Combination Bronchodilator Therapy in COPD*

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A number of agents are available for the treatment of patients with COPD. For agents whose suggested mode of action is quite distinct (Table 1), a combination of various agents in a single therapeutic regimen is commonplace. The rationale for combination therapy, however, is less clearcut in the use of bronchodilators. Three major classes of bronchodilators are available: β-agonists, anticholinergics, and theophyllines. Data defining the optimal use of these various classes of bronchodilators are, as yet, incomplete. While many issues remain controversial, this review will describe some of the information that supports the use of combined bronchodilator therapy in patients with COPD.

**METHODOLOGIC CONSIDERATIONS**

One limitation to the clinical assessment of drug combinations is the method used to assess benefit. Survival studies have not been performed because of the expense and length of time required. Studies assessing symptoms and quality of life have been more practical, but the end points measured have often been regarded as subjective. Current studies assessing cost of care may provide additional information; however, experience with pharmacoeconomic analyses is limited and how such studies will change practice is undetermined. In general, bronchodilators have been assessed using physiologic measures, predominantly measures of airflow. In this regard, spirometry has been paramount.

The spirogram has been of tremendous use in studies of patients with obstructive airways disease both because it provides an objective measure of airflow and because the test is relatively reproducible both within and among centers. Nevertheless, it has been recognized for many years that the forced expiratory maneuver is not “natural” breathing and, in some patients, the FEV₁ will not be strictly reflective of symptoms or clinical status. In addition, changes in functional residual capacity can lead to alterations in tidal breathing, concurrently in symptoms and clinical status, without there being similar changes in FEV₁. Moreover, COPD is a complex and heterogeneous syndrome. Even with the same degree of airflow obstruction, for example, the “pink puffer” differs dramatically from the “blue bloater.” Thus, spirometry, while the single most useful proximate end point in the assessment of bronchodilator drugs in COPD, should not be regarded as a tool by which all clinical benefits can be assessed.

**THEOPHYLLINE AND β-AGONISTS**

Bronchodilator therapy in COPD using β-agonists combined with theophylline has a long history. It is well recognized that both classes of drugs can have diverse effects. With respect to bronchodilation, β-agonists are thought to work directly on smooth muscle. Following binding of β-agonists to receptor on the surface of smooth muscle cells, adenylcyclase is activated through the mediation of a G-protein. The increase in intracellular cyclic adenosine monophosphate (AMP) then leads directly to smooth muscle relaxation. Theophylline is thought to work in this pathway by virtue of its ability to inhibit broadly cellular phosphodiesterase enzymes. By inhibiting

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**Table 1—Drugs for COPD**

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<td>Bronchodilators</td>
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<td>Theophylline</td>
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<td>β-agonists</td>
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<td>Anticholinergics</td>
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<td>Anti-inflammatory drugs</td>
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<td>Glucocorticoids</td>
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these enzymes, cellular levels of cyclic AMP remain elevated, and bronchodilation results. Inasmuch as β-agonists stimulate the production of and theophylline inhibits the degradation of cyclic AMP, it is rational to assume the drugs may have synergistic or at least additive effects.

A number of clinical studies support the combined use of theophylline and a β-agonist. Tandon and Kailis,\textsuperscript{11} for example, in a study of 30 patients with COPD, evaluated theophylline, terbutaline, and the combination. Airflow, measured by FEV\textsubscript{1}, was superior when the patients were taking both drugs than when either drug was used alone and individual drugs were superior to a double placebo. While similar results have been observed by other investigators,\textsuperscript{12-16} this added benefit has not been universally observed, may depend on mode of administration,\textsuperscript{17,18} and has not always been associated with clinical benefit.\textsuperscript{19,20} Handslip et al\textsuperscript{21} for example, assessed ten asthmatic subjects taking either theophylline, albuterol, or the combination in varying doses for short-term effects on airflow as assessed by FEV\textsubscript{1}. In general, albuterol was a superior bronchodilator to theophylline and albuterol alone was equivalent to albuterol combined with theophylline. Filuk and colleagues,\textsuperscript{22} in contrast, could identify two classes of patients with COPD: responders and nonresponders. In a study of 13 patients, all of whom had COPD, short-term improvements in airflow were assessed following the sequential administration of albuterol or theophylline 90 min apart. Nonresponders had no improvement in airflow following either drug. Responders, in contrast, had improvement in airflow following the administration of both bronchodilators when used as the initial therapeutic agent and had further bronchodilation when given the second drug. Interestingly, the additive benefit of a second bronchodilator seemed to be superior when theophylline was given prior to administration of albuterol, suggesting that a sequential effect may be important. Thus, it is possible that studies not demonstrating a benefit of theophylline combined with a β-agonist may have included a number of “nonresponders” or may have failed to reveal acute effects because of the importance of a sequential effect.

While the subject remains controversial, many prominent pulmonologists continue to believe that combined therapy is important.\textsuperscript{1,2,23,24} Snider,\textsuperscript{24} for example, has summarized clinical approaches: “Because theophylline has a different mode of action, it continues to have a useful place in the ambulatory management of chronic obstructive pulmonary disease.”

While the utility of this combination may well depend on improvements in airflow as assessed by FEV\textsubscript{1}, it is important to remember that both agents can have a variety of other beneficial effects. Thus, clinical benefits may exceed apparent improvements in FEV\textsubscript{1}. Taylor and colleagues,\textsuperscript{12} for example, studied 25 patients with chronic bronchitis using a double crossover design similar to that used by Tandon and Kailis.\textsuperscript{11} While they found that the combination resulted in superior FEV\textsubscript{1} to either drug alone or to the placebo, the benefits were very small, 7% improvement for the combination compared with 4% for theophylline and 2% for albuterol used alone. When the patients, however, rated their own response to the various drugs, more than 50% ranked the combination as the best therapy while more than 50% ranked the double placebo as the worst. Thus, while the precise modes of action remain to be fully delineated, the weight of clinical evidence would, at present, seem to support the use of β-agonists and theophylline in combination in patients with COPD both because of improved airflow as assessed by FEV\textsubscript{1} and by improved symptoms.

**Anticholinergics**

The third major class of bronchodilator currently available for use in COPD is anticholinergic drugs.\textsuperscript{8,9,25} These drugs are thought to inhibit the action of acetylcholine released at cholinergic nerve endings on smooth muscle which, through actions on the M3 muscarinic receptor on smooth muscle, lead to smooth muscle contraction. It is important to note that currently available anticholinergics are not selective and can inhibit other classes of muscarinic receptor. Anticholinergics, therefore, can reduce “cholinergic tone” in the airways and improve airflow. Because β-agonists are thought to directly induce bronchodilatation, it has been suggested that a maximal degree of bronchodilatation can be achieved, and that a single drug used to maximum effect can induce all possible improvements in airflow. Several studies would seem to support this argument.\textsuperscript{26-28} Karpel and colleagues,\textsuperscript{29,30} for example, administered either the β-agonist albuterol or the anticholinergic ipratropium and followed airflow short term. Thirty minutes after the first drug, the alternative drug was added. In 32 patients with COPD in acute exacerbation, both drugs resulted in a significant improvement in airflow short term. Addition of a second drug resulted in no further bronchodilatation. Thirty subjects were restudied several weeks following the acute exacerbation, and a similar effect was observed: both drugs caused initial bronchodilatation, but addition of a second drug had no additional effect. Interestingly, when the patients were in stable condition, airflow was considerably better than the “maximum” obtained during the exacerbation, suggesting that “maximal airflow” in

172S

Innovations in Combination Bronchodilator Therapy

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these subjects is, in fact, somewhat variable. This led to the accompanying editorial comment by Levy:31 “We must be clear regarding maximal bronchodilatation, a relative term not an absolute one.”

A number of studies have been conducted comparing various strategies for adding anticholinergics and β-agonists in COPD. While several of these studies clearly show additive benefits,28-30 others do not.26-28,35,41-43 This may depend on the nature of the circumstances of the patient at the time when the study was done and may depend on the design by which the studies were conducted and the drugs administered. A large multicenter clinical trial comparing albuterol, ipratropium, and a combination suggests significant benefit is obtained with the combination.44 Even in the absence of a synergistic mechanistic effect within a single cell, combination therapy with an anticholinergic and a β-agonist may have benefits by virtue of their site of action. That is, β-agonists may be relatively more effective in the distal airways while anticholinergics may be of more benefit in the proximal airways. In addition, these drugs have differing time courses for their bronchodilator effect. Thus, a combination may have time course benefits not seen by either drug alone.

A recent double-blinded, parallel, placebo-controlled study assessed the hypothesis that ipratropium bromide solution added to albuterol increases bronchodilatation over a 90-day period.45 One group received ipratropium bromide, 500 μg added to albuterol, 2.5 mg, administered via a nebulized solution. The second group received a placebo added to 2.5 mg of albuterol administered by the same route. All subjects had to be smokers (≥10 pack-years) or ex-smokers, over age 40 years, and have stable COPD with an FEV₁ <65% of predicted and an FEV₁/FVC ratio <75%. Asthma, significant complicating medical illnesses, recent upper respiratory tract infections, and any problems that might put participants at risk with the administration of anticholinergics were exclusionary criteria. Albuterol administered alone resulted in a significant improvement in FEV₁ and in forced vital capacity. Ipratropium, when added in combination with albuterol, resulted in improved maximal airflow, and the improvement in airflow was more long lasting. These benefits of the combination over albuterol alone were observed both on the first day of the trial and after 90 days.

**Other Drugs and Bronchodilation**

Drugs other than direct bronchodilators can also have significant effects on airflow. Inflammation of the airway, for example, is thought to play an important role in chronic bronchitis. By causing tissue edema and by distorting tissue architecture through the infiltration of inflammatory cells, inflammatory processes can alter airway architecture. Not only is airflow dependent on airway structure, but the effects of bronchodilatation greatly depend on airway diameter: smaller airways are much more sensitive to bronchoconstriction than are larger ones.46 Thus, in the face of edema or inflammation, a relatively small degree of bronchoconstriction can have an increased effect in reducing airflow. Conversely, an agent that reduces airflow inflammation can augment the effects of bronchodilators. In this regard, most studies have found that glucocorticoids, while not direct bronchodilators, improve airflow in a number of patients when administered by both inhaled and systemic routes.49-52 However, this has not been a universal finding,53 and patient selection may be critical.52 The effects of glucocorticoids on airflow, as would be expected from an effect on inflammation, develop more slowly than direct bronchodilators. It is, as yet, unclear how long a clinical trial of glucocorticoids is required to determine if a given patient will benefit from such therapy.50,54,55 In current practice, a trial of several weeks is recommended as a minimum.1,2 One current strategy is to administer 0.5 to 1 mg prednisone or equivalent orally each morning for 2 to 3 weeks. Improvement in FEV₁ of 20 to 25% compared with baseline should be regarded as a positive response.

The long-term benefits of glucocorticoids administered together with bronchodilators in patients with COPD are not completely understood. In one study, Dompeling and colleagues56 noted that beclomethasone added to a regimen of bronchodilators resulted in improved lung functioning. When followed up over a period of 2 years, however, subjects with COPD treated with beclomethasone continued to demonstrate a decline in lung function at the same rate as that prior to beclomethasone, although their decline was occurring from an improved level. Thus, current data would certainly support the addition of glucocorticoids in combination with bronchodilators to improve airflow at least in selected individuals. Whether such combination therapy would alter the long-term outcome in patients with COPD, however, remains unresolved.

It is also important to realize that other therapeutic modalities can be effectively combined with bronchodilators. Oxygen therapy for appropriate individuals can both prolong life and improve level of functioning.57,58 Mucolytic drugs are often associated with symptomatic relief.59,60 While controversial, immunization with polyvalent pneumococcal polysaccharide vaccine probably reduces the severity if not the incidence of pneumococcal pneumonia in patients with COPD.61 Vaccination with an appropriate strain of influenza vaccine can reduce occurrence and mortality of influenza A infections 70 to
As new therapeutic modalities are developed, it is almost certain that they will be added to already existing combination therapeutic regimens. The assessment of such combinations in individual patients will require skill and care on the part of the attending physicians.

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