Changing Practices in COPD*
A New Pharmacologic Treatment Algorithm

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Chronic obstructive pulmonary disease (COPD) is a serious public health problem, due largely to cigarette smoking. COPD is now the fourth-leading cause of death in the United States; more than half of patients with COPD die within 10 years of diagnosis.1 COPD is a progressive disease. Mortality rates are related to level of airway obstruction, and a decline in progressive loss of lung function improves long-term survival rates.

Data from the Lung Health Study demonstrate that the rate of decline in lung function in smokers with mild to moderate COPD can be significantly slowed by smoking cessation,2 but not by the anticholinergic bronchodilator ipratropium bromide (Atrovent). In this large clinical trial, ipratropium bromide improved lung function while it was used, corroborating other evidence that it is an effective bronchodilator in COPD.3-5

There are now three main classes of bronchodilators available for the treatment of COPD, each with specific clinical benefits: an anticholinergic (ipratropium bromide), β-agonists (eg, albuterol), and methylxanthines (theophylline). The preferred route of administration for bronchodilator therapy is by inhalation using a metered-dose inhaler (MDI). The MDI allows for direct delivery of drug into the lungs, thus minimizing systemic side effects. Self-treatment with an MDI is not trouble free, as many patients do not use the inhaler properly.6 This seems especially true in the elderly, who often have difficulty coordinating actuation of the spray. Spacer devices may be of use in such patients. If not, the patient can benefit from inhalation therapy by use of the small updraft nebulizers that are now readily available.

The introduction in the last decade of ipratropium, an improved understanding of optimal dosing with inhalers in COPD, and the availability of bronchodilators with distinctly different mechanisms of action has led to the development of a new treatment algorithm for COPD.7-8 This algorithm undoubtedly will continue to be refined as the health-care system seeks to streamline itself and become more cost-efficient.

Rationale for Bronchodilator Therapy
Most patients with COPD have a reversible component to their airway obstruction, as evidenced by an increase in FEV₁ following use of an inhaled bronchodilator. In a recent study involving a combination ipratropium bromide/albuterol MDI, about 80% of patients with COPD demonstrated a significant improvement in airflow (ie, >15% increase in FEV₁) when optimal bronchodilators were used.9 In addition to improving symptoms, regular use of inhaled bronchodilators in responsive patients may improve prognosis. Anthonisen et al9 analyzed data from the IPPB Trial Group and discovered that the conditions of patients with small responses to bronchodilators tended to decline rapidly, while the reverse was true of those with large responses. These results seemed to conflict with studies that indicated that bronchial hyperreactivity was a risk factor in decline of function.3,10 Since the main difference between the studies was the use of the bronchodilator, the authors postulated that bronchodilator therapy may have some potential to change the course of the disease for the better. Postma et al11 demonstrated a favorable rate of change in lung function in bronchodilator-responsive patients with long-term use of an anticholinergic bronchodilator. A long-term study from the Netherlands suggests that such an improvement may require the coordination of anti-inflammatory therapy with the bronchodilators.12 The Lung Health Study followed almost 6,000 smokers and ex-smokers with mild-to-moderate COPD for 5 years. Smoking cessation resulted in an appreciable improvement in lung function and slowing of the rate of decline in FEV₁. Ipratropium bromide caused a short-term increase in FEV₁ in this population (an on-off effect) but no apparent change in the rate of decline of FEV₁.2 Compliance may be an important variable in the analysis of such data. It is not known what effect the various bronchodilators might have on rate of decline in responsive patients who are compliant over time.

In the past 20 years, inhaled β-adrenergic agonists have gained increasing acceptance as useful therapy for COPD. These agents are effective bronchodilators in hyperresponsive patients with COPD and are generally well-tolerated. They have a rapid onset of action, which makes them particularly useful in

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acute exacerbations. The limitations of β-adrenergic use in the older population with COPD are suggested by their agonist mechanism of action, particularly their potential to cause cardiac side effects. Recently, there has been some evidence that long-term use of β-agonists may contribute to hyperreactivity,13,14 related perhaps to the aerosol itself or to the uncontrolled development of underlying inflammation.

The introduction of inhaled ipratropium bromide, a quaternary amine anticholinergic, has added flexibility to bronchodilator therapy in COPD. A study by Braun et al15 indicates that ipratropium is a more potent bronchodilator in COPD than albuterol; other studies demonstrate roughly equivalent effects between the two drugs.16 A large, multicenter trial found ipratropium to be significantly superior to metaproterenol in COPD.17 The difference between these reports may be attributable to the populations with COPD under study or to the investigators’ definitions of what constitutes COPD. Ipratropium appears to be more effective in patients with stable COPD than in patients with asthma, either because of increased cholinergically mediated airway smooth-muscle tone in patients with stable COPD or because of decreased response to adrenergic agents in these patients owing to lack of mediators in modulating smooth-muscle tone.18,19

Because ipratropium and albuterol are distinct classes of drugs with differing mechanisms of action, it seems reasonable to expect that they might have additive, complementary effects when combined. A recent 12-week, double-blind, parallel-group study compared the use, in standard doses, of ipratropium MDI, albuterol MDI, and a new aerosol combining the two in COPD.9 The mean peak increases in FEV1 over baseline were 31 to 33% for the combination, 24 to 25% for ipratropium, and 24 to 27% for albuterol. The differences between the combination and its components were significant on all test days. The area under the curve (AUC)0-4 means for the combination were 21 to 44% greater than the ipratropium means, and 30 to 46% greater than the albuterol means. No additional side effects were noted in the combination drug group. Similar results were demonstrated in a separate study of a combination of the solution form of the two drugs.20

Recent published data, based on dose-ranging studies, indicate that administration of a high-dose solution form of ipratropium bromide leads to more prolonged bronchodilation in patients with COPD than MDI dosing, with equivalent safety.21 As portable, uncomplicated nebulizers are now readily available for outpatient use, the safety and improved efficacy of solution dosing over the MDI provides a significant treatment option to the clinician. It may not be necessary to add theophylline to combination ipratropium-albuterol therapy; in many patients, a more logical third step may be to switch from combination aerosol to a combination of the inhalation solutions of the two drugs.

Not long ago, theophylline preparations were the mainstay of COPD treatment. Theophylline is a potent bronchodilator in COPD and has an advantage over the MDIs in the ease of oral administration. But theophylline also has a narrow therapeutic index. Theophylline preparations can be more difficult to prescribe than inhalers because of their known interactions with other drugs and because of alterations in the theophylline metabolism in patients with hepatic or cardiac diseases. Long-acting theophylline preparations are useful for reducing nocturnal symptoms. This class of bronchodilators may have additional beneficial effects on respiratory muscle performance and central respiratory drive.7,22

The use of corticosteroids in the management of COPD has still not been completely clarified.7 A 4-year study by Dompeling et al12 suggests that addition of beclomethasone to bronchodilator therapy can slow the unfavorable course of asthma and COPD; the effect was most evident in asthmatic patients, who are now thought to have a significant underlying inflammatory component to their disease. Clearly some patients with COPD experience symptomatic benefit from corticosteroids. Since study reports are inconsistent,23-25 it is recommended that such patients be chosen on the basis of carefully monitored clinical trials. As with β-agonists, use of corticosteroid inhalers minimizes the potential side effects of such therapy.

Therapeutic Algorithm

As reviewed, a new therapeutic algorithm for the treatment of patients with COPD is emerging. This algorithm is based on data demonstrating that most patients derive symptomatic relief as a result of improvement in the airways obstruction component of their disease with inhaled bronchodilators. Additionally, the improvement in airways obstruction seen with bronchodilators, if maintained by patient compliance, results in an improved level of lung function, and may have a positive effect on survival rates. The emerging algorithm is also based on an improved understanding of the complexity of COPD and the variable response of patients to the three classes of bronchodilators now available and to corticosteroids.

One such treatment algorithm is depicted in Figure 1. The treatment regimen is dependent on the severity of the disease process. Monotherapy using the MDI is the preferred initial choice, because of low side effects compared with systemic dosing, the convenience of the MDI, and the lower cost associated with monotherapy. Current algorithms place ipra-
Ipratropium as a first option because of its bronchodilating potency in patients with COPD and its low incidence of side effects. Optimal use of ipratropium requires regular dosing. The recommended dose is two puffs four times daily, but may be increased to six puffs in most patients without significant risk. As discussed, higher dosing with ipratropium solution will lead to more prolonged bronchodilation without additional side effects or decline in responsiveness with long-term therapy.

As the airway obstruction associated with COPD becomes more severe, the next therapeutic option is to add an inhaled β-agonist (albuterol) to ipratropium. The standard MDI dosing is four times daily. A new MDI combining ipratropium and albuterol in standard doses may improve compliance. Albuterol alone is not preferred to ipratropium in current algorithms because of its potential side effects and ongoing questions about hyperreactivity with prolonged use.

If patients do not respond adequately to combination aerosol therapy, the attending physician has two options. One is to switch to a combination of the ipratropium and albuterol solutions. This regimen improves bronchodilation by delivering higher doses of the drugs than can be safely accomplished with MDIs; the higher dose of ipratropium also favors more prolonged effect. The two solutions can be mixed conveniently, and nebulizer therapy may be easier for many patients to self-administer than MDI therapy.

An alternative to switching to combination solution would be to add a long-acting theophylline preparation to the combination MDI. Some patients may find this simpler and more convenient than using a nebulizer. Such a regimen, however, does require careful monitoring of serum theophylline levels, and may increase the side effects of drug therapy. Following the algorithm as described, theophylline may also be added to combination nebulizer therapy with the ipratropium and albuterol solutions.

Since corticosteroids are effective in some patients with COPD, particularly those with an inflammatory component to their disease, these drugs should be kept in mind by the clinician. Use of corticosteroids should be carefully monitored. If a positive response is obtained, the dose should be titrated down to minimize side effects. Oral corticosteroids are a useful option in patients who have difficulty administering aerosols.

**CONCLUSION**

The growing realization in recent years that airways obstruction in patients with COPD can be significantly relieved with the use of bronchodilators has changed the clinical approach to treating this disease. As demonstrated by the Lung Health Study, the physician’s first priority is to encourage all patients.
who smoke to stop. If significant airways obstruction persists, stepped-care implementation of bronchodilator therapy is indicated. The current treatment algorithm begins with inhaled ipratropium, which can be successfully supplemented with β-agonists and theophylline. Cautious use of corticosteroids may also be beneficial.

REFERENCES
5 Anthonisen NR, Wright EC, IPPB Trial Group. Response to inhaled bronchodilators in COPD. Chest 1987; 91:365-395
9 COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. Chest 1994; 105:1411-19
10 Barter CE, Campbell AH. Relationship of constitutional factors and cigarette smoking to decrease in 1-second forced expiratory volume. Am Rev Respir Dis 1976; 113:305-14
20 Levin DC, Little KS, Laughlin KR, et al. Ipratropium bromide solution in COPD augments extent and duration of FEV₁ increases achieved by albuterol up to 85 days. Chest 1993; 104(suppl):112s