Optimizing Bronchodilator Therapy in Emphysema

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The treatment objectives for chronic obstructive pulmonary disease (COPD) include relieving symptoms such as dyspnea and cough, slowing the accelerated decline in lung function, decreasing exacerbations, and improving quality of life. All major guidelines for COPD management recommend beginning treatment with bronchodilators. There are several classes of bronchodilators, including β-agonists, anticholinergics, and phosphodiesterase inhibitors, each with a specific mechanism of action. The overall approach to managing stable COPD involves a stepwise increase in treatment. Because of the progressive nature of emphysema, such an approach often involves combining bronchodilators from different pharmacologic classes. This review focuses on the pharmacologic properties of various bronchodilators and on recent studies that have examined combination therapy as a means to optimize treatment.

Keywords: chronic obstructive pulmonary disease; β-agonists; anticholinergics; theophylline

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease defined as airflow obstruction that is not fully reversible (1). The airflow obstruction may be due to parenchymal lung destruction resulting in the loss of elastic recoil (emphysema) or small airways obstruction that results from smooth muscle hyperplasia, mucus hypersecretion, peribronchial inflammation, and fibrosis (2). In some patients that undergo lung volume reduction surgery, the presence of significant small airways pathology has been noted along with upper-lobe predominant emphysema (identified by chest computed tomography [CT]) (3). In theory, bronchodilators, which act directly on the airways, should have limited benefit in emphysema. However, in clinical practice many patients with COPD, even those with predominantly an emphysematous phenotype, benefit from bronchodilator therapy.

Recent investigations using chest high-resolution computed tomography (HRCT) provide some insight regarding bronchodilator-induced airflow reversibility in emphysema (4, 5). In a study of 172 patients with COPD (mean FEV_1 ~45% of predicted), Fujimoto and colleagues used HRCT to characterize the COPD phenotype (4). Three groups were identified: group E patients had predominant emphysema; group A patients had little or no emphysema, with no bronchial wall thickening by HRCT; and group M patients had mixed emphysema and bronchial wall thickening by HRCT (4). The mean increase in FEV_1 following acute bronchodilator challenge was significantly lower in Group E patients (10.7%) compared with those in Group M (16.8%) or Group A (13.1%). Pechulis and colleagues, however, have presented preliminary data suggesting that changes in FEV_1 alone provide an incomplete picture of the spirometric bronchodilator reversibility of the patient with emphysema (5). These investigators examined the acute bronchodilator response of a population of 354 patients with HRCT-documented emphysema, and 88% had moderate to severe disease (GOLD stage 3 or 4). Spirometric bronchodilator reversibility was present in 50% of GOLD stage 4 subjects, 61% of GOLD stage 3 subjects, and 21% of GOLD stage 2 subjects. Importantly, 94% of GOLD stage 4 patients with a significant bronchodilator response met reversibility criteria by forced vital capacity (FVC) parameters only. The authors concluded that in patients with advanced emphysema, acute bronchodilator reversibility is predominantly a volume, not a flow response. Substantial changes in FVC and inspiratory capacity (IC) are fairly common after bronchodilator administration, but significant change in the FEV_1 is not (5). Although quite preliminary, these studies call attention to the potential relevance of determining COPD phenotypes to profile the response to bronchodilator therapy. Unfortunately, most COPD trials do not differentiate between the different phenotypes, such as emphysema and chronic bronchitis. As a result, no bronchodilator has been approved specifically for the emphysema phenotype. As such, we will focus on the general population of patients with COPD for the majority of this review.

International guidelines for COPD treatment have emphasized the importance of using a stepwise approach to optimize pharmacologic management (1, 6). Because of the progressive nature of emphysema, such an approach often involves combining bronchodilators from different pharmacologic classes. In this review, we will briefly discuss the pharmacologic properties of various bronchodilators and focus on recent studies that have examined combination therapy as a means to optimize therapy.

TYPES OF BRONCHODILATORS

β-Agonists

β_2-agonists bind to the β_2-receptors located on the smooth muscle of the trachea to the level of the terminal bronchioles (7). Binding of β_2-agonists to the β_2-receptors activates a receptor-associated G protein that in turn activates adenyl cyclase. Adenyl cyclase converts adenosine triphosphate (ATP) to cyclic 3′5′-adenosine monophosphate (c-AMP), which then activates protein kinase A (8). The activated protein A prevents phosphorylation of the myosin light chain as well as activation of the Na^+/Ca^{2+} exchange pump. This results in a fall in intracellular calcium and leads to smooth muscle relaxation, as less calcium is available for the calcium-dependent myosin–actin interaction required for smooth muscle contraction (8).

Long-acting bronchodilators, including salmeterol and formoterol, have an affinity for the β_2 receptor that is approximately 100 times higher than that of short-acting bronchodilators, such as albuterol, pirbuterol, and salbutamol (9). Evidence exists that the long duration of action of these agents is related

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both to their high affinity for the β_2 receptor and to the interaction of these drugs with the lipid membrane (10).

It should be noted that long-acting bronchodilators may have important effects on the lung that are independent of their effects on airway smooth muscle. For example, in certain experimental models they have demonstrated effects on inflammatory cells and mucociliary transport. The clinical relevance of these effects is unclear (11).

Anticholinergics

Anticholinergics agents, including short-acting ipratropium bromide and long-acting tiotropium, interact with the three muscarinic receptors (M_1, M_2, M_3) located on the airway smooth muscle. The M_1 receptor is responsible for cholinergic neurotransmission in parasympathetic ganglia that augments cholinergic bronchoconstriction. Blocking the M_2 receptor causes increased release of acetylcholine, potentially offsetting the effects of bronchodilation. M_3 receptors post-junctionally mediate bronchoconstriction and mucous gland secretion in the airways (12). Tiotropium binds M_1, M_2, and M_3 muscarinic receptors, with slow dissociation from the M_1 and M_3 receptors and rapid dissociation from the M_2 receptors (13). Tiotropium has a greater affinity for muscarinic receptors compared to ipratropium (14), and dissociation from M_1 and M_3 occurs at least 100 times more slowly than with ipratropium bromide (15). This produces a bronchodilator effect that lasts far longer than that of ipratropium bromide. Furthermore, the rapid dissociation from M_2 minimizes increased acetylcholine release by providing feedback inhibition (16).

Both ipratropium bromide and tiotropium have a quaternary ammonium structure that leads to poor gastrointestinal absorption. Indeed, clearance of the nonabsorbed form of the drug is mainly through the gastrointestinal tract. Ipratropium bromide has an approximate onset of action of 15 minutes, with a duration of action of approximately 6 hours. Tiotropium has an onset of action within 30 minutes, with a duration of action of 24 to 32 hours.

Phosphodiesterase Inhibitors

Currently, theophylline remains the only phosphodiesterase inhibitor available for use in the United States. Theophylline is a nonselective phosphodiesterase inhibitor that is felt to cause bronchodilitation by decreasing breakdown of c-AMP, thereby increasing intracellular c-AMP levels. This ultimately leads to a fall in intracellular calcium concentrations and to bronchial smooth muscle relaxation. The newer agents, cilomilast and roflumilast, which are specific oral phosphodiesterase-4 (PDE-4) inhibitors, have demonstrated modest increases in post-bronchodilator FEV_1 in moderate COPD (17, 18). In addition, in severe COPD, roflumilast provided a modest increase in lung function, and patients with very severe disease experienced fewer exacerbations (19).

THERAPEUTIC APPROACH

Although patients with COPD at an early stage and with minimal symptoms can be managed with an as-needed short-acting bronchodilator, there is broad consensus endorsing the use of inhaled long-acting bronchodilators as first-line treatment in patients with COPD with chronic symptoms (1, 6, 11). These agents include long-acting β_2 agonists (salmeterol and formoterol) and long-acting anticholinergics (tiotropium). Indeed, numerous studies have documented that long-acting bronchodilators have multiple beneficial effects in COPD (11, 20–25). These effects include improvement in respiratory symptoms, airflow, quality of life, rate of exacerbations, and exercise performance (11, 20–25). While recent data suggest that long-term compliance and effects on health-related quality of life may be superior with tiotropium, insufficient data exist to declare conclusively that one long-acting bronchodilator is superior to another (11, 24, 26). Indeed, recent GOLD guidelines recommend the addition of one or more long-acting bronchodilators for moderate stage COPD, but the choice of which long-acting bronchodilator is dependent on availability of the medication and the patient's response. Theophylline has been relegated to third-line use in COPD, after β-agonists and anticholinergics, due to its relatively weak bronchodilator effects and its narrow therapeutic window (1). An important principle of COPD management involves the individualization of care, and it should be recognized that certain patients may respond better to one bronchodilator over another (1).

Hyperinflation, characterized by a reduced IC and increased residual volume (RV), is a key determinant of dyspnea in patients with COPD and warrants specific discussion (27). Because patients with emphysema typically have a greater degree of hyperinflation than others with COPD, alleviating hyperinflation may be a particularly important consideration in this group of patients. Bronchodilators have been shown to improve hyperinflation at rest and during exercise (dynamic hyperinflation).

Newton and coworkers performed a retrospective analysis of the effect of a short-acting β-agonist, salbutamol, on lung volumes in 676 patients with moderate hyperinflation defined by a total lung capacity (TLC) of 115 to 133% predicted and 281 patients with severe hyperinflation (TLC >133% predicted). They found that there was a significant fall in the TLC, RV, functional residual capacity (FRC), and a rise in IC following the administration of salbutamol (28). There was a response to flow (FEV_1 improvement) in only 33% of severely hyperinflated patients and in 26% of moderately hyperinflated patients, but a change in lung volumes occurred in 76% and 62% of the respective patient groups (28). Salmeterol alone also significantly reduced FRC and RV in a group of patients with moderate COPD (FEV_1 51% predicted) (29). Furthermore, during exercise, salmeterol has been shown to significantly decrease the amount of dynamic hyperinflation at iso-exercise times (30). Studies also show that patients treated with tiotropium for 4 weeks were shown to have greater improvements in IC than those given placebo (31–33). Spirometric improvements in these studies evaluating exercise tolerance were accompanied by functional and symptomatic improvements.

COMBINATION THERAPY

With progressive disease, patients with COPD often develop symptoms that are suboptimally controlled when using a single bronchodilator alone. Combination therapy, using agents of different classes, may result in maximizing bronchodilatation without increasing medication side effects.

Short-acting β-Agonists and Short-acting Anticholinergics

The rationale for the use of different combinations of bronchodilator therapy has been firmly established for short-acting agents, as numerous studies have demonstrated the safety and efficacy of combined ipratropium bromide and albuterol therapy (34–36). Leitch and colleagues performed one of the earliest double-blind placebo trials evaluating combination short-acting β-agonists (SABAs) and short-acting anticholinergics (34). Twenty-four patients were treated with either ipratropium bromide, salbutamol, or combination therapy. The combination therapy group had a larger increase in FEV_1, FVC, and 12-minute walking distance; although none of these reached statistical significance.

Barros and Rees retrospectively evaluated 296 patients who had incomplete reversibility of their airway obstruction with salbutamol (35). Ipratropium bromide was added to salbutamol, and 33% of patients experienced additional increases in their FEV_1 and FVC.

The Combivent Inhalational Aerosol Study, a large, multicentered, double-blind, randomized-controlled trial, evaluated the effectiveness of ipratropium, albuterol, and combination therapy in 534 patients with COPD (36). After 85 days, there was a significantly greater increase in FEV_1 in the combination group (33% improvement) compared with the other two groups (25% increase with ipratropium bromide; 27% with albuterol). Thus, in this trial combination therapy with a short-acting β-agonist and a short-acting anticholinergic resulted in greater improvement in FEV_1 than with either agent alone. There was no difference in adverse events between the groups.

While it is evident that combining SABAs and short-acting anticholinergics leads to greater improvement in lung function when compared with monotherapy, the relatively short half-life of combination albuterol and ipratropium bromide makes these agents inconvenient to use as regularly scheduled agents.

Long-acting β-Agonists and Short-acting Anticholinergics

Long-acting β-agonists (LABAs) are appealing due to the increased likelihood of compliance with twice a day dosing (as opposed to four times a day with short-acting agents), and thus have become a mainstay of COPD treatment (1). The use of LABAs in combination with short-acting anticholinergics has been examined in several studies (37–39). van Noord and colleagues performed a 12-week multi-centered, randomized, double-blind trial in 144 patients with moderate-severe COPD (mean age 65; mean FEV_1 44% of predicted) (37). Patients were randomly assigned to receive salmeterol (50 μg twice daily) plus placebo, salmeterol (50 μg twice daily) plus ipratropium bromide (40 μg four times daily), or placebo via metered dose inhaler. Both active treatment groups demonstrated significant improvements in FEV_1, FVC, and peak expiratory flow (PEF) compared with placebo. Furthermore, combination therapy provided a greater increase in FEV_1 and FVC compared with salmeterol alone. While symptom scores did not vary significantly between the two treatment groups, the salmeterol–ipratropium bromide group, but not the salmeterol group alone, demonstrated a significant reduction in exacerbations compared with placebo. Adverse events were similar in all three groups.

Chapman and coworkers performed a double-blind, randomized, parallel group trial in 408 patients with COPD who were suboptimally controlled on ipratropium bromide (38). Patients continued on ipratropium bromide 40 μg four times daily and were randomized to either salmeterol (50 μg twice daily) or placebo as add-on therapy. The investigators found evidence of significantly improved airflow in the salmeterol group compared with placebo at 4, 8, 16, and 24 weeks after the initiation of therapy (38). While the salmeterol group had fewer acute exacerbations of COPD (26% versus 33%), the results did not reach statistical significance ($P = 0.117$). Combination therapy was not associated with any increase in adverse events.

D'Urzo and colleagues performed a randomized, double-blind, cross-over trial to determine the effectiveness of add-on therapy with salbutamol or formoterol in 172 patients with COPD (mean age, 65; mean FEV_1, 51.3% of predicted) suboptimally controlled with ipratropium bromide (39). Each patient received inhaled ipratropium bromide (40 μg four times daily) plus the add-on treatment (inhaled formoterol 12 μg twice daily or inhaled salbutumol 200 μg four times daily) in 3-week treatment periods assigned randomly. The investigators found that PEF, FEV_1, and FVC had the greatest improvement in the formoterol group. There was also a significantly greater improvement in mean total symptom scores in the formoterol group. Adverse events were similar in both groups.

It appears that the combination of LABAs and short-acting anticholinergics provide greater improvement in lung function than monotherapy or combination short-acting bronchodilators. However, the effect of this combination on long-term outcomes, including health-related quality of life, has not been established.

LABAs and Long-acting Anticholinergics

Tiotropium is currently the only long-acting anticholinergic available in the United States. Recently, a 1-year trial of tiotropium and a large meta-analysis have suggested that it reduces exacerbations and hospitalizations and improves the health status of patients with COPD more effectively than short-acting bronchodilators (40, 41). Based on this as well as on the effectiveness of LABAs, it is conceivable that the combination of these classes of agents may provide a substantial benefit to patients with COPD. Indeed, a small (n = 20) 3-day study by Cazzola and colleagues demonstrated that the combination of salmeterol with tiotropium can improve FEV_1 more than either agent alone (42). A similar study, by the same group of investigators, found that the combination of formoterol and tiotropium resulted in a significantly faster onset of action compared with either agent alone. However, the absolute change in FEV_1 in the formoterol–tiotropium combination group was not significantly different from that for either agent alone (43).

van Noord and colleagues divided 95 patients into three treatment groups: tiotropium 18 μg once daily plus placebo, tiotropium 18 μg once daily plus formoterol 12 μg once daily, or tiotropium 18 μg once daily plus formoterol 12 μg twice daily (44). At 2 weeks, measurements of lung function, use of rescue medication, and number of adverse effects were evaluated. Compared with the tiotropium–placebo group, the tiotropium–formoterol groups showed significant improvements in FEV_1 and FVC that were sustained for 12 hours in the once-daily group, and for 24 hours in the twice-daily group. In addition, combination therapy significantly improved PEF and IC and reduced rescue inhaler use compared with tiotropium alone. Adverse events did not differ among the treatment groups.

Recently, Aaron and colleagues completed a randomized trial comparing tiotropium in combination with placebo, salmeterol, or salmeterol-fluticasone in 449 patients with COPD treated for 1 year (45). The primary outcome that was measured was the proportion of patients experiencing an acute exacerbation of COPD. Secondary outcomes included exacerbations per patient per year, health care utilization, quality-of-life changes, and lung function. The proportion of patients experiencing at least one COPD exacerbation was similar (~60%) in all treatment groups. Similarly, there was no difference between groups in the mean number of exacerbations per year or time to first exacerbation. There was, however, a significant reduction in the number of severe COPD exacerbations requiring hospitalization in subjects taking tiotropium plus fluticasone–salmeterol compared with tiotropium plus placebo. This effect was not seen in the tiotropium plus salmeterol group (45). Health-related quality of life, but not dyspnea index, was significantly better in both the tiotropium–salmeterol group and the tiotropium–salmeterol–fluticasone group compared with the tiotropium placebo group. Tiotropium plus fluticasone–salmeterol, but not tiotropium plus salmeterol, improved lung function compared with tiotropium plus placebo. Adverse events were similar among all groups. An important limitation to this trial was that more than 40% of

TABLE 1. STUDIES EXAMINING COMBINATION BRONCHODILATOR THERAPY, INCLUDING AT LEAST ONE LONG-ACTING BRONCHODILATOR FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Trial	Duration	Treatment	Control	Pulmonary Function	Symptoms	Exacerbations
Van Noord (2000)	12 wk	Salmeterol + ipratropium	Salmeterol; ipratropium	+	+	+
Chapman (2002)	24 wk	Salmeterol + ipratropium	ipratropium; placebo	+	–	–
D'Urzo (2001)	3 wk	Formoterol + ipratropium	Salbutamol + ipratropium	+	+	n/a
Cazzola (2004)	24 h	Salmeterol + tiotropium	Salmeterol; tiotropium	+	n/a	n/a
Cazzola (2004)	24 h	Formoterol + tiotropium	Formoterol; tiotropium	+	n/a	n/a
Van Noord (2006)	2 wk	Formoterol + tiotropium	Formoterol; tiotropium	+	n/a	n/a
Aaron (2007)	52 wk	Salmeterol + tiotropium	Tiotropium*	–	–	n/a
ZuWallack (2001)	12 wk	Salmeterol + theophylline	Salmeterol; theophylline	+	+	+
Cazzola (2007)	4 wk	Formoterol + tiotropoium + theophylline	Formoterol + tiotropium	–	–	n/a

A + denotes that the Treatment group patients showed improvement compared to the Control group patients. A – indicates no significant difference between groups.
* This study also included combination salmeterol–fluticasone–tiotropium; these data not included in table.

patients taking tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely.

In summary, it seems that treatment with long-acting anticholinergics along with LABAs is well tolerated and increases FEV_1 more than either agent alone. However, additional long-term trials involving more patients are needed to account for the higher drop out rates and to better define potential benefits and understand the effect of such combination therapy on the natural history of disease and health-related quality of life.

Addition of Theophylline

ZuWallack and coworkers compared the combination of salmeterol and theophylline versus either agent alone in a 12-week, randomized, double-blind, parallel group trial involving 943 patients with COPD (46). After open-label treatment with theophylline (titrating to serum levels of 10–20 μg/ml), patients were randomized to salmeterol alone (42 μg twice daily), theophylline alone, or the combination of theophylline–salmeterol. Combination therapy resulted in a significantly greater increase in pulmonary function and a significantly greater decrease in respiratory symptoms and albuterol use than either agent alone. Although combination therapy was generally well tolerated, monotherapy with salmeterol was associated with significantly less adverse drug effects than either regimen that contained theophylline (46).

A recent single-blind trial enrolling 36 patients with moderate to severe COPD investigated whether the addition of theophylline to a regimen of formoterol and tiotropium improves pulmonary function and/or respiratory symptoms (47). All patients were treated with the combination of formoterol and tiotropium for 4 weeks. After this, half were randomized to receive placebo and the other half to receive theophylline slow release 200 or 300 mg twice daily for 2 weeks. While patients exhibited significant improvement in pulmonary function and respiratory symptoms after 4 weeks of combination therapy with tiotropium and formoterol, the addition of theophylline conferred no significant improvement in mean FEV_1 or dyspnea index as determined by visual analogue scores. Five subjects in the theophylline group noted improvement in dyspnea and the authors concluded that a subset of patients may benefit from the addition of theophylline to tiotropium and formoterol. However, insufficient evidence exists to recommend this treatment regimen routinely and the significant side effects of this medication often limit its use.

CONCLUSIONS

COPD is a chronic, progressive disease for which no treatment currently exists to improve mortality or prevent disease progression. However, for patients with symptoms or recurrent exacerbations, treatment is recommended, as it can lead to improvement in these areas.

As the patient with emphysema develops progressive dyspnea, combination therapy that includes a long-acting bronchodilator represents a reasonable approach to patient management. Such therapy is well tolerated, appears to maximize airflow, and may also improve respiratory symptoms (Table 1). However, few of these studies have followed patients beyond several months. Additional longer-term studies are needed to determine the effect of such therapy on important clinical outcomes such as health-related quality of life and exacerbation rate.

It should be reiterated that even patients with the predominant emphysema phenotype have significant small airways pathology and many show spirometric bronchodilator reversibility. Additional long-term studies are needed that include careful phenotyping of the population of patients with COPD to determine the effects of bronchodilator therapy on subtypes of patients with COPD.

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