Eur Respir J 2002; 19: 639–644
DOI: 10.1183/09031936.02.00238002
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease

J.A. van Noord*, J.J. Smeets*, F.L.J. Custers*, L. Korducki#, P.J.G. Cornelissen¶

Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease. J.A. van Noord, J.J. Smeets, F.L.J. Custers, L. Korducki, P.J.G. Cornelissen. ©ERS Journals Ltd 2002.

ABSTRACT: Tiotropium (Spiriva®) is a new once-daily inhaled anticholinergic that has its effect through prolonged muscarinic $(M)_3$ receptor antagonism. It has a clinically documented, long duration of action with once-daily dosing in chronic obstructive pulmonary disease (COPD). A single-centre, double-blind, ipratropium-controlled study was conducted in order to characterize the onset of pharmacodynamic steady state of tiotropium in patients with COPD. Thirty-one patients (25 male, six female) with a mean age of 62 yrs and a mean forced expiratory volume in one second (FEV_1) of 1.13 L (38% of predicted) were randomly assigned to receive either tiotropium 18 µg once-daily from a dry-powder inhaler (HandiHaler®, 20 patients), or ipratropium 40 µg four-times daily from a pressurized metered-dose inhaler (11 patients) for a period of 1 week. FEV_1 and forced vital capacity (FVC) were measured 1 h prior to, and just before inhalation (mean value of the two measurements on test-day 1 was the baseline value, while on all other test days it was the trough value), and 0.5, 1, 2, 3, 4, 5, and 6 h after inhalation of the morning dose of the study drug (one capsule and two puffs) on days 1, 2, 3, and 8.

Trough FEV_1 following 8 days of tiotropium was 0.19 L (18%) above baseline. Approximately 90% of this increase was achieved within 24 h of the first dose (0.17 L, 16%). Trough FVC increased 0.67 L (27%) on test-day 8. Approximately 70% of the improvement was observed after two tiotropium doses (0.47 L, 19%). Achievement of FVC steady state was delayed compared to FEV_1. Ipratropium performed typically with an onset of action within 30 min, a peak response between 1–2 h postdosing and a duration of action of ~4 h. It was concluded that forced expiratory volume in one second steady state with tiotropium is reached within 48 h, while continued improvements in forced vital capacity can be expected over or beyond the first week of therapy. The continued increases in forced vital capacity beyond 48 h suggests that maintenance bronchodilator therapy is required to achieve maximal changes in hyperinflation.

Eur Respir J 2002; 19: 639–644.

*Dept of Respiratory Diseases, Atrium Medical Centre, Heerlen, the Netherlands. #Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA. ¶Boehringer Ingelheim br, Alkmaar, the Netherlands.

Correspondence: J.A. van Noord
Dept of Respiratory Diseases
Atrium medisch centrum
Henri Dunantstraat 5
6419 PC HEERLEN
The Netherlands
Fax: 31 455767534
E-mail: longarts.om@wolmail.nl

Keywords: Anticholinergic
chronic obstructive pulmonary disease
hyperinflation
ipratropium
spirometry
tiotropium

Received: April 20 2001
Accepted after revision October 18 2001

Tiotropium (Spiriva®) is a newly developed anticholinergic bronchodilator, which is structurally related to the quaternary ammonium compound ipratropium. *In vitro* studies of isolated guinea pig and human airway have shown that the drug has a very long duration of action and a unique kinetic selectivity for muscarinic $(M)_3$ and M_1 over M_2-subtypes of the M receptor [1–3]. In early clinical, single-dose studies in chronic obstructive pulmonary disease (COPD) and asthma it was found that tiotropium produced a bronchodilator effect that was sustained for at least 24 h [4–6]. Recently published long-term studies demonstrated that 18 µg of tiotropium is a safe and effective bronchodilator, suitable for maintenance therapy in COPD with once-daily dosing [7–9]. Statistically significant and clinically relevant increases in the forced expiratory volume in one second (FEV_1) value before the next dose and 24 h after the previous dose, were evident at 1 week into therapy, which confirmed the long bronchodilating effect.

From a therapeutic standpoint it is relevant to know the onset of maximum bronchodilator response for a drug intended for maintenance therapy, *i.e.* its pharmacodynamic steady state. Therefore, the present study was performed in a subset of patients participating in an ipratropium-controlled long-term efficacy and safety study in COPD [8]. Serial measurements of FEV_1 and forced vital capacity (FVC) were conducted on the first 3 days as well as after 1 week of treatment in order to characterize the onset of pharmacodynamic steady state.

Methods

Patients

Patients were required to have a clinical diagnosis of COPD according to the American Thoracic Society (ATS) criteria [10]. On the initial screening visit, they

had to show stable airways obstruction with FEV1 ⩽65% pred [11] and FEV1/FVC <70%, to be ⩾40 yrs of age and to have a smoking history of at least 10 pack-yrs. Patients with a history of asthma, allergic rhinitis, atopy or an elevated total blood eosinophil count were excluded. In addition, patients with any of the following were excluded from the study: a significant disease other than COPD, a recent history of myocardial infarction, heart failure or cardiac arrhythmia requiring drug therapy, oxygen therapy, an upper respiratory tract infection in the 6 weeks prior to screening, a known hypersensitivity to anticholinergic drugs, known symptomatic prostatic hypertrophy, and narrow-angle glaucoma.

Study design

The trial was designed as a randomized, double-blind, double-dummy, parallel group study and was approved by the hospital Medical Ethics Committee. All patients gave written informed consent before any study procedure was undertaken. The 1-week treatment period was preceded by a run-in period of 2 weeks. The patients continued to take the permitted medication for their COPD in stable doses, which included inhaled steroids, oral steroids up to 10 mg·day^{-1} prednisone and mucolytics. Long-acting inhaled β_2-agonists, oral β_2-agonists and cromolyn sodium were not allowed for at least 1 month before the screening visit as well as throughout the study period. Anticholinergics were allowed during the run-in period, but were discontinued at the randomization visit. Patients were given open-label salbutamol to use as rescue medication. Patients were randomly assigned to receive either tiotropium 18 μg once-daily (Spiriva®) + ipratropium-matched placebo *q.i.d.* (two-thirds of the patients) or ipratropium 40 μg *q.i.d.* (Atrovent®) + tiotropium-matched placebo (one-third of the patients). Tiotropium was inhaled from the HandiHaler®, a dry-powder inhaler system [12], between 08:00–10:00 h. Ipratropium (two puffs of 20 μg) was inhaled from a pressurized metered-dose inhaler (pMDI) between 08:00–10:00 h, at lunch, dinner and before going to bed.

Measurements

Pulmonary function testing always started between 08:00–09:00 h. FEV1 and FVC were obtained 1 h prior to, and just before inhalation and at 0.5, 1, 2, 3, 4, 5 and 6 h after inhalation of the morning dose (one capsule and two puffs from the pMDI). While the sampling interval chosen was not optimal to identify the time of onset of action, the intervals chosen were a practical compromise of the need to perform repeated pulmonary function measurements in a COPD population. When the 6-h postdosing measurement was completed, the second daily dose from the pMDI (two puffs) was administered and pulmonary function testing was continued at 0.5, 1 and 2 h. These measurements were performed with a spirometer meeting ATS criteria [13]. The highest values of FEV1 and FVC from three technically adequate measurements were retained. Short-acting β_2-agonists and inhaled steroids were withheld 12 h before the lung function test. None of the randomized patients were receiving theophylline. In conjunction with the spirometry, measurements of blood pressure and pulse rate were collected. The laboratory safety evaluation, an electrocardiogram recording and physical examination were performed after 3 months of treatment as part of the long-term study [8].

Statistical analysis

Baseline FEV1 was defined as the mean of the two FEV1 readings in the morning of the randomization visit before inhalation of the study drug. For the other test days, the mean of the two morning predose FEV1 values was defined as trough FEV1 (*i.e.* ~23–24 h after the preceding dose of tiotropium or 8–9 h after the preceding dose of ipratropium). The trough FEV1 response was defined as the change from baseline to trough FEV1; this parameter was chosen as the primary efficacy end point in order to establish pharmacodynamic steady state. As an additional bronchodilator parameter the peak FEV1 response during the 6-h period after inhalation on the pulmonary function test days was examined. Analogous definitions were used for FVC-based parameters.

Only randomized patients with complete baseline data and data at the end of the first week were eligible for the efficacy analysis. Descriptive statistics were used to evaluate the baseline comparability of the two treatments groups and no formal statistical comparison of the treatment groups was made. Change from baseline was evaluated using a paired t-test for each treatment group. The onset of pharmacodynamic steady state was verified using a repeated measures analysis applied to the repeat measurements for each tiotropium patient taken on test-days 2, 3 and 8. Test-day was specified as a fixed effect and patient as a random effect. The model was fit using maximum likelihood with an unstructured covariance matrix for the repeated measures. The randomization list was generated using a validated internal software program. The randomized list was based on block sizes of three.

Results

Of the 35 patients screened for entry into the study, 31 were eligible. Twenty patients were randomly assigned to the tiotropium and 11 to the ipratropium group. The groups were well balanced for all demographic and baseline data (table 1). On the second test-day one patient in the tiotropium group was withdrawn from the study because of an exacerbation of COPD. Two other patients in the tiotropium group were excluded from all efficacy analysis due to incomplete data in the 1-week observation period. The mean (SEM) baseline FEV1 at the start of treatment period was 1.04 (0.09) L for the tiotropium

Table 1. – Demographics and baseline characteristics of the randomized patients

	Tiotropium	Ipratropium
Subjects n	20	11
Sex M:F	15:5	10:1
Age yrs	61±9	64±9
Height cm	170±8	173±8
Weight kg	72±14	73±14
Smoking history pack-yrs	29±12	38±16
Duration of disease yrs	11±8	10±10
FEV_1 L	1.13±0.27	1.12±0.42
FEV_1 % pred	39±11	37±11
FVC L	2.87±0.83	2.83±0.77
FEV_1/FVC %	41±9	39±9
Prestudy medication for COPD n (%) of patients		
Anticholinergics	5 (25)	5 (46)
β_2-agonists inhaled	20 (100)	10 (91)
Steroids inhaled	15 (75)	10 (91)
Steroids oral	0	0

Data are presented as mean±SD unless otherwise stated. M: male; F: female; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease.

group and 1.07 (0.12) L for the ipratropium group. The FEV_1 time/response curves after inhalation of the morning doses of tiotropium and ipratropium on test-days 1, 2, 3 and 8 are shown in figure 1.

Thirty minutes after inhalation of the first dose of tiotropium, there was a statistically significant increase of 21% in FEV_1 over baseline ($p<0.01$). The peak increase in FEV_1 at 3–4 h after inhalation was 30%, while an improvement of 23% was still found after 8 h. On test-day 2 the mean FEV_1 trough response was 16% and there was a further increase to 32% over baseline FEV_1 at 3 h after inhalation of the second day dose. This profile was maintained on test-days 3 and 8 with FEV_1 trough increases of 13% and 18% over baseline ($p<0.01$), respectively. The rapid onset of trough response following tiotropium is illustrated in figure 2. Approximately 90% of the FEV_1 improvement was achieved within 24 h after the first tiotropium dose. The repeated measures analysis showed no significant difference ($p>0.05$) among test-days 2, 3, and 8 for trough and peak response.

The inhalation of the first dose of ipratropium produced a statistically significant increase in FEV_1 of 24% over baseline after 30 min ($p<0.01$). The peak increase in FEV_1 of 26% was achieved 1–2 h after dosing, while 6 h after inhalation the response had dropped to 8% above baseline. The benefit of the additional ipratropium dose given after the 6-h measurement was evident. On test-day 2, *i.e.* after four doses of ipratropium on test-day 1, the mean FEV_1 trough response was 5%. The FEV_1 time/response curves of ipratropium on test-days 1, 2, 3 and 8 were comparable.

The mean (SEM) baseline FVC was 2.49 (0.22) L for the tiotropium group and 2.68 (0.22) L for the ipratropium group. The time/response curves on the four test days are shown in figure 3. The trough and peak response in FVC for the two drugs are illustrated in figure 2. Approximately 70% of the day 8 FVC trough response in the tiotropium group was seen on test-day 2, *i.e.* 24 h after the first dose. An additional increase was observed on test-day 3, while the peak effect was reached on day 8. The repeated measures analysis showed no significant difference ($p>0.05$) among test days for peak response. However, there was a significant difference ($p<0.05$) for trough response. Also, in the ipratropium group there was a small trough FVC response (day 8), which was of similar magnitude on test-days 2 and 3. However, as with tiotropium the trough response continued to improve from day 1–8.

Discussion

Tiotropium represents a new generation anti-muscarinic agent that has been shown to provide effective bronchodilation with once-daily dosing [7–9]. This once-daily dosing, coupled with its sustained

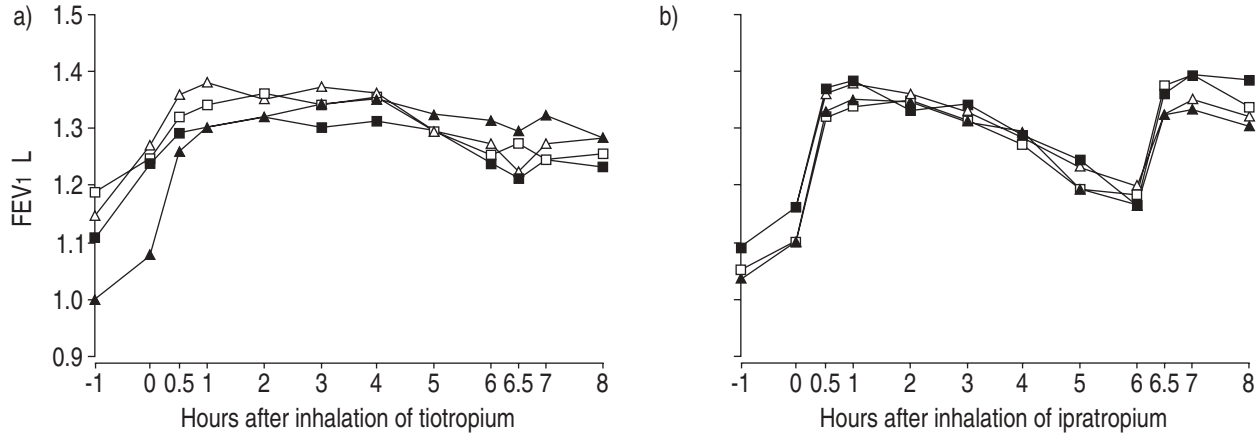

Fig. 1. – a) Mean value (SEM ranged from 0.08–0.10 L) of forced expiratory volume in one second (FEV_1) before and during 8 h after inhalation of tiotropium. b) Mean value (SEM ranged from 0.09–1.06 L) of FEV_1 before and during 8 h after inhalation of ipratropium. ▲: day 1; △: day 2; ■: day 3; □: day 8.

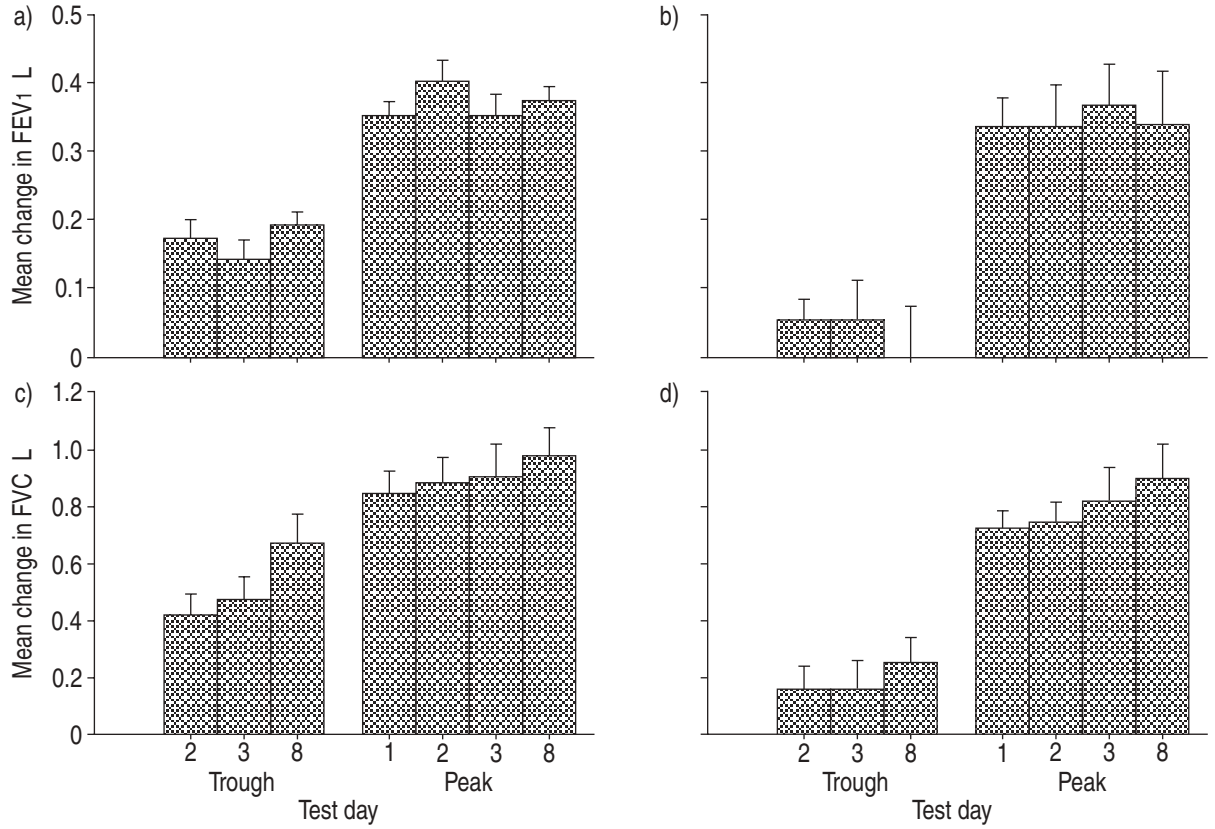

Fig. 2. – Mean and SEM (whiskers) changes in trough and peak (over 6 h) response in forced expiratory volume in one second (FEV_1) following inhalation of a) tiotropium and b) ipratropium and forced vital capacity (FVC) following inhalation of c) tiotropium and d) ipratropium on test-days 2, 3 and 8.

effects throughout the dosing period [7–9] makes it an attractive agent for maintenance therapy. In general, published information on the spirometric characterization of bronchodilators in COPD has included measurements at the beginning of testing and often 1 week or 1 month later. This study sought to define precisely the achievement of spirometric steady state in order to fully characterize tiotropium by monitoring serial spirometry daily for the first 8 days of therapy. The primary finding was that trough FEV_1 improvement reached steady state over the first 2 days of therapy.

This rapid steady state in the lung is not unexpected as the topical concentration following inhalation of 18 μg rapidly equilibrates with lung fluid and membrane-bound receptors in the lung tissue. These

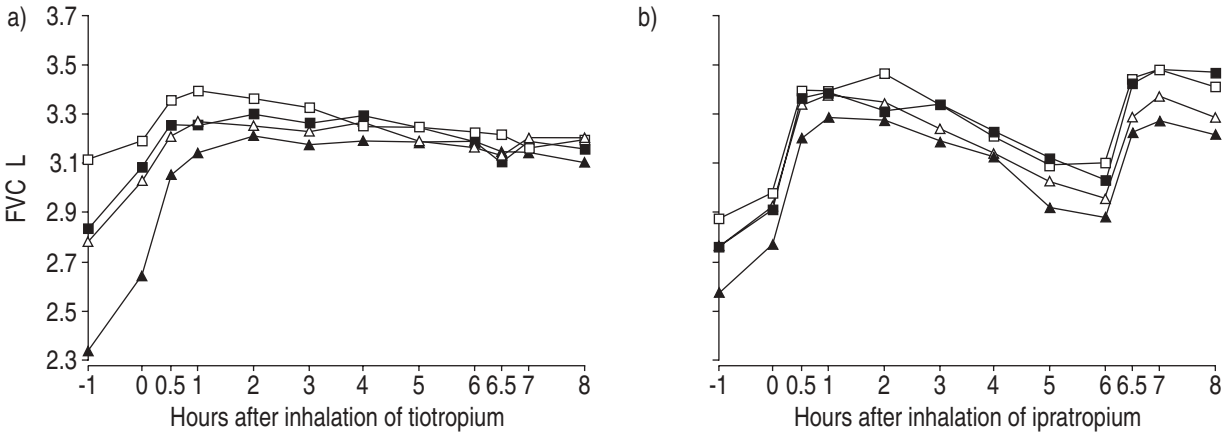

Fig. 3. – a) Mean value (SEM ranged from 0.18–0.24 L) of forced vital capacity (FVC) before and during 8 h after inhalation of tiotropium. b) Mean value (SEM ranged from 0.15–0.27 L) of FVC before and during 8 h after inhalation of ipratropium. ▲: day 1; △: day 2; ■: day 3; □: day 8.

concentrations are high in relation to the affinity constant of tiotropium at M_3-receptors and probably leads to saturation of >90% with the first dose [3]. The rapid onset of pharmacodynamic steady state is in contrast to the achievement of steady state in plasma. Here, as with many long-acting agents, which achieve a long duration of action by long plasma half-lives, there is a slow linear accumulation in plasma with steady state achieved at very low levels (*i.e.* 5 $pg \cdot mL^{-1}$) by the second to third week of treatment. Thus, there is no chronic accumulation beyond this level as evidenced by steady plasma levels for several months [14].

While the FEV1 trough response reached pharmacodynamic steady state rapidly, the maximum FVC response appeared to lag behind improvement in FEV1 during the first week of therapy. In fact, continued improvement in FVC was observed at the last measurement (day 8). However, it is likely that FVC improvements with tiotropium plateau between day 3–8, as the report by VAN NOORD *et al.* [8] indicates no significant difference between day 8–51 values. Of interest, a similar pattern of FEV1 and FVC changes was observed with ipratropium, although the magnitude of changes was clearly superior with tiotropium. The changes in FVC observed over 8 days with tiotropium are unlikely to be explained by slowly accumulating M_3-receptor occupancy alone, given the observations seen with ipratropium. Hence such changes may reflect slow improvement of the ventilatory condition of the lung by permanent or longer patency of previously closed airways.

Recent data suggests that volume changes are more important for improving the patient's perception of breathlessness. O'DONNELL *et al.* [15] has reported that changes in hyperinflation are significantly correlated to improvements in dyspnoea during exercise testing in patients with COPD. While other measures of static lung volume were not measured in the present study, the improvement in FVC most likely reflects improvements in hyperinflation. The gradual increase in FVC over many days is consistent with the clinical observations of improvements being a continuing process that may not be fully appreciated within the first few days of treatment with inhaled bronchodilators. Studies with other classes and formulations of agents would also be useful in understanding these observations.

Further implications relate to what constitutes a bronchodilator response in patients with COPD. The classic assessment of a "bronchodilator response" is an FEV1 improvement higher than a predefined threshold acutely seen with a short-acting inhaled β-agonist, a test profiled primarily in patients with asthma. These data and the increased emphasis on objective monitoring of dyspnoea in clinical trials suggests that therapeutic decisions based on an acute β-agonist response may not be the most appropriate test of a bronchodilator response in patients with COPD, and a negative acute test should not exclude a relevant clinical response. Therefore, bronchodilator studies in patients with COPD should consider specifying volume changes after several days to weeks as an important end point, in addition to changes in FEV1 after the first dose. These data suggest that simple spirometric testing during clinical studies after the first dose should not lead to definitive conclusions about a bronchodilator's benefits in COPD.

Future investigations may consider extending the period of observation to determine more precisely when FVC pharmacodynamic steady state occurs following tiotropium administered once-daily and assess whether the attainment of steady state is similar for other static lung volumes including slow vital capacity, residual volume, inspiratory capacity, functional residual capacity and total lung capacity. Furthermore, the sample size in the present study is insufficient to determine the influence of severity of disease on the time required to attain steady state. It is quite probable that the extent of differing time constants within the lung would influence the time required to reach a steady state lung volume following pharmacological intervention. Clinically, this phenomenon provides a rationale for prolonged trials of inhaled bronchodilators before conclusions of clinical benefit can be stated. It is possible that a longer trial might have allowed time for a similar long-term improvement in lung function with ipratropium [16]. A recent 12-week trial with salmeterol in patients with COPD did also indicate progressive improvements in morning predose FEV1 and FVC after 4 weeks of treatment [17].

To conclude, once-daily tiotropium provides sustained bronchodilation over 24 h with rapid improvements in spirometric measurements. The majority of bronchodilation is achieved with one to two doses; however continued improvements in lung volumes may be expected over or even beyond the first week of therapy.

References

1. Disse B, Reichl R, Speck GA, Traunecker W, Rominger KL, Hammer R. Ba679 Br., a novel anticholinergic bronchodilator. *Life Sci* 1993; 52: 537–544.
2. Takahaski T, Belvisi MG, Patel H, *et al.* Effect of BA679 Br, a novel long-acting anticholinergic agent, on cholinergic neurotransmission in guinea pig and human airways. *Am J Respir Crit Care Med* 1994; 150: 1640–1645.
3. Disse B, Speck GA, Rominger KL, Witek TJ Jr, Hammer R. Tiotropium (Spiriva™): Mechanistical considerations and clinical profile in obstructive lung disease. *Life Sci* 1999; 64: 457–464.
4. Maesen FPV, Smeets JJ, Costongs MAL, Wald FDM, Cornelissen PJG. BA679 Br, a new long-acting antimuscarinic bronchodilator: a pilot dose-escalation study. *Eur Respir J* 1993; 6: 1031–1036.
5. Maesen FPV, Smeets JJ, Sledsens TJH, Wald FDM, Cornelissen PJG. Tiotropium bromide, a new long-acting antimuscarinic bronchodilator: a pharmacodynamic study in patients with chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8: 1506–1513.
6. O'Connor BJ, Towse LJ, Barnes PJ. Prolonged effect of tiotropium bromide on metacholine-induced bronchoconstriction in asthma. *Am J Respir Crit Care Med* 1996; 154: 876–880.

7. Littner MR, Ilowite JS, Tashkin DP, *et al.* Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1136–1142.
8. van Noord JA, Bantje THA, Eland ME, *et al.* A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000; 55: 289–294.
9. Casaburi R, Briggs DD, Donohue JF, Serby CW, Menjoge SS, Witek TJ Jr. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD. A 13-week multicenter trial. *Chest* 2000; 118: 1294–1302.
10. ATS Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: S77–S120.
11. Quanjer PH, Tammeling GJ, Cotes JE, Pederson OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flow. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
12. Chodosh S, Flanders J, Serby CW, Hochrainer D, Witek TJ Jr. Effective use of HandiHaler® dry powder inhalation system over a range of COPD severity. *Am J Respir Crit Care Med* 1999; 159: Suppl. 3, A524.
13. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; 144: 1202–1218.
14. Disse B, Rominger K, Serby CW, Souhrada JF, Witek TJ Jr. The pharmacokinetic (PK) profile of tiotropium during long-term treatment in stable COPD. *Am J Respir Crit Care Med* 1999; 159: Suppl. 3, A524.
15. O′Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 542–549.
16. Rennard SI, Serby CW, Ghafouri M, Johnson PA, Friedman N. Extended therapy with ipratropium. Ipratropium is associated with improved lung function in patients with COPD – a retrospective analysis of data from seven clinical trials. *Chest* 1996; 110: 62–70.
17. Rennard SI, Anderson W, ZuWallack R, *et al.* Use of a long-acting inhaled B2-adrenergic agonist, salmeterol xinafoate in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1087–1092.