

NEW DRUG EVALUATION

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TIOTROPIUM

Tiotropium is a long-acting, inhaled antimuscarinic bronchodilator for the maintenance treatment of COPD. Clinical trials over 6 - 12 months demonstrate that it improves lung function, respiratory symptoms and quality of life scores compared with ipratropium or salmeterol. Compared with ipratropium it also reduces frequency of exacerbations and use of rescue medication. These differences are not large and in view of its expense, tiotropium should be reserved for those patients who remain symptomatic with alternative therapy and where there is objective improvement following a therapeutic trial.

What is it?

Tiotropium is a long-acting inhaled antimuscarinic bronchodilator for the maintenance treatment of chronic obstructive pulmonary disease (COPD). Its prolonged duration of action is due to persistent binding to bronchial muscarinic M3 receptors, which is significantly longer than that of ipratropium¹. It has a slow onset of action (1 - 2 hours), making it unsuitable for acute symptomatic relief². The recommended dose is 18 mcg once daily, taken at the same time each day. It is administered via a breath-actuated dry powder inhaler.

How effective is it?

Tiotropium has been compared in 2 pooled analyses of 4 one-year double-blind trials with placebo (n=921)³ and ipratropium (n=535)⁴, in patients with moderately severe COPD (FEV₁ 46% of predicted).

Compared with placebo³, chronic dosing with tiotropium was associated with significantly improved lung function (pre-dose FEV₁; increased over placebo by 0.12 - 0.15 L, p<0.01). Tiotropium was also associated with a reduced COPD symptom score, an absolute reduction of 6% in exacerbations and 3.9% fewer admissions for exacerbations. Over the five assessment points during the year, clinically meaningful improvement in breathlessness was reported by 42 - 47% of patients treated with tiotropium compared with 29 - 34% of those taking placebo. Shortness of breath and wheezing were improved but there was no significant change in cough or chest tightness. After one year, patients taking tiotropium were using significantly fewer daily rescue doses of salbutamol (3.2 vs. 4.1) compared with placebo. There was no evidence of tachyphylaxis³ or rebound effects following discontinuation².

Compared with ipratropium 40 mcg qds, tiotropium was associated with significantly greater improvements in FEV₁ (0.12 L vs -0.03 L, p<0.001) and

symptom scores⁴. Clinically meaningful improvement in dyspnoea occurred in 31% of patients treated with tiotropium and 18% with ipratropium (NNT = 8). Meaningful improvement in quality of life scores occurred in 52% of patients with tiotropium and 35% with ipratropium (NNT=6). Fewer patients taking tiotropium experienced exacerbations (35% vs. 46% with ipratropium, p=0.014) or were admitted to hospital (7.3% vs. 11.7%, p=ns). Tiotropium was also associated with less use of rescue salbutamol.

In a double-blind, placebo controlled comparative trial with salmeterol 50 mcg bd (n=623)⁵, tiotropium was associated with a significantly greater pre-dose FEV₁ compared with salmeterol after 6 months, though the difference was small (0.05 L). The dyspnoea score worsened after 3 months in patients taking salmeterol or placebo but continued to improve in those taking tiotropium until at 6 months the difference between tiotropium and salmeterol was significant (0.78 U, p<0.05). There were no significant differences between the bronchodilators in the incidence of exacerbations or use of rescue salbutamol. There was a clinically meaningful change in health-related quality of life score in 51% of patients taking tiotropium, significantly more than with salmeterol (40%) or placebo (42%).

How safe is it?

The commonest adverse event associated with tiotropium is dry mouth. This occurs in approximately 10% of patients (twice as many as with ipratropium)^{4,5}; it is reportedly mild and resolves during treatment⁴. Other reported events include constipation, sinusitis, pharyngitis and moniliasis; constipation and dry mouth may be more common in elderly patients⁶.

When should it be used?

Tiotropium is an alternative to ipratropium or a long-acting beta-2 agonist for maintenance treatment for

patients with moderate to severe COPD who are symptomatic despite as-required use of a short-acting bronchodilator. In view of its cost, a trial of therapy should be reserved for patients who remain symptomatic in spite of optimised treatment with ipratropium or salmeterol. Tiotropium should be continued where there is objective evidence of improvement.

Patients will need to be supported in the use of the new device; until more experience is available with COPD patients it is not possible to predict its acceptability or ease of use.

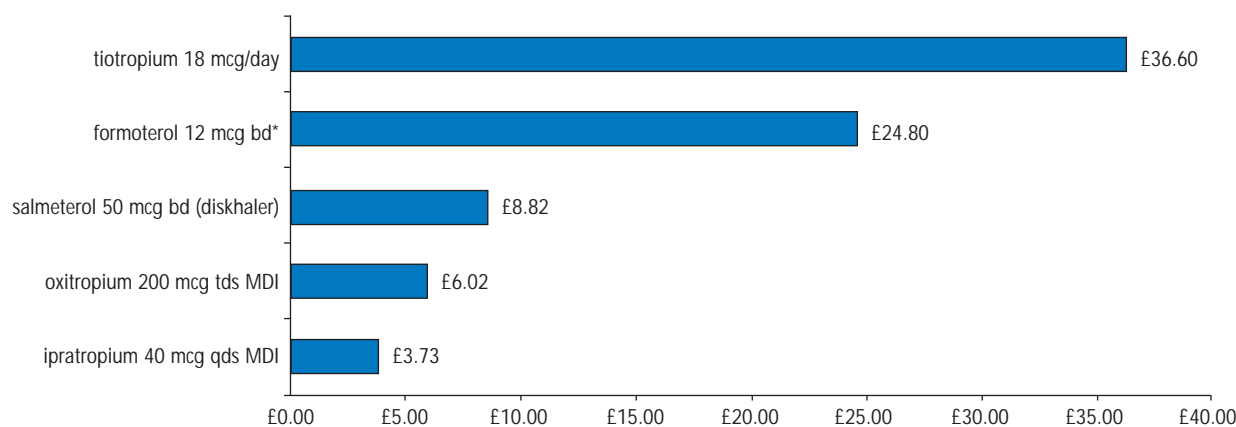
What other options are there?

The British Thoracic Society guidelines⁷ (due to be updated by NICE, Spring 2003) suggest that an inhaled short-acting beta-2 agonist such as salbutamol is indicated for acute symptomatic relief in patients with

COPD. Ipratropium has a slower onset but longer duration of action than salbutamol and is preferred for patients with stable COPD who are symptomatic despite as-required use of a beta-2 agonist⁸. The place of the antimuscarinic agent oxitropium, which requires fewer daily doses than ipratropium, is uncertain. A limited trial of high dose inhaled steroids or oral steroids should be considered for patients with moderate airflow obstruction to determine the extent of the airway reversibility and to ensure that asthma has not been overlooked.⁹ The long-acting beta-2 agonists salmeterol and formoterol are options for additional treatment if objective evidence of improvement is available; both are superior to ipratropium^{10,11}. Combined treatment with an antimuscarinic agent and a beta-2 agonist may be useful when optimal monotherapy is insufficient.⁸

How much does it cost?

Cost for 30 days treatment (prices from MIMS November 2002)



* 28 days
NB Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, A- abstract, E-editorial

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