Editorial

Should long-acting β₂-agonists be considered an alternative first choice option for the treatment of stable COPD?

M. CAZZOLA AND M. G. MATERA

"S. Maugeri" Foundation, Institute of Care and Research, Medical Centre of Rehabilitation, Clinical Pharmacology Unit and Respiratory Pharmacology Center, Veruno, (NO), Italy

Current opinion is that β₂-adrenoceptor agonists are more active than anticholinergic drugs in the symptomatic treatment of bronchial asthma, whereas anticholinergic agents are equally effective and/or more efficacious than β₂-adrenoceptor agonists in chronic obstructive pulmonary disease (COPD) or emphysema. The acceptance of anticholinergic drugs for the reduction of dyspnoea in stable COPD outpatients, as opposed to β₂-agonists, is mainly due to its slightly longer duration of action and very low incidence of adverse effects when used at the recommended dosages (1). In effect, 36 out of 38 published studies which compared anticholinergic agents and β₂-adrenoceptor agonists on various spirometric parameters found anticholinergic agents to be at least equal, and generally superior, to β₂-adrenoceptor agonists (2). Consequently, the recent guidelines from the American Thoracic Society (3) suggest the inhaled administration of an anticholinergic agent as first-line therapy in stable COPD.

The mechanisms by which anticholinergics may have a greater effect on airway function in COPD are uncertain as, if cholinergic tone were the only reversible component, it might be predicted that β₂-agonists would be equally effective in inhibiting cholinergic tone. In any case, in normal airways vagal bronchomotor tone has little effect on airway calibre but when the airways are narrowed to the same degree of tone in COPD this has a marked effect on airway resistance (which is proportional to the fourth power of the radius). Consequently, reversing this tone by anticholinergic drugs will have a significant beneficial effect (4).

β₂-agonists remain first-line therapy only for the acute relief of COPD symptoms because of their rapid onset of action (1). However, the introduction of long-acting β₂-adrenoceptor agonists (e.g. salmeterol and formoterol) gives physicians additional therapeutic options for stable COPD. Both salmeterol and formoterol induce an improvement in airflow limitation after long-term therapy (5,6).

Unfortunately, only a few studies have compared the efficacy of long-acting β₂-agonists with anticholinergic agents. We (7) have recently proved that the onset of bronchodilation after 400 µg ipratropium bromide is slower than that after 200 µg salbutamol, but ipratropium bromide produces a longer-lasting bronchodilation than salbutamol. However, 50 µg salmeterol is as effective as ipratropium bromide in terms of the degree of bronchodilation and has a longer duration of action than ipratropium bromide. A later American study (8) has confirmed our finding and showed that a single administration of 42 µg salmeterol produced a greater improvement in pulmonary function than two administrations of 36 µg ipratropium in patients who demonstrated reversibility to ipratropium. We must highlight that the clinically recommended dose of ipratropium used in both studies might be considered too low as forced expiratory volume in 1 sec (FEV₁) reached a plateau only after administration of a cumulative dose of 280 µg (14 puffs) in patients with COPD (9). It is unlikely that a patient suffering from COPD would inhale 14 cumulative puffs in rapid succession 3-4 times daily. In any case, we (10) have also shown that four puffs (400 µg) of oxtitropium bromide, another anticholinergic drug which produces a similar degree of bronchodilation to that obtained with ipratropium bromide but with a longer-lasting effect (11), would approximate two puffs of salmeterol (50 µg) in terms of mean peak response, but that salmeterol has a longer duration of action than oxtitropium. We emphasize that 200 µg oxtitropium and 50 µg salmeterol are dosages recommended for regular therapy, but our study demonstrated that 200 µg oxtitropium bromide was not sufficient to achieve optimal bronchodilation.

Recently, salmeterol (42 µg bid) has been compared with ipratropium (36 µg qid) over 12-week periods in a double-blind, placebo-controlled, cross-over study involving 813 patients with mild to moderate COPD. During salmeterol treatment, subjects did statistically better in terms of all the measured parameters (12) and, equally importantly, salmeterol was as safe as ipratropium (13).
Continue therapy

Optimal outcome achieved

Long-acting \( \beta_2 \)-agonist

Add anticholinergic, 2–6 puffs every 3–6 h

Add long-acting theophylline 300–900 mg day\(^{-1}\) (serum level, 8–12 \( \mu \)g ml\(^{-1}\))

Add corticosteroids; prednisone 40 mg day\(^{-1}\) for 14 days

Improvement but suboptimal outcome

No change

Discontinue anticholinergic

Discontinue theophylline

Discontinue corticosteroids

**Fig. 1.** Proposed new regimen for treating stable COPD.

As \( \beta_2 \)-agonists and anticholinergic agents are distinct classes of drugs with different mechanisms of action, an additive effect may be expected (4). For these reasons the American Thoracic Society (3) suggests increasing the dosage of ipratropium to as high as six puffs every 6–8 h and then adding up to four puffs of a short-acting \( \beta_2 \)-agonist four times daily as needed or as scheduled. However, a number of clinical studies have shown a benefit of combining low doses of a \( \beta \)-agonist with an anticholinergic agent. For instance, in 534 patients suffering from COPD the combination of ipratropium and salbutamol was more effective than either of the two drugs alone after 12 weeks of treatment (14). We have documented in 12 patients with stable COPD that 40 \( \mu \)g ipratropium does not produce any further bronchodilation than that achieved with 50 \( \mu \)g salmeterol alone, although the onset of action after the combination of the two drugs may be faster than after salmeterol alone (15). It is conceivable that the subjects studied in this specific clinical situation were at the top of their bronchodilation response curve after inhalation of salmeterol. In any case, the results of this study apparently refute the assertion that airways obstruction secondary to increased vagal tone is the only dominant reversible element in patients suffering from COPD. Nonetheless, van Noord et al. (16) have recently demonstrated that a 12-week treatment with 50 \( \mu \)g salmeterol bid plus 40 \( \mu \)g ipratropium bromide qid was more effective than 50 \( \mu \)g salmeterol bid in improving FEV\(_1\) and specific airway conductance (SGaw) in 144 patients with moderate to severe COPD, although the patients did not experience any additional effect in symptom control. In any case, the use of salbutamol as rescue medication in order to cause rapid relief of bronchospasm in patients suffering from partially reversible COPD is always possible after single conventional inhaled dose of a long-acting \( \beta_2 \)-adrenoceptor agonist (17).

All these recent findings with long-acting \( \beta_2 \)-agonists raise the question if it is still correct to consider an anticholinergic drug as the bronchodilator therapy of first choice in the treatment of stable COPD. The late British Thoracic Society guidelines (18) for the management of COPD suggest starting with short-acting \( \beta_2 \)-agonists used as required and adding or substituting an anticholinergic when \( \beta \)-agonists do not control symptoms or if regular maintenance therapy is desired. Moreover, these guidelines recommend limiting the use of long-acting \( \beta_2 \)-agonists to patients with a demonstrable response to short-acting \( \beta_2 \)-agonists. This limitation is not correct. In fact, we (19) have demonstrated that patients with COPD who do not manifest early reversibility to salbutamol can still benefit from salmeterol. Therefore, treatments with long-acting \( \beta_2 \)-agonists must always be tried.

For all considerations, we believe that long-acting \( \beta_2 \)-agonists should be considered an alternative first-choice option to the algorithm supplied by Ferguson and Cherniack (20) (Fig. 1). However, since those patients suffering from COPD with pre-existing cardiac arrhythmias being treated with long-acting \( \beta_2 \)-agonists could be at special risk of developing new arrhythmias or of aggravating pre-existing ones (21), the use of anticholinergic drugs is preferable in COPD patients suffering from pre-existing cardiac arrhythmias and hypoxaemia.

### References


