), supplemental SABA use (WMD −0.67 puffs/d, 95% CI −1.11 to −0.23), and HRQL measured with the Chronic Respiratory Questionnaire (WMD 0.4, 95% CI 0.1 to 0.7) and St George's Respiratory Questionnaire (SGRQ) (WMD 2, 95% CI −3.49 to 0.52).[57,58,61]

Yildiz et al evaluated 12 weeks of either ipratropium plus theophylline, or formoterol plus theophylline, or ipratropium plus formoterol. The combination therapy significantly affected quality of life, measured with the Turkish version of SGRQ,[62] but there was no significant difference in the mean change in symptom scores (WMD −1.89, 95% CI −11.11 to 7.34), the number of subjects who had an exacerbation, or the rate of adverse effects (OR 1.08, 95% CI 0.83 to 1.4).

Barr et al recently reported a meta-analysis of 10 randomized controlled trials, which included 8,002 patients.[63] One of the included trials compared tiotropium with ipratropium,[42] one compared tiotropium with a LABA (salmeterol),[64] 7 compared tiotropium with placebo,[41,65–70] and one compared tiotropium with placebo and with salmeterol.[65] The mean duration of the trials was 7 months. The severity of COPD was generally moderate to severe, 38%–80% of the patients were taking ipratropium at enrollment, 32%–50% were taking LABA, and 42%–80% were taking inhaled corticosteroids. In one study, tiotropium (18 μg once daily) resulted in statistically greater increases in trough and peak FEV_1 and area-under-the-curve than either ipratropium (36 μg 4 times daily) or salmeterol (42 μg twice daily).[65] In another study, tiotropium was associated with increases in FEV_1 and FVC from baseline up to a year, compared with placebo, ipratropium, and LABA. In another study, the rate of FEV_1 decline was significantly slower with tiotropium than with placebo and ipratropium (WMD 30 mL, 95% CI 7 to 53).[42]

It has been suggested that tiotropium therapy increases endurance by reducing hyperinflation.[71] Tiotropium significantly reduces the odds of a COPD exacerbation (OR 0.73, 95% CI 0.66 to 081), compared with placebo, and compared with ipratropium. Though the incidence of ex-

acerbations was lower with tiotropium than with salmeterol, this difference was smaller and not statistically significant. Tiotropium was not associated with statistically significant differences in cardiovascular mortality (OR 1.17, 95% CI 0.54 to 2.51), cancer mortality (0.77, 95% CI 0.28 to 2.12), or mortality from other causes (OR 2.77, 95% CI 0.81 to 9.45). No significant differences were found in all-cause mortality between tiotropium and placebo, ipratropium, or salmeterol (OR 0.96, 95% CI 0.63 to 1.47). The mean change in SGRQ over the course of the trials was larger with tiotropium than with placebo (WMD −3.3, 95% CI −4.6 to −2.0) or with ipratropium (WMD −3.3, 95% CI −5.6 to −1.0). A smaller and nonsignificant difference was observed when compared with salmeterol (WMD −1.4, 95% CI −3.2 to 0.4).[63] A review by Rodrigo and Nannini of 13 randomized controlled trials reported similar findings.[72]

A recent randomized controlled trial analyzed outcomes in 50 patients with COPD who received either tiotropium plus pulmonary rehabilitation program or tiotropium alone over a 6-week period. Tiotropium was associated with significant improvement in 6-min walk distance, dyspnea, PEF, and Chronic Respiratory Questionnaire scores. Although the improvement was sustained at 3-month follow-up, the 6-week pulmonary rehabilitation program did not provide any additional significant benefit in patients who were already receiving tiotropium bromide.[73]

COPD Exacerbation

COPD exacerbation is caused by increased mucus production, inflammation, and bronchoconstriction, and is characterized by worsening dyspnea and increased sputum or sputum purulence. It may be accompanied by fever, chest discomfort, and other constitutional symptoms. Treatment typically requires antibiotics, corticosteroids, and bronchodilators. The most common outcome reported in the clinical trials included in this review was FEV_1. Most studies have described changes in FEV_1 24 h after initiation of treatment. Short-term (90 min) FEV_1 changes were reported in only 2 studies.[74,75] Other important outcome measures have been arterial blood gas values, symptom scores, quality-of-life assessments, endurance tests, and health care resource utilization.

Anticholinergic agents and SABAs, either alone or in combination, are the mainstay of treatment for COPD exacerbation. However, comparative trials of anticholinergics alone or in combination with SABAs for COPD exacerbation found no additional bronchodilation over SABA alone.[76,77] Nevertheless, current clinical guidelines recommend the addition of an anticholinergic if prompt response to a SABA does not occur.[78,79] Since COPD exacerbation is sometimes life-threatening, initiation of treatment with a combination of anticholinergic plus a SABA seems appropriate and does not significantly increase cost or the occurrence of adverse effects. Four randomized clinical trials have compared the short-term effects of ipratropium bromide versus a SABA.[80–83] FEV_1 changes at 90 min showed no significant difference between patients treated with SABA and ipratropium bromide, or when combined (WMD 0.0 L, 95% CI −0.19 to 0.19). In 5 different studies there was no significant additional increase in FEV_1 after adding ipratropium bromide to SABA (WMD 0.02 L, 95% CI −0.08 to 0.12).[74–76,84,85] Evaluation after 24 h with combination therapy showed similar results (WMD 0.05 L, 95% CI −0.14 to 0.05). The data on changes in blood gas values are limited to 2 studies, which found no significant changes in either short-term or long-term P_{aO_2},[80,82] whereas 2 other studies reported significant changes in P_{aO_2} in patients who received ipratropium, versus SABA.[74,75]

Although tiotropium is associated with fewer exacerbations,[63] it has not been evaluated in randomized clinical trials for treatment of COPD exacerbation. Therefore, it should not be used as monotherapy for COPD exacerbation, and it is recommended that patients continue tiotropium if already receiving it.

Adult Asthma

SABAs have been considered the primary bronchodilators for the treatment of asthma.[86–88] Addition of other types of bronchodilators has typically been reserved for refractory asthma.[89] Though anticholinergics are often prescribed in the symptomatic treatment of chronic stable asthma,[6,7] they have been believed to provide less bronchodilation than SABAs.[90,91] There appears to be variability in anticholinergic response among asthmatics, probably related to the amount of parasympathetic generating symptoms in various subgroups. The patients most likely to respond to anticholinergic agents are older,[90–93] intolerant of β_2 adrenergic agents,[94] or have nocturnal[23] or intrinsic asthma.[95–97]

Consideration has been given to the adverse effects associated with β_2 adrenergic agents and anticholinergics. Though anticholinergics have relatively few adverse effects, β_2 adrenergic agents may increase heart rate, bronchial activity, and mortality.[98,99] Some studies have suggested that the adverse effects of SABAs occur in patients who have a genetic polymorphism that results in homozygosity for arginine (arg/arg) rather than glycine (gly/gly) at amino acid residue 16 of the β_2 adrenergic receptor.[100–102] Patients with this polymorphism might benefit from as-needed ipratropium bromide instead of albuterol as rescue therapy.[103]

Since the risk/benefit ratio of inhaled corticosteroids is lower at high doses in asthma,[89,104] inhaled anticholinergics have also been considered a reasonable alternative

in conjunction with moderate amounts of inhaled corticosteroids.[89]

Although a recent review of the Cochrane Airways Group asthma and wheeze database expressed concern about the poor quality of the methods in the clinical trials reported, anticholinergic agents (in comparison with placebo) significantly decreased symptom scores, by 15%, particularly daytime dyspnea (WMD −0.09, 95% CI −0.14 to −0.04).[105] Despite the statistical significance, the 7% change in daily PEF over placebo does not correspond to comparable clinical importance (morning PEF WMD 14.38 L/min, 95% CI 7.69 to 21.08). In the same meta-analysis,[105] 7 studies included ipratropium bromide and 8 studies included oxitropium bromide. The primary outcome measure was daytime and nighttime asthma symptom scores. Other outcomes included daily PEF, bronchodilator use for symptom relief, HRQL, asthma exacerbation rate, hospital admissions, and adverse events. A total of 9 trials compared the combination of anticholinergic plus SABA to SABA alone.[106–113] There was no significant difference in daily symptom scores between combination therapy and SABA monotherapy, regardless of the trial design. The results were similar for lung function measurements, patient preference, drug-related withdrawal, number of patients with exacerbations, and adverse effects.[114] Unfortunately, since these trials had important differences in design, pooled data are not presented in a table format.

Gosens et al[115] found that treatment with inhaled tiotropium bromide inhibits the increase in airway smooth-muscle mass, myosin expression, and contractility in allergic asthma. That suggests a prominent role for acetylcholine in allergen-induced airway smooth-muscle remodeling in vivo.[116,117] It has been suggested that anticholinergic agents could help prevent airway remodeling in asthmatic airways. Furthermore, airway response to anticholinergic and β_2 adrenergic agents is different between asthma and COPD. Inflammation in COPD is characterized by increased numbers of CD8+ T lymphocytes, whereas asthma is due in great part to CD4+ T lymphocytes.[118]

Pediatric Asthma

The initial treatment of pediatric asthma exacerbation focuses on inhaled bronchodilators to relieve bronchospasm.[94,119–122] If the asthma is refractory or incompletely responsive to bronchodilators, glucocorticoids are typically added.[123,124] Though SABAs are considered the most effective bronchodilators,[125,126] the addition of anticholinergics may particularly relieve airway obstruction associated with increased cholinergic bronchomotor tone, mucosal edema, and secretions.[127–129] The role of ipratropium seems to be similar to that in adults, but studies with adequate statistical power or long duration in pediatric patients are lacking.[122,130] The recently revised British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network guidelines[131] no longer recommend anticholinergics for chronic asthma in children.

Some of the studies included in this review compared anticholinergic to placebo, and the combination of anticholinergic plus SABA to SABA alone. Thirteen studies, which included over 1,500 patients, ages 24 months to 17 years, are summarized. Most children received systemic corticosteroids as a co-intervention. The treatment protocols differed among the trials. Two or 3 doses (250–500 μg) of ipratropium bromide were administered with 2–7 doses of SABA every 20–60 min. The most frequently reported outcomes were hospital admission rate and lung function measurements.[132] Clinical scores were used for the younger patients who were unable to perform spirometry.[133–135]

Four trials compared the efficacy of adding a single 250-μg dose of ipratropium bromide to SABA. There was no difference in hospital admission (relative risk [RR] 0.93, 95% CI 0.65 to 1.32). Addition of the anticholinergic increased FEV_1 by 16% at 60 min (standard median difference [SMD] 0.57 L, 95% CI 0.21 to 0.93) and by 17.5% at 120 min (SMD 0.53, 95% CI 0.17 to 0.90). There were no significant group differences in clinical score at 60 min (WMD −0.06, 95% CI −0.26 to 0.14) or 120 min (WMD 0.13, 95% CI −0.22 to 0.48), in oxygen saturation at 60 min (RR 0.75, 95% CI 0.55 to 1.01) or 120 min (RR 1.10, 95% CI 0.76 to 1.60), in the need for additional inhalations after the standard protocol (RR 1.05, 95% CI 0.78 to 1.41), or in relapse to additional care (RR 1.17, 95% CI 0.56 to 2.45).[132,136–139]

The effect of multiple doses of combined ipratropium bromide plus SABA in a fixed protocol was examined in 7 trials, which included 1,045 children.[135,138,140–144] The combination therapy was associated with a 25% reduction in hospital admissions (RR 0.75, 95% CI 0.62 to 0.89).[144] The number-needed-to-treat with a multiple-dose fixed protocol to prevent a single admission was 12 (95% CI 8 to 32). Baseline severity greatly influenced the reduction in hospital admission attributed to anticholinergics. A significant reduction was observed only in children with severe exacerbations (RR 0.71, 95% CI 0.58 to 0.89). The number-needed-to-treat with anticholinergics to prevent one admission among patients with severe exacerbation was 7 (95% CI 5 to 20). Four trials reported a significant change in percent-of-predicted FEV_1 with anticholinergics (WMD 9.68, 95% CI 5.70 to 13.68) 60 min after the last inhalation, which is a significant reduction in the need for additional inhalations after the standard protocol (RR 0.81, 95% CI 0.66 to 0.99).[133,140,142,145]

The most recent meta-analysis conducted by the Cochrane Airways Group, after an updated search conducted in February 2006, included only 8 clinical trials, which

included 194 pediatric patients.[146] All the studies were described as randomized and double-blind. Five of the 8 studies were crossover studies,[147–151] and the 3 remaining studies were parallel studies.[152–154] Similar to the clinical trials in asthmatic adults on the effect of anticholinergics, the results were questioned by the reviewers. In the specific case of the pediatric trials, it is probably due to the lack of uniformity in the patients' asthma severity, the intensity of their anticholinergic use, and, more importantly, the study power.[134,140,141,145] Between inhaled anticholinergic therapy and placebo there was no statistically significant difference in morning PEF (SMD 0.05, 95% CI −0.31 to 0.40), night PEF (SMD 0.02, 95% CI −0.33 to 0.38), hospital admissions (OR 0.14, 95% CI 0.02 to 1.25), or need for additional oral steroids (OR 0.79, 95% CI 0.21 to 3.03). The authors also reported that although symptom scores were significantly lower with ipratropium bromide than with placebo, there was no significant difference in the percentage of symptom-free nights or days.

The addition of a single dose of anticholinergic to SABA did not reduce hospital admission (RR 0.93, 95% CI 0.65 to 1.32). However, significant differences in lung function, which supports the combination of anticholinergic and SABA, were observed 60 min (SMD 0.57, 95% CI 0.21 to 0.93) and 120 min (SMD 0.53, 95% CI 0.17 to 0.90) after the dose of anticholinergic. When multiple doses of anticholinergic were added to the ongoing treatment with SABAs, the risk of hospital admission was reduced by 25% in children with predominantly moderate and severe exacerbations (RR 0.75, 95% CI 0.62 to 0.89).[144] Twelve (95% CI 8 to 32) children would need to be treated to avoid one admission. When restricting this strategy to children with severe exacerbations, 7 (95% CI 5 to 20) children need to be treated to avoid an admission. At 60 min after the last anticholinergic inhalation, the change in percent-of-predicted FEV_1 favored anticholinergic use (WMD 9.68, 95% CI 5.70 to 13.68). In the 2 studies in which anticholinergics were systematically added to every SABA inhalation, irrespective of asthma severity, no group differences were observed for the few available outcomes. The addition of anticholinergics to SABAs have not unanimously demonstrated significant benefit from the long-term use of combination therapy versus SABA alone in pediatric patients with asthma.[146]

Treatment of airway obstruction in infancy and early childhood remains controversial because it does not improve dramatically after bronchodilator therapy. Several studies have clearly demonstrated that the smooth-muscle airway receptors and the airways of children less than 2 years of age respond to aerosolized medications. Therefore, other variables, such as airway geometry, excessive airways secretions, and mucosal edema, may be largely responsible for the airways obstruction and the individual response to bronchodilators in these young wheezing patients. Most wheezing episodes in infancy are induced by viral infections. Although anticholinergics and SABAs are frequently administered to infants and young children with viral-induced wheeze, there is relatively little evidence to support routine use of anticholinergics or combination therapy for symptomatic relief of airway obstruction.

Six randomized clinical trials in infants have compared the combination of ipratropium bromide plus SABA to SABA alone.[155–160] The outcome measures included symptom scores and parental perception at home, requirement for additional inhaled therapy, respiratory rate, oxygenation in the emergency department, duration of hospital stay, symptom scores, and oxygenation in the hospital setting. The use of ipratropium was not associated with a significant difference in the relief of symptoms (OR 0.60, 95% CI 0.19 to 1.88).[155] In one study, combination therapy (compared with SABA alone) in the emergency department resulted in significantly fewer patients requiring further therapy 45 min after initial therapy (OR 0.22, 95% CI 0.08 to 0.61),[156] but Schuh et al[157] found no difference between those same 2 interventions. There was also no difference in the change in respiratory rate or improvement in oxygen saturation.[157] When comparing ipratropium versus placebo, there was no significant difference in the number of days hospitalized (WMD −0.4, 95% CI −1.4 to 0.61).[158] The addition of ipratropium to SABA did not significantly affect days of hospitalization, compared with SABA alone (WMD −0.4, 95% CI −1.41 to 0.61).[158]

Adverse Effects

The actions and adverse effects of each of the anticholinergic agents are very similar. Since they are very poorly absorbed, all of the currently approved inhaled anticholinergic agents have a very wide therapeutic margin and are very well tolerated. Ipratropium, oxitropium, and tiotropium bromide have been studied for the well known adverse effects of atropine on pulmonary mucociliary clearance, increased intraocular pressure, and urinary outflow.[161,162] These agents do not alter either mucociliary clearance or the volume or viscosity of respiratory secretions. If any of these agents makes inadvertent contact with the eye, they can cause pupillary dilation and blurred vision. Several case reports have correlated the use of a loose-fitting mask while administering ipratropium bromide to anisocoria due to unilateral mydriasis (Fig. 8).[163–179]

Acute anisocoria is clinically relevant because its workup is costly and sometimes invasive, and may include computed tomography, magnetic resonance imaging, electroencephalography, lumbar puncture, and neurologic consultations to rule out serious neurological conditions.[180]

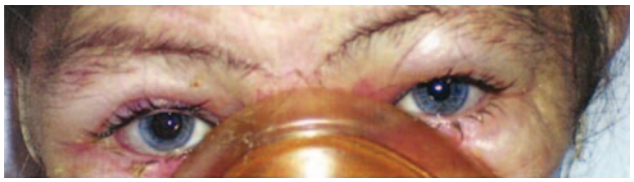

Fig. 8. If the conjunctiva is inadvertently exposed to aerosolized anticholinergics (from a nebulizer, metered-dose inhaler, or powder inhaler) the patient may develop anisocoria. The left pupil is normal and the right pupil is dilated (mydriatic). (From Reference 163, with permission.)

This effect on the eye is particularly important in the case of tiotropium, because its prolonged duration of action may precipitate acute glaucoma.

Dryness of the mouth is a common adverse effect of all these agents,[76,181] but it is rarely reason enough for the patient to discontinue therapy. Bad taste and a brief coughing spell are occasional complaints. Paradoxical bronchospasm is a rare idiosyncratic effect that occurs in about 0.3% of patients.[80,182,183] When comparing individual adverse effects of anticholinergics with placebo, there is not a statistically significant difference between the groups (OR 1.87, 95% CI 0.51 to 6.81).[184–187]

Though 2 studies reported that, at recommended doses, ipratropium bromide does not produce clinically important changes in pulse rate or blood pressure,[77,84,181] the Lung Health Study showed that after 5 years of follow-up, ipratropium was associated with hospitalizations for supraventricular tachycardia, and with overall cardiovascular disease morbidity and mortality.[188]

Studies with adequate statistical power in children with asthma are lacking. However, adult doses have been used without adverse effects in children down to 4 years of age.[122,130]

A recent meta-analysis by Barr et al[63] reported that dry mouth was significantly more common with tiotropium than with placebo, ipratropium, or salmeterol, and urinary tract infection was significantly more common than with placebo or ipratropium. Consistent but not statistically significant increases were observed for systemic anticholinergic adverse events (constipation and urinary retention). The frequency of arrhythmias was significantly higher with tiotropium than with placebo (OR 2.33, 95% CI 1.11 to 4.88). By contrast, in a pooled analysis of placebo-controlled trials of patients who received tiotropium, Kesten et al found that cardiovascular mortality (RR 0.57, 95% CI 0.26 to 1.26), cardiac arrest (RR 0.90, 95% CI 0.26 to 3.15), and myocardial infarction (RR 0.74, 95% CI 0.26 to 2.07) did not occur more frequently than among patients who received placebo. The relative risk for serious tachycardia was 1.16 (95% CI 0.33 to 4.03). There was no apparent excess of other arrhythmias classified as serious (RR 0.92, 95% CI 0.27 to 3.14) or left-heart failure, compared with patients who received placebo (RR 0.46, 95% CI 0.21 to 1.00).[189]

Since tiotropium may worsen signs and symptoms associated with prostatic hyperplasia, narrow-angle glaucoma, or bladder-neck obstruction, it should be used with caution in patients with any of these conditions. Patients with moderate-to-severe renal impairment (creatinine clearance of $\leq$50 mL/min) should be closely monitored, because tiotropium is predominantly excreted by the kidneys through active secretion.[190] With the exception of dry mouth, the tolerability profile of tiotropium seems similar to that of placebo, ipratropium, or salmeterol. Other reactions reported in individual patients included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.[190]

Pharmacoeconomics

Recent estimates show that COPD consumes $18 billion in direct health care costs.[191] The cost of ipratropium bromide and its combination with SABAs is higher than SABAs alone. Friedman et al[192] conducted pharmacoeconomic evaluations of health care resource utilization, with data from 2 clinical trials,[43,44] to determine the costs associated with COPD exacerbations. Their analysis showed that combination therapy was associated with a 20% reduction in COPD exacerbations, a 44% reduction in hospitalizations, and a 50% reduction in hospital days, compared to albuterol therapy. The cost of hospital admissions accounted for 48% of the total direct medical costs in that study. The duration of hospital stay (and cost per medication per patient) was 103 days ($269) with albuterol, 20 days ($156) with ipratropium, and 46 days ($197) with combination therapy. Although albuterol therapy was more expensive, there was no significant difference in the costs between the ipratropium and combination-therapy groups. The mean difference in the cost of hospitalization (resulting from all causes, including COPD) between treatment groups was $1,056 (95% CI −2,078 to 34) and the difference in total health care costs (excluding study drug acquisition cost) was $1,043 (95% CI −2,136 to 48) in favor of ipratropium.

Combination therapy with anticholinergics plus LABAs is more expensive. In Australia, for example, the predicted government cost of supplying salmeterol and ipratropium MDIs is respectively 8-fold and 7-fold higher than the cost of one month's albuterol supply.[193] This analysis highlights the need to identify patients who benefit from this combination, in light of sometimes a very marginal clinical importance.

Oostenbrink et al conducted a one-year cost-effectiveness analysis of the substitution of tiotropium for ipratropium in patients with COPD. Tiotropium was associated with significantly better SGRQ score (ipratropium 34.6%

vs tiotropium 51.2%). Hospital admissions (46%), hospital days (42%), and unscheduled visits to health care providers (36%) were significantly fewer with tiotropium. The mean annual health care cost, including the acquisition cost of the study drugs, was €1,721 in the tiotropium group and €1,541 in the ipratropium group (difference €180). Incremental cost-effectiveness ratios were €667 per exacerbation avoided and €1,084 per patient with a relevant improvement on the SGRQ. Substituting tiotropium for ipratropium in that trial resulted in improved health outcomes but was associated with higher acquisition costs (€180, $233) per patient per year.[194] A similar cost-effective analysis in Spain revealed that tiotropium was more cost-effective than ipratropium and, to a lesser extent, than salmeterol, as measured by objective clinical variables.[195]

Summary and Recommendations

Potential limitations inherent to review articles and meta-analyses include double-counting of patients from overlapping publications, publication bias, reporting bias, and selection bias from differential inclusion of available trials. This review has tried to avoid selection bias by using the rigorous criteria exemplified in Cochrane reviews and selected meta-analyses before making the following recommendations:

I. Given the available evidence, this review does not support the routine first-line use of ipratropium alone or the combination, over initial short-acting β_2 agonist therapy alone, for patients with symptomatic COPD, over a range of severities.[53]

Available data indicate that long-term treatment with ipratropium bromide provides no significant improvements in post-bronchodilator FEV_1, compared with SABA therapy alone. The small increase in pre-bronchodilator FVC and the post-bronchodilator increase in FVC area-under-the-curve suggest that the lung-function benefits of ipratropium over SABA are small. Combination of ipratropium with SABA offers statistically and clinically important benefits over placebo and SABA alone in post-bronchodilator lung-function outcomes, which demonstrates a potential role for combination therapy in the maintenance therapy of patients with stable COPD of all severities. Except for the report by Campbell et al,[52] the impact of therapy with ipratropium alone or in combination with SABA on the reduction of symptom scores and HRQL outcomes seems to be in discordance with the positive responses in lung function. Even the subjects on combination therapy who experienced significant lung function benefits experienced no significant HRQL improvements (measured with the Chronic Respiratory Questionnaire), which suggests no subjective benefit from adding the anticholinergic agent. The significant differences in favor of monotherapy with ipratropium in regards to the requirement of oral steroids (number-needed-to-treat 15) and the number of adverse effects, compared with SABA therapy, suggest the positive impact of preventing exacerbations or deterioration of health status in patients with COPD.[47,196]

Though existing evidence recommends inhaled bronchodilators as first-line therapy, the BTS and European Respiratory Society do not recommend preferential use of anticholinergic agents over β_2 adrenergic agents as initial therapy.[78,197] Nevertheless, the Global Initiative for Chronic Obstructive Pulmonary Disease report (updated November 2006)[79] recommends the use of the longer-acting anticholinergic tiotropium for moderate-to-very-severe COPD.

Only one study was found that compared 2 different combinations of anticholinergic plus LABA head-to-head.[198] In that clinical trial, D'Urzo et al compared the combination ipratropium/formoterol with ipratropium/albuterol over a period of 3 weeks at the recommended daily dose for each β_2 adrenergic agent. Though the combination anticholinergic plus LABA was typically associated with a statistically significant increase in mean pre-bronchodilator PEF and FEV_1 values, post-bronchodilator FEV_1 change on the order of 0.15 L was shown to be significantly increased with the formoterol combination. These marginal clinical benefits need to be weighed against the additional costs of adding a LABA to anticholinergics.

It appears that the level of dynamic lung hyperinflation, measured via inspiratory capacity, has better correlation with exertional dyspnea in patients with severe COPD[199–202] than do expiratory flow measurements.[201] Future studies of bronchodilator therapy in patients with COPD require the incorporation of lung hyperinflation in spirometric assessments.

II. Although evidence from the trials in the review indicates that tiotropium significantly reduces exacerbations and related hospitalizations and improves quality of life and symptoms in patients with moderately severe COPD, there is still not enough long-term evidence to recommend tiotropium across all severities of COPD.[63]

Available data regarding use of tiotropium for stable COPD suggest a significant reduction of COPD exacerbations and related hospitalizations, as well as improved HRQL, compared with placebo or ipratropium. Increases in FEV_1 and FVC from baseline seem significantly larger with tiotropium than with placebo, ipratropium, or LABA. A recent clinical trial by Aaron et al concluded that addition of fluticasone/salmeterol to tiotropium therapy did not statistically influence the COPD exacerbation rate but did improve lung function, quality of life, and hospitalization rate in patients with moderate-to-severe COPD.[203] Although the decline in FEV_1 from steady state was slower with tiotropium than with placebo or ipratropium, no data are available for the comparison with LABAs. Prospective evaluation is required to study the possibility that tiotropium may reduce the long-term decline in lung function.[204]

Tiotropium seems to be safe and cost-effective compared with ipratropium.

III. Ipratropium bromide provides bronchodilation similar to SABAs during COPD exacerbations.[77]

The few trials that have compared ipratropium bromide to SABAs in COPD exacerbation suggest that ipratropium bromide results in short-term improvement of FEV_1 and PEF, at least equivalent to SABAs. Combined treatment appears to be no more effective than the use of either as a single agent.

IV. Tiotropium bromide should not be used as monotherapy for COPD exacerbation, because that use has not been evaluated in randomized clinical trials.[63]

Although tiotropium is associated with fewer exacerbations and related hospitalizations,[63] it has not been evaluated for treating COPD exacerbation. Since it is a long-acting anticholinergic with an onset of 30 min (versus ipratropium 15 min) and peak action at 3 h, its use as a quick-relief agent may have the same limitations and precautions as LABAs. During COPD exacerbations, patients who are already using tiotropium should continue using it.

V. The existing evidence does not support the routine introduction of anticholinergics as part of add-on treatment in adult patients whose asthma is not well controlled on standard therapies.[105]

The primary goals in treating asthma are preventing long-term damage due to airway remodeling, managing airflow obstruction, and minimizing mortality. Pharmacologic intervention is aimed at the control of symptoms, including nocturnal symptoms, preventing exacerbations, and achieving the best possible lung function, with minimum adverse effects.[131] Although anticholinergics are frequently used in patients with asthma,[6,7] the evidence for their use remains limited and less clearly defined. The 2005 revision of the BTS guidelines includes anticholinergics as one of the options for short-term bronchodilator relief at Step 1 in mild intermittent asthma, and in managing acute severe asthma. However, anticholinergics receive no mention as regular add-on treatment for use in combination with inhaled steroids and LABAs.

Though the present review does not support the routine addition of short-acting anticholinergics in adult patients with asthma, some data suggest possible benefit from anticholinergics in a certain subset of patients, but this needs formal assessment in long-term studies. The role of long-acting anticholinergics in chronic asthma and asthma attacks has yet to be established.

VI. Although there are small but beneficial reports in favor of anticholinergic therapy, there are insufficient data to support its use in routine maintenance therapy in children with chronic asthma.[146]

The number of clinical trials suitable for analysis was small, included very limited numbers of patients with different degrees of asthma severity, and the studies were not easily combined because of differences in their methods.[205] Despite those limitations, anticholinergics are associated with better symptom scores than is placebo. The clinical importance of the 7% higher PEF (over placebo) is questionable. There were no significant differences between anticholinergic and placebo in use of rescue medication, patient preference, or adverse effects. There were no significant differences between ipratropium monotherapy and ipratropium plus SABA combination therapy in primary outcome measures, symptom scores, or PEF. However, it may be that the studies were insufficiently powered to detect significant differences.

VII. The available evidence only supports the addition of a multiple-dose protocol with anticholinergics to ongoing SABA therapy for the treatment of school-age children with severe asthma exacerbation.[148]

Previous guidelines from the BTS/Scottish Intercollegiate Guidelines Network[206] recommended ipratropium as regular maintenance therapy in asthmatic children who are already taking high doses of inhaled steroids (Step 4), but they did not recommend them for managing chronic asthma in children under the age of 5 years. The new revision of the BTS/Scottish Intercollegiate Guidelines Network guidelines withdrew anticholinergic agents as maintenance treatment for chronic asthma in children, based on the little evidence to support their use. They also state that lung measurements cannot be reliably used to guide asthma management in children under 5 years of age.[131]

Although there are small but beneficial reports in favor of anticholinergic therapy, there are insufficient data to support its use in routine maintenance therapy for chronic asthma in children.[76] The intensity of the anticholinergic treatment protocol may considerably influence the treatment response in pediatric acute asthma. Important clinical heterogeneity among patients was noticed in studies that evaluated anticholinergics in a single-dose protocol. Though the study by Ducharme and Davis[132] found no significant improvement in lung function in patients with mild-to-moderate asthma, Beck et al[136] and Schuh et al[138] evaluated a similar protocol that added anticholinergics in children with severe asthma, and they found significant FEV_1 improvement 60 min after the combined inhalation. Only the addition of multiple doses of anticholinergic seemed to result in a significant (25%) reduction in hospital admission. Because only a few trials have met standard criteria, a larger, sufficiently powered trial with standardized criteria and methods is needed to determine the clinical benefit of anticholinergics in patients with asthma.

The present review does not include occasional reports of the use of ipratropium in other pediatric diseases such as cystic fibrosis, viral bronchiolitis, exercise-induced asthma, and bronchopulmonary dysplasia. The body of evidence is insufficient to make any recommendation in those conditions.

VIII. The results presented in the present review do not support the uncritical use of anticholinergic for the treatment of wheeze in infancy. Further work is required to clarify its exact role, if any.[207]

Clinical trials have failed to demonstrate reduction in the duration of hospitalization of infants with airways obstruction and associated wheeze when treated with ipratropium versus placebo or in combination with SABA. However, combination therapy is associated with a faster improvement in clinical score at 24 h than is placebo alone. Although the addition of ipratropium to a single dose of SABA in one emergency-setting study reduced the requirement for further therapy, compared to a SABA-only study, no benefit was observed in a second study that compared the same 2 interventions. No references were found about clinical trials to compare ipratropium bromide with or without SABAs to placebo in an emergency setting. In the home setting, 2 months of ipratropium therapy did not significantly reduce the frequency of reported symptoms.

Conclusion

Inhaled anticholinergics are among the most commonly investigated medications in pulmonary medicine. Longer-duration trials with measures of health care utilization will probably capture effects on COPD exacerbation rate. Before suggesting a particular drug combination for managing COPD or asthma airway obstruction, evaluation of agents such as tiotropium in combination with β_2 adrenergic agents is warranted. Evaluation of the additional cost of such combinations will be necessary, because the cost may impact patient adherence to treatment. The advent of newer anticholinergic agents with better selectivity, longer action, and potential to impact the natural course of airway obstruction opens the door to new and exciting horizons in respiratory therapy.

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