Tiotropium improved lung function more than ipratropium in chronic obstructive pulmonary disease

van Noord JA, Bantje Th A, Eland ME, et al, on behalf of the Dutch Tiotropium Study Group. ***A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease****. Thorax 2000 Apr;**55**:289–94.*

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QUESTION: In patients with stable chronic obstructive pulmonary disease (COPD), what is the long term effectiveness and safety of tiotropium compared with those of ipratropium?

Design
Randomised {allocation concealed*}†, blinded (patient and outcome assessor),* controlled trial with 13 weeks of follow up.

Setting
14 centres in the Netherlands.

Patients
288 patients ≥40 years of age (mean age 64 y, 83% men) who were current or past smokers with a diagnosis of COPD and stable airways obstruction, an FEV_1 < 65% of the predicted normal rate, and a ratio of FEV_1 to forced vital capacity (FVC) of <70%. Exclusion criteria included a history of asthma, allergic rhinitis, or atopy; a recent history of myocardial infarction, heart failure, or cardiac arrhythmia requiring drug treatment; upper respiratory tract infection in the past 6 weeks; and hypersensitivity to anticholinergic drugs. 90% completed all tests.

Intervention
191 patients were assigned to tiotropium, 18 µg once daily, delivered by a dry powder inhaler system; and 97 were assigned to ipratropium, 40 µg 4 times daily, delivered by a metred dose inhaler. Each group also received placebo doses of the other treatment.

Main outcome measures
Lung function, peak expiratory flow (PEF), use of concomitant salbutamol, and adverse effects.

Main results
Trough, peak, and mean FEV_1 response and trough and mean FVC response showed greater improvement with tiotropium than with ipratropium (table). Morning and evening PEF was consistently better with tiotropium ($p < 0.05$). Use of concomitant salbutamol was lower in the tiotropium group ($p < 0.05$). The groups did not differ for adverse effects.

Conclusions
In patients with chronic obstructive pulmonary disease, tiotropium improved lung function more than ipratropium. The safety profiles of the 2 drugs were similar.

*See glossary.

†Information provided by the author.

Tiotropium v ipratropium at 13 weeks in chronic obstructive pulmonary disease (lung function improvement, in litres, compared with baseline at start of study)‡

Outcomes	Tiotropium	Ipratropium	Mean difference (95% CI)
FEV_1 trough	0.16	0.03	0.13 (0.08 to 0.18)
FEV_1 peak (at 50 d)	0.38	0.30	0.08 (0.02 to 0.15)
FEV_1 mean (over 6 h)	0.26	0.18	0.08 (0.03 to 0.13)
FVC trough	0.39	0.18	0.21 (0.10 to 0.32)
FVC mean (at 50 d)	0.62	0.45	0.17 (0.50 to 0.29)

‡FVC=forced vital capacity.

COMMENTARY

The anticholinergic agent ipratropium bromide is frontline treatment for patients with non-asthmatic COPD.[1] In most of these patients, ipratropium used alone is more effective as a bronchodilator than is an inhaled β-agonist used alone. (Combination therapy, however, is often more effective than either agent used alone.) Ipratropium bromide has a relatively short duration of action, requiring inhalation every 6 to 8 hours. In addition, ipratropium non-selectively inhibits all 3 of the known muscarinic receptors in the human airway (M_1, M_2, and M_3). This is of theoretical concern because the M_2 receptor normally acts as a feedback inhibitory receptor; blockade of the M_2 receptor results in increased acetylcholine release in the airway and could attenuate or reverse the bronchodilation achieved by blockade of the M_1 and M_3 receptors.[2] The clinical relevance of this issue is uncertain.

Tiotropium is a potent and long lasting muscarinic antagonist that has "kinetic selectivity" for M_1 and M_3 receptors over M_2 receptors.[2] A single dose of inhaled tiotropium produces bronchodilation for 24 hours in patients with COPD,[3] and attenuates methacholine induced bronchoconstriction for 48 hours in patients with asthma.[4] Once daily dosing for 4 weeks in stable patients with COPD provides sustained bronchodilation with an excellent safety profile.[5]

The study by van Noord *et al* provides important data, showing the superiority of tiotropium (18 µg once/d) over the usual dose of ipratropium (40 µg 4 times/d). Patients were permitted to use many of their own usual medications (including methylxanthines, inhaled steroids, and oral steroids up to 10 mg of prednisone/d) during the course of the trial, showing the effectiveness of tiotropium in a meaningful clinical context. Tiotropium, not yet approved for use in the United States, appears to have great potential in the long term maintenance treatment of COPD.

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