The Bronchodilators

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The cardinal manifestations of the major obstructive lung diseases (emphysema, chronic bronchitis, and asthma) include wheezing, breathlessness, chest tightness, and cough and are generally attributed to variable airflow limitation and associated air trapping. The importance of inflammation in the pathophysiology of asthma has been established, and successful control of all but mild intermittent asthma involves the use of a corticosteroid. Pharmacologic agents that cause bronchodilation by modulation of the autonomic nervous system play a key role in the management of symptoms, even though they do not change the natural history of the obstructive lung diseases. Airflow obstruction in chronic obstructive pulmonary disease (COPD) is structural as well as inflammatory, with inflammation mediated more by neutrophils, which are less responsive to steroids. Because obstruction generally is less reversible in COPD, control of symptoms with bronchodilators is even more important in this progressive obstructive disease. This manual discusses 2 classes of bronchodilators that play a key role in the management of the obstructive lung diseases, the \( \beta \)-adrenergic-receptor agonists and the cholinergic antagonists.

**PHYSIOLOGIC MEDIATORS OF BRONCHIAL TONE**

The baseline tone of the airways is governed by a circadian pattern, with tone being highest during the night and early morning hours. This pattern is surmised to be one of the etiologies of the classic manifestation of predawn worsening of asthmatic symptoms. The human lung is richly innervated by the cholinergic system, with the muscarinic receptor subtype M3 mediating smooth muscle contraction. The parasympathetic system is the primary mediator of basal bronchial tone and probably controls most of the mucus secretion under neural control. In contrast, the direct sympathetic innervation of smooth muscle is limited. \( \beta \)-Receptors residing on bronchial smooth muscle respond primarily to circulating epinephrine, with little direct sympathetic innervation. The primarily \( \beta_2 \) and \( \alpha \)-agonist norepinephrine has no effect on bronchial tone in asthmatics or controls. Obstructive lung diseases for the most part are not disorders of the autonomic control system of the lung, although the general importance of this system is demonstrated by the dramatic efficacy of sympathetic agonists and muscarinic antagonists.

**HISTORICAL PERSPECTIVE**

\( \beta_2 \)-Adrenergic-receptor agonists are the cornerstone bronchodilatory treatment for asthma, despite a lack of high-quality data regarding the long-term safety and efficacy of this class of agents. However, the utility of \( \beta_2 \)-agonists as the primary bronchodilator in asthma (and to less extent in COPD) is supported by the weight of years of clinical experience. In traditional Chinese medicine, the botanical *ma huang* has been used for more than 2000 years for the short-term treatment of respiratory ailments and asthmatic symptoms. The efficacy of this treatment results from the sympathomimetic alkaloids the plant contains.

The history of sympathetic agonism for obstructive lung diseases is an excellent example of empiric use of drugs that directly lead to the elucidation of the physiology of the underlying condition, followed by the development of increasingly precise receptor-directed therapeutics. At the beginning of the twentieth century, the nonselective \( \alpha \)-agonist and \( \beta \)-agonist adrenaline (epinephrine) was administered by the subcutaneous route and later was delivered by aerosolization using a squeeze-bulb. Initially, interest in the sympathomimetic amines focused upon vasoconstrictive rather than bronchodilatory effects, and there were no significant advances in the pulmonary use of this class of agents until the development of isoproterenol in the 1940s. Isoproterenol had specificity for the \( \beta \) receptor, and indeed, characterization of its effects was key in the subsequent identification of the \( \alpha \) and \( \beta \) receptors. Inhaled isoproterenol became the standard-of-care bronchodilator, although its use was complicated by a short duration of action (~1 hour after inhalation) and, more concerning, tachycardia and arrhythmias mediated by \( \beta_1 \) receptors. Metaproterenol, a
The Bronchodilators

**The Bronchodilators**

noncatechol resorcinol-derivative of isoproterenol, was developed in the early 1960s. However, metaproterenol is less selective than other currently available \( \beta_2 \)-selective agonists, which has limited its use.

The modern era of \( \beta_2 \)-selective agonists began with the simultaneous discovery of albuterol and terbutaline. These agents were orally available and had a significantly improved side-effect profile over the nonselective agents. Both compounds are noncatechol derivatives of epinephrine that result from substitutions around the benzene ring. This structure confers resistance to endogenous catechol O-methyltransferase (COMT)–mediated degradation, resulting in the prolonged duration of action seen with these compounds compared to drugs in the catecholamine class. None of the subsequently developed short-acting \( \beta_2 \)-agonists has had a major advantage over albuterol, and this drug continues to be the most commonly used \( \beta_2 \)-agonist worldwide. The nomenclature of these agents in the literature has been complicated by geographic variations (eg, albuterol/salbutamol and isoproterenol/isoprenaline).

The next advance for this class of medications was the development of the longer-acting agents salmeterol and formoterol. Both drugs are also noncatechol derivatives and thus are resistant to COMT degradation. This property along with unique side chain additions to the nitrogen atom confers the long-acting properties of salmeterol and formoterol.

Following a suggestion of antagonism of bronchodilatation by 1 of the 2 chiral forms of albuterol (Salbuterol), the pure \( R \)-albuterol enantiomer (levalbuterol) was developed and has been approved for use in the United States. Although it is more potent than the racemate, a clinical advantage of the enantiomer remains to be demonstrated. Some evidence supports the contention that levalbuterol is superior to the racemic mixture in both efficacy and side-effect profile, but the balance of evidence suggests that levalbuterol does not provide significant clinical advantage over the racemic mixture to justify the increased cost. A reasonable approach is to reserve levalbuterol for those patients with acute asthmatic attack at particular risk of tachycardia-related adverse effects. Salmeterol is also a racemate, with both enantiomers having a similar duration of action and pharmacologic effects.

An enantiomer form of formoterol called arformoterol tartrate was approved in October 2006. At present, it is available only by nebulization. Bronchodilators presently available in the United States are listed in the Table.

**Table. Bronchodilators Available in the United States**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Onset of Action</th>
<th>Peak Activity</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting ( \beta_2 )-agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol MDI or nebulization</td>
<td>Proventil, Ventolin, others</td>
<td>5 min</td>
<td>1−2 hr</td>
<td>4−6 hr</td>
</tr>
<tr>
<td>Albuterol oral</td>
<td>Volmax</td>
<td>30 min</td>
<td>2−3 hr</td>
<td>6 hr</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>Maxair</td>
<td>5 min</td>
<td>30−60 min</td>
<td>5 hr</td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>Alupent</td>
<td>5 min</td>
<td>1 hr</td>
<td>2−4 hr</td>
</tr>
<tr>
<td>Isoproterenol (( \beta_2 )- and ( \beta_2 )-agonist)</td>
<td>Isuprel, Medihaler-Is0</td>
<td>~5 min</td>
<td>Not available</td>
<td>1 hr</td>
</tr>
<tr>
<td>Epinephrine (( \beta_1 ), ( \beta_2 ), and ( \beta_2 )-agonist)</td>
<td>Primatene</td>
<td>5−10 min</td>
<td>20 min</td>
<td>1 hr</td>
</tr>
<tr>
<td><strong>Enantiomer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Xopenex</td>
<td>15 min</td>
<td>1.5 hr</td>
<td>6 hr</td>
</tr>
<tr>
<td><strong>Long-acting ( \beta_2 )-agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent</td>
<td>1 hr</td>
<td>3 hr</td>
<td>12 hr</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradil, Brovana</td>
<td>5 min</td>
<td>1−3 hr</td>
<td>12 hr</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Atrovent</td>
<td>5−15 min</td>
<td>1 hr</td>
<td>3−6 hr</td>
</tr>
<tr>
<td>Tiotropium bromide</td>
<td>Spiriva</td>
<td>15 min</td>
<td>4 hr</td>
<td>36 hr</td>
</tr>
</tbody>
</table>

MDI = metered-dose inhaler.

PHARMACOKINETICS

Short-Acting Agents

Bronchodilation begins 30 minutes after oral administration of albuterol with peak effects at approximately 3 hours and a duration of action up to 6 hours. In contrast, after inhalational delivery most of the short-acting agents demonstrate approximately 70% of maximum bronchodilation within 5 minutes of administration and have a duration of action of approximately 6 hours. Inhalational delivery of albuterol is associated with improved bronchodilation compared to oral or sublingual administration but with significantly less tremor.
Albuterol is primarily biotransformed to a sulfate metabolite. There are no significant race or sex differences in albuterol pharmacokinetics.\textsuperscript{33}

### Long-Acting Agents

As with most inhaled bronchodilators, only 10\% of an inhaled dose of salmeterol reaches the lungs. At standard doses, the inhaled fraction of salmeterol is generally not detectable in the blood, although small amounts of the swallowed drug can be detected in the systemic circulation. Onset of action of bronchodilatation is slower than that of the short-acting agents, with peak bronchodilatation occurring 2 to 3 hours after inhalation. Plasma half-life is 3 to 4 hours, but clinical duration of effects is from 12 to 16 hours.\textsuperscript{14} Duration of action for formoterol is similar to that of salmeterol, although onset of action is more immediate (~5 minutes). Despite this more rapid onset of action, neither formoterol nor salmeterol is indicated for immediate symptomatic relief.

### Dose-Response Characteristics

Aggressive \(\beta_2\)-agonist therapy in asthmatics (ie, albuterol by metered dose inhaler [MDI] with spacer, 4 puffs at 10 min intervals or 2.5 mg by nebulization every 20 min) leads to a more rapid increase in lung function, earlier discharge from the emergency department, and fewer hospitalizations.\textsuperscript{15} A single 7.5 mg nebulized dose of albuterol and three 2.5 mg doses have equivalent clinical efficacy, while the side effects of the large single dose are greater.\textsuperscript{16} In fact, continuous administration of a \(\beta_2\)-agonist by nebulization is as safe as intermittent dosing (3 doses/hour) and is associated with a lower hospitalization rate, especially in those with a more severe presentation.\textsuperscript{17} In the setting of severe acute asthmatic attack, most patients will respond to high-dose \(\beta_2\)-agonists. Those who do not respond within 2 to 3 hours represent a group that will require significant anti-inflammatory therapy and will not benefit from continued high-dose \(\beta_2\)-agonists.\textsuperscript{18}

In acute exacerbations of COPD, an inhaled \(\beta_2\) agonist is the preferred initial therapy,\textsuperscript{19} although in practice it is usually combined with ipratropium. COPD patients generally have more comorbidities than asthmatics and are thus at higher risk of \(\beta_2\)-agonist–mediated adverse reactions, especially hypokalemia and tachycardia. For this reason as well as the lack of convincing evidence of improved outcomes, continuous nebulization of \(\beta_2\)-agonists in COPD patients should be avoided.

### Partial Agonist Effects: Short-Acting and Long-Acting \(\beta_2\)-Agonists in Combination

Partial agonists produce less receptor activation than full agonists at full receptor occupancy. Efficacy is the degree to which a drug activates a receptor. Salmeterol is a partial agonist at the \(\beta_2\) receptor and is estimated to have less than 2\% of the intrinsic efficacy of full agonists epinephrine and isoproterenol.\textsuperscript{20} In contrast, formoterol has 20\% of the efficacy of full agonists. Under conditions of high receptor occupancy, a partial agonist actually acts as a partial antagonist. Theoretically, occupancy of the \(\beta_2\) receptor by a partial agonist is a mechanism by which full bronchodilation may be prevented. Some studies have demonstrated an attenuated response to albuterol after administration of long-acting \(\beta_2\)-agonists.\textsuperscript{21} Other studies have not reproduced this finding\textsuperscript{22,23} although they have been criticized on methodologic grounds.\textsuperscript{24} Some of the attenuation is likely due to receptor subsensitivity, and in practice the clinical significance of differences in intrinsic efficacy between formoterol and salmeterol is unclear.\textsuperscript{25} The regular use of long-acting \(\beta_2\)-agonists does not increase the risk for status asthmaticus,\textsuperscript{26} and a consensus view is that the partial agonism/antagonism effects of long-acting agents on short-acting agents are of modest clinical significance.

### Adverse Effects

The favorable side-effect profile of the \(\beta_2\)-agonists stems in part from the lower density of \(\beta_2\) receptors in skeletal muscle and the heart relative to the bronchial wall.\textsuperscript{27} Relatively weak agonists such as albuterol and salmeterol activate skeletal muscle and heart cells bearing receptors less than the more richly populated bronchial muscular cells.\textsuperscript{28}

### Tremor

Albuterol is generally well tolerated. Tremor is caused by the interaction of slow and fast muscle twitch fibers that is augmented by \(\beta_2\)-agonists.\textsuperscript{29} The propensity for tremor varies among individuals. The onset of tremor generally mirrors onset of bronchodilation and is a dose-dependent response seen in short-acting and long-acting \(\beta_2\)-agonists. The onset of tremor is delayed in salmeterol compared with albuterol and may be less pronounced.\textsuperscript{29} Similarly, as could be expected with a larger systemic exposure, oral albuterol causes more tremor than inhaled albuterol. In general, tremor is noted in the setting of acute administration of inhaled albuterol, although tachyphylaxis will generally develop.\textsuperscript{30} The Gly-16 polymorphism does not appear to influence the development of tolerance to tremor or tachycardia.\textsuperscript{31} Thus, tremor is primarily seen in acute administration of high doses or in patients with infrequent or intermittent use of \(\beta_2\)-agonists.
Hypokalemia

Activation of $\beta_2$-adrenergic receptors causes the movement of potassium from the extracellular to intracellular spaces, and indeed, $\beta_2$-agonists are used in the acute treatment of hyperkalemia. Decreases in potassium are dose-dependent, and tolerance to this effect develops with repeated use. Hypokalemia is more of a concern as an arrhythmogenic risk in patients who have underlying cardiac disease. Older patients with COPD and comorbid heart disease are at risk, especially those who are hypertensive and those taking non-potassium-sparing diuretics. Salmeterol and formoterol decrease serum potassium by approximately 0.45 mmol/L in hypoxic patients with COPD and asthma. Albuterol decreases serum potassium to a similar degree.

Tachycardia

In clinical trials, tachycardia or palpitations were seen in 5% of patients receiving oral albuterol and in 1% of those receiving aerosolized albuterol. Maintenance doses of the long-acting agent salmeterol do not cause increased heart rates in COPD patients. Tachycardia is more of a concern in patients with preexisting cardiac disease and hypoxia, especially at the higher doses associated with an acute exacerbation. The practice of using levalbuterol to prevent tachycardia in critically ill patients has been questioned, although use of this agent in hospitalized patients at risk for heart rate-related morbidity is reasonable.

QT Effects

The modest prolongation of the QTc interval caused by albuterol is mediated by its $\beta_2$-agonist activity and is a class effect. Accordingly, salmeterol and formoterol prolong the QTc interval, although only at doses approximately 10 times the clinically recommended dose. Adding albuterol to the long-acting $\beta_2$-agonist salmeterol causes little change in heart rate or QTc interval. Thus, the clinical significance of QT prolongation with standard use is unclear; although at usual doses it is unlikely that $\beta_2$-agonists cause torsades des pointes. With the exception of sinus tachycardia, arrhythmias tend to be uncommon in patients with near-fatal asthma attacks, suggesting that the mechanism of death from asthmatic attacks is not a drug-induced arrhythmia. However, it is prudent to avoid $\beta_2$-agonists or to use them sparingly in patients with a congenital long QT syndrome.

Cardiovascular Mortality

As the product inserts for most $\beta_2$-agonists state, the heart contains a sizable number of $\beta_2$ receptors. The clinical significance of these receptors in the setting of $\beta_2$-agonist use has not been elucidated. However, a number of case reports as well as a meta-analysis by Sal彼得 suggest that increased cardiovascular mortality in asthma and COPD patients may be due to $\beta_2$-agonist use. The meta-analysis demonstrated a trend, but not a significant increase, in cardiovascular events when sinus tachycardia as a cardiovascular event was excluded from the analysis. Additionally, $\beta_2$-agonist use in veterans increased the risk of unstable angina and myocardial infarction in a dose-dependent fashion, with an odds ratio of 4 for those using 1 or more MDI canisters of albuterol per month. Notably, this increased risk was eliminated in patients also prescribed a $\beta$-receptor antagonist.

DRUG INTERACTIONS

Drug interactions are of minor importance for bronchodilators administered by the inhalation route because minimal amounts of these drugs are systemically absorbed. Thus, while salmeterol is a cytochrome P450 3A substrate, systemic exposure is likely so small that no significant increase in concentration occurs when the drug is given in conjunction with a known inhibitor of this enzyme. Formoterol is metabolized by multiple phase I and II enzymes, making adverse events based upon the inhibition of any one even less likely. Oral albuterol can decrease digoxin levels, although for inhaled albuterol this effect is not clinically significant. Diuretics are of concern due to a baseline hypokalemia that can be acutely worsened following administration of the $\beta_2$-agonists.

USE OF $\beta$-ANTAGONISTS IN OBSTRUCTIVE LUNG DISEASE

$\beta$-Blockers traditionally have been thought to antagonize asthma and COPD treatment and to decrease responsiveness to albuterol. This notion is based upon the seeming antagonistic mechanisms of action of these agents and on observations in which treatment with $\beta$-blockers induced acute asthma attacks or exacerbated airflow obstruction. However, a more comprehensive look at the existing literature suggests that in fact $\beta_1$-selective antagonists are safe and well tolerated in mild asthma and COPD. Initial treatment is associated with a modest drop in forced expiratory volume in 1 second (FEV$_1$). After 3 to 4 weeks of treatment, there is no significant change in FEV$_1$ and an 8% increase in responsiveness to a $\beta$-agonist. Potential risks associated with $\beta$ blockade on airway caliber are likely more of a concern for asthma than for COPD patients, and COPD patients are more likely to have comorbidities responsive to $\beta$-antagonists.
The profound efficacy of the β-antagonists in cardiovascular disease generally outweighs the theoretical risks of worsening obstructive lung disease. Indeed, the use of β-blockers in asthmatic and COPD patients following a myocardial infarction is associated with significant overall mortality benefit. For example, β-blocker use in patients with COPD and non-Q-wave myocardial infarction reduced mortality by 40%. β₂-selective-antagonists are preferable to the nonspecific antagonists, although even the selective agents become nonselective at higher doses (eg, metoprolol 200 mg/day). Thus, for mild to moderate asthma and for all COPD patients, β₂-selective-antagonists should be used in the presence of a compelling comorbid condition. Clinical monitoring during the initiation of therapy is warranted.

Ophthalmic β-antagonist use in the treatment of glaucoma has been associated with a modestly increased risk of pulmonary complications. As the systemic exposure from topical eye preparations will be much less than from orally administered β-antagonists, these agents should be administered as needed for control of increased intraocular pressure. Increasingly, the prostaglandin agents have found favor due to efficacy and an attractive side-effect profile, and these agents should be first-line treatment in glaucoma patients with obstructive airways disease.

ATTENUATION OF EFFICACY AND TACHYPHYLLAXIS OF β-AGONISTS

Within the past 15 years, an association between asthma mortality and chronic treatment with β₂-agonists has been suggested by a number of case-control studies in Canada and New Zealand. The cohort studies went as far as to suggest that this increase in mortality may in fact be a class effect. These studies and the commentaries that followed also suggested that the higher mortality might be due to the loss of the “bronchoprotective effect” of β₂-agonists, which is typically demonstrated through protection against bronchoconstriction by chemical/allergen challenge. In further support of this hypothesis, blood albuterol concentrations have been found to be 2.5 times greater among patients who have died of asthma compared to controls. Loss of the bronchoprotective effect is believed by some investigators to be an important predictor of poor responsiveness to β₂-agonists resulting from chronic therapy. It has been suggested that the mechanism for the loss of the bronchoprotective effect may be desensitization and/or downregulation of the β₂-adrenoceptor as a result of prolonged activation. Although a diminution in the bronchoprotective response with chronic β₂-agonist treatment has been demonstrated, this response is not actually lost; therefore, the clinical significance of this effect has remained debatable. Furthermore, diminution of the bronchoprotective effect can be demonstrated more readily than reduced bronchodilator effect, calling into question the clinical relevance of this mechanism. This issue was addressed in a large-scale double-blinded, randomized placebo control trial designed to examine the safety and efficacy of short-acting β₂-agonist use on a regular versus as-needed schedule in patients with mild asthma. This study found that albuterol administration 4 times per day did not lead to a worsening of asthma control or to an increase in severity of exacerbations. On the other hand, regular use had no benefit over as-needed use, and the authors recommended that inhaled albuterol should be prescribed for patients with mild asthma on an as-needed basis.

Further analysis of the Canadian and New Zealand studies has revealed that the association of asthma death with β₂-agonist use was largely due to confounding by severity and other study-specific issues. The case-control design of these studies limits their interpretation in that only an association, not causality, can be determined from a case-control study. However, these studies have shown that patients with increasing severity of asthma more frequently use their inhalers as their asthma worsens.

Concerns were also raised regarding the use of long-acting β₂-agonists when the US Food and Drug Administration (FDA) received postmarketing reports of several asthma deaths associated with the use of salmeterol. The Salmeterol Multicenter Asthma Research trial (SMART) was a large-scale trial of salmeterol conducted in response to this concern. The trial was stopped early following an interim analysis that demonstrated a trend towards increases in asthma deaths and serious asthma episodes. In particular, the study suggested that the risk of death in African-Americans might be greater, although the reasons for this potential association remain unclear. The SMART trial has been criticized on methodologic grounds, most notably the lack of accurate accounting for concomitant use of inhaled corticosteroids.

Although some studies of long-term therapy with salmeterol have not found differences in the bronchodilatory effects of albuterol, other studies have suggested tolerance to the acute bronchodilating effects of albuterol as well as to bronchoconstrictor provocation testing following treatment with salmeterol. Studies that have demonstrated tolerance to long-acting β₂-agonists have not clearly shown that tolerance results in loss of asthma control or increased severity of exacerbations. A Cochrane systematic review that examined daily use of...
long-acting β₂-agonists compared to daily regular use of short-acting β₂-agonists found clear clinical advantages to the use of long-acting β₂-agonists in both adults and children. This is in contrast to a more recent meta-analysis by Salpeter, which linked long-acting agents to increased mortality. This meta-analysis has been criticized on a number of grounds. Most notably, the analysis relied too heavily on data from the SMART trial, excluded a number of studies, and lacked control for disease severity or inhaled corticosteroid dose. It should also be noted that while salmeterol was approved in the early 1990s, asthma hospitalizations and mortality have actually declined in North America and Australia since 1995.

What conclusions can be drawn in light of these controversies? Long-acting β₂-agonists clearly improve symptoms and lung function but have no anti-inflammatory properties and should not be used without an inhaled corticosteroid. Inhaled corticosteroid use reduces the rate of exacerbations more effectively than the β₂-agonists. The complementary mechanisms of action make combination use attractive and affirms published guidelines endorsing the use of long-acting β₂-agonists as the preferred first add-on agent to inhaled corticosteroids in a stepped up asthma treatment regimen. Clinical trial data also support combined use in COPD.

ANTICHOLINERGICS

HISTORICAL PERSPECTIVE

A treatment for wheezing in ancient India was inhalation of Datura stramonium (Jimson weed). The efficacy of this treatment was due to the anticholinergic properties of atropine contained in the plant but at the cost of systemic anticholinergic adverse effects. Because ipratropium’s bronchodilatory properties are inferior to those of the β₂-agonists even at high doses, this drug is a second-line bronchodilator in asthma. However, the unique mechanism of action, safety, and possible additive effects with sympathomimetics make this drug and the longer-acting tiotropium useful adjuncts, especially in COPD.

PHARMACOKINETICS

As highly polar quaternary ammonium compounds, both ipratropium and tiotropium poorly cross membrane bilayers, and systemic absorption is minimal. This concept has been applied in the enteral tract for the quaternary ammonium antimuscarinics glycopyrrolate and methscopolamine bromide. Not surprisingly, serum levels of ipratropium and tiotropium do not correlate to bronchodilatation because this effect is mediated by the drug deposited in the airways. In COPD, ipratropium has onset of bronchodilatation after 15 minutes but does not reach peak effectiveness for 1 hour. The onset of action in asthma may be shorter. Improvement in FEV₁ generally last for 3 to 4 hours, although some patients have benefited up to 6 hours after dosing. The highly polar nature of the drug prevents extensive distribution within the body, especially into the central nervous system (CNS). Thus, there are no CNS side effects. Tiotropium is measurable in the blood at very low concentrations shortly after inhalation and is excreted largely unchanged in the urine. As acetylcholine receptors can elicit a full response even with approximately 50% of receptors bound to an antagonist, systemic anticholinergic effects after inhalation are negligible. Bronchodilatation is noted within 15 minutes of a dose of tiotropium and lasts 36 hours after a single dose.

The higher lung concentrations of the drug administered by inhalation allow for full antagonism of the muscarinic receptors. Ipratropium and tiotropium bind M₁, M₂, and M₃ receptors with similar affinity, but tiotropium has a much slower dissociation rate from M₁ and M₃, accounting for continued bronchodilation more than 24 hours after a dose. As M₂ receptors act as autoreceptors on postganglionic cholinergic nerves and inhibit acetylcholine release, tiotropium has a theoretical advantage over ipratropium. However, the full clinical implications of this reduced M₂ occupancy of tiotropium remain to be elucidated.

ADVERSE EVENTS

Although intravenous administration of anticholinergics causes potent anticholinergic effects, inhaled delivery causes remarkably few side effects. Accordingly, there are no immediate cardiovascular or hypokalemic effects even with high doses of ipratropium. Patients randomly assigned to ipratropium in the Lung Health Study had an increase in cardiovascular events compared with those assigned to placebo but this was not a primary endpoint of the study. There have not been other troubling pharmacovigilance signals, and another study was reassuring with regard to the long-term safety of ipratropium. Established side effects consist of occasional dry mouth and, much less commonly, worsening of urinary outflow obstruction. Narrow angle glaucoma may worsen if the eyes are exposed to drug aerosol. The ocular effects can be prevented with eye protective measures and antiglaucoma therapy.
SELECTION OF A BRONCHODILATOR

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Anticholinergics have been shown to have greater efficacy and safety in chronic COPD than β-agonists in multiple studies, probably reflecting the relative differences in vagal tone between COPD and asthma. Because there is often overlap in the clinical expression of COPD and asthma, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines do not specify a first-line class of bronchodilator. Therefore, while the anticholinergics are generally a good first choice for GOLD stage 1 disease and more severe disease, the ultimate decision will depend upon the clinical response of the individual patient.19 The side effects of the β2-agonists are modest, but those of the anticholinergics are even less severe. As with the β2-agonists, ipratropium provides symptomatic relief in COPD but does not change the long-term rate of decline of lung function.20 The anticholinergics provide symptomatic relief beyond what would be expected on the basis of improvements of FEV1 alone. A clinical correlate is that tiotropium results in long-term improvements in lung function, dyspnea, and health status, even in those patients who did not initially demonstrate reversibility following the first dose.74 One possible mechanism to account for decreases in air trapping is a parasympathetic-mediated decrease in mucus production.

Acute Exacerbations

In the treatment of acute exacerbations of COPD, β2-agonists have an advantage over anticholinergics. However, the relative merits of each agent in isolation become less important because in an acute attack the agents generally are given together. Although a recent Cochrane review reported no significant improvement in FEV1 for combination therapy compared to either agent alone,75 the limited downside risk of combination therapy and potential benefits beyond the measured lung function make combination therapy first-line therapy in this setting.

β2-Agonists Versus Ipratropium

Given the concerns of tachyphylaxis and receptor desensitization, scheduled use of a short-acting β2-agonist as a single agent is not recommended. Using the same dosing schedule of 2 puffs 4 times a day, ipratropium alone or in combination with albuterol was associated with fewer exacerbations and reduced health care costs compared to albuterol alone.76 Thus, albuterol or another short-acting β2-agonist should be used on a symptomatic and not on a controller basis, while use of either ipratropium or tiotropium is appropriate as a longer-term controller.

Long-Acting β-Agonist Versus Tiotropium

Salmeterol and tiotropium show similar improvements in FEV1 at the time of initiation of therapy. Beginning at 2 weeks, tiotropium begins to show a sustained superiority with regard to FEV1,77 probably due to the attenuation of β2-agonist bronchodilatory effects. The superiority of tiotropium relative to salmeterol and formentol extends to symptoms, exacerbation rates, and health status,78 making this agent an excellent choice for treatment of disease classified as GOLD stages 2 and above.

Ipratropium Versus Tiotropium

The convenience and likely increased compliance with once-daily administration compared to 4 times daily administration is a clear advantage for tiotropium. In a direct comparison, an advantage in lung function difference for tiotropium just before a scheduled ipratropium dose was noted and not unexpected. However, tiotropium was also noted to have modest improvements in peak and average FEV1 relative to ipratropium.79 The safety profile of the 2 agents appears to be similar, although tiotropium may be associated with modestly increased dry mouth symptoms. The relative clinical benefits and ease of once-daily administration of tiotropium must be balanced with the increased cost compared to ipratropium.

Combination Therapy

Several factors support the use of combination therapy in COPD: (1) lack of additive side effect profile; (2) differing mechanisms of action coupled with the effects of anticholinergics primarily on the larger proximal airways and the effects of β2-agonists primarily on the smaller airways; (3) complementary onset of action, with immediate bronchodilatation produced by the β2-agonists followed by the delayed but prolonged action of the anticholinergic; and (4) availability of simultaneous delivery, either by means of a single multidose inhaler or a nebulization chamber containing both products. Combination therapy provides synergistic efficacy in terms of improvements in FEV1, with a greater improvement than either agent alone, without any change in the side-effect profile.80 This benefit applies to both MDI and nebulization delivery of the medications.81 Because many patients with milder disease can be managed with monotherapy, combination therapy should
be reserved for patients with suboptimal response to a single agent.

ASTHMA

In conjunction with anti-inflammatory controller therapy, the β2-agonists remain the first-line bronchodilators in asthmatic patients. A short-acting agonist used on an as-needed basis is the mainstay of symptomatic treatment. Over-the-counter aerosolized or oral epinephrine should be avoided due to its side-effect profile, which includes pronounced tremor, tachycardia, and potentially cardiac arrhythmias associated with α and β1 activation. The use of epinephrine is also contraindicated in patients taking β-blockers, as unopposed α activation tends to worsen side effects. Their use by patients is generally a marker of poor follow-up with physicians or access to care. Differences between specific short-acting β2 agents are minor.

Despite previously mentioned issues of potential receptor subsensitivity and partial agonist effects, the long-acting β2-agonists are useful adjuncts in the treatment of asthma. They provide significant improvements in lung function and quality of life. Although the potential of the long-acting agents to mask an inflammatory process and increase exacerbations and airway remodeling remains controversial,82 it is prudent to use these agents only in conjunction with an inhaled corticosteroid. Whether the increased efficacy of formoterol compared to salmeterol at the β2 receptor translates into a different safety or efficacy profile is unknown at this point (see Partial Agonist Effects).

Use of the anticholinergics in conjunction with β2-agonists is beneficial in acute asthma, although this benefit appears to be primarily limited to patients with the most severe disease.83 Given the excellent safety profile and ease of administration with nebulized albuterol, both agents should be given to patients who present to the emergency department with moderate or severe acute asthma exacerbation. Ipratropium does not appear to provide additional benefit in the long-term management of asthma.84

DRUG DELIVERY

INHALATION DEVICES

A full exploration of the relative merits of various delivery devices is beyond the scope of this review. However, for the delivery of bronchodilators in the setting of acute asthma, MDI has been shown to be as effective as nebulized therapy. MDI is appropriate for acute asthma in either the emergency department or outpatient office. Despite the decreased efficiency in delivery of administered dose compared to MDI, nebulized administration is typically used in the emergency department based upon ease of administration, lack of need for intensive staff oversight, ability to administer continuous therapy, and the perception by patients that nebulization is more effective. The ease and availability of nebulization has made this a preferred delivery mechanism in patients unable or unwilling to master the inhalational technique of MDI use. Nebulized therapy is preferable in severe attacks where patients cannot generate significant inspiratory effort. For nonacute bronchodilator therapy, there is no advantage of nebulization over MDI administration. A nebulized long-acting β2-agonist (aformoterol tartrate) will soon be commercially available.

ORAL ADMINISTRATION

Bronchodilatation begins 30 minutes after oral administration of albuterol, and peak effects are not obtained for 2 to 3 hours. After a single oral 4-mg dose of albuterol elixir, peak plasma levels of 18 ng/mL were noted, compared to a peak level of 2.1 ng/mL following a single nebulized dose of 3 mg.85 Because efficacy is mediated by lung effects of the drug and toxicity is mediated by systemic actions, it is difficult to justify the use of oral albuterol in the adult population. This is particularly true for those at risk for cardiovascular toxicity, especially in light of recent concerns over the longer-term toxicity of the β2-agonists in this population.44

PARENTERAL ADMINISTRATION

Intravenous administration of β2-agonists is not associated with clinical improvement compared with inhalational delivery and is associated with significant risk of adverse effects.86 It should be noted that intravenous albuterol is currently not available in the United States.

MECHANICAL VENTILATOR ASSOCIATED DELIVERY

Bronchodilator therapy can be delivered with good therapeutic effect by either nebulization or MDI.82 MDI is the preferred device due to ease of use, decreased risk of ventilator pneumonia, and similar efficacy with a smaller total administered dose compared to nebulized delivery. The standard humidity in ventilator circuits will decrease aerosol delivery via an MDI by approximately 50%. However, stopping humidification during drug administration is generally not practical, and the effect of cool, dry air on ventilated patients with bronchoconstriction is not well studied.87 The reason for this decreased drug delivery is not the temperature of the
humidified air but the inhibition of the initial atomization following actuation. The effects of humidification can be overcome to a large degree by the use of a large inline spacer device and actuation during an inspiratory cycle. Clinically significant bronchodilatation is seen with 4 puffs of a β₂-agonist, although given the loss in the circuit, higher doses will result in greater bronchodilatation.

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**CONCLUSION**

The β₂-agonists and inhaled anticholinergics play a key role in the management of asthma and COPD. These medications do not change the natural history of either disease, but they do significantly improve quality of life and patient well-being. For COPD, the anticholinergics and β₂-agonists are first-line therapy. Long-acting agents of both classes are efficacious. Given the recent attention to the potential cardiovascular toxicity of long-term β₂-agonism in patients with existing heart disease, the exact role of these agents in COPD will continue to evolve. β₂-agonists remain the first choice for bronchodilation in asthma. When used in conjunction with inhaled corticosteroids, the long-acting agents appear to be safe and efficacious.

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