Tiotropium bromide, a new long-acting antimuscarinic bronchodilator: a pharmacodynamic study in patients with chronic obstructive pulmonary disease (COPD)

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ABSTRACT: The objective of the present study was to investigate the dose-dependent bronchodilator efficacy and duration of action of the newly developed antimuscarinic agent tiotropium bromide in patients with chronic obstructive pulmonary disease (COPD).

In a randomized, double-blind, placebo-controlled, crossover design, patients inhaled single doses of 10–80 µg tiotropium bromide and placebo, formulated in lactose powder capsules. The washout period between test doses was 72 h. Thirty five patients were enrolled in the trial (32 males and 3 females; mean age 64 yrs). Baseline forced expiratory volume in one second (FEV_1) (mean 1.34 L) was less than 65% of predicted and was <70% of forced vital capacity (FVC). All subjects had a smoking history of more than 10 pack-years. The mean reversibility of FEV_1 after inhalation of 40 µg ipratropium bromide was 28%. Pulmonary function testing was performed before and at regular time intervals for up to 32 h after test drug administration.

Compared to placebo, tiotropium bromide produced significant improvements in FEV_1, FVC, peak expiratory flow rate (PEFR) and forced mid-expiratory flow ($FEF_{25-75\%}$). The bronchodilator response was almost immediate; peak improvement in FEV_1 was reached 1–4 h after test drug inhalation, and the duration of action extended to 32 h after the 20, 40 and 80 µg doses. A clear dose-response relationship was seen for peak FEV_1 and for the average FEV_1 over differing time periods during the 32 h observation period, 80 µg of test drug being superior to the 10 µg dose. Peak improvement in FEV_1 ranged 19–26% of test-day baseline for tiotropium bromide doses compared to 16% for placebo. The large improvement for placebo is probably due to carry-over effect which was significant. After excluding carry-over effect, the peak response to placebo decreased to 11%, whilst for tiotropium bromide doses it ranged 20–25%; standard error for mean difference was about 4%. There was no evidence of systemic anticholinergic effects.

In this population of patients with COPD, tiotropium bromide was found to be a safe and long-acting bronchodilator, demonstrating a clear dose-response relationship following single dose administration.
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Cholinergic mechanisms play an important role in the pathophysiology of diseases characterized by chronic airways obstruction, particularly in chronic obstructive pulmonary disease (COPD) and acute asthma and to a lesser extent in stable asthma [1]. The introduction of antimuscarinic bronchodilators has been hampered by the narrow safety margin of tertiary compounds, such as atropine. The new class of quaternary compounds are poorly absorbed and, thus, have an excellent safety profile [2]. Numerous clinical trials have demonstrated the efficacy and safety of antimuscarinic agents, particularly ipratropium bromide and oxitropium bromide, in

the short- and long-term management of patients with COPD and asthma [3–11].

Tiotropium bromide is a newly developed, long-acting antimuscarinic agent, which is structurally related to ipratropium bromide. During *in vitro* receptor binding studies, tiotropium bromide showed kinetic receptor subtype selectivity, with rapid dissociation from Hm2 and slow dissociation from Hm1 and Hm3 [12]. This prolonged pharmacological action has been observed not only in animal studies [12], but also in patients with COPD [13]. In this preliminary study, it was shown that inhaled tiotropium bromide induced bronchodilatation in

COPD patients, and that it has a prolonged duration of action. Because of the limitations of the study design (open) and small number of patients (n=6), a firm conclusion on the dose-response and duration of action could not be established. In mild asthmatic patients, tiotropium bromide protected against methacholine-induced bronchoconstriction for up to 72 h, and the duration of its pharmacological activity was shown to be dose-dependent [14].

The purpose of the present study was to investigate, by means of a double-blind, randomized, placebo-controlled, crossover design, the dose and time-response of inhaled tiotropium bromide (10–80 µg) in an appropriate number of patients with COPD.

Patients and methods

Patients

The 35 patients admitted to the study all had the diagnosis of COPD according to the criteria of the American Thoracic Society [15]. On an initial screening visit, the patients had to show a relatively stable, mild to moderately severe airways obstruction with a forced expiratory volume in one second (FEV_1) <65% of predicted, and FEV_1 <70% of forced vital capacity (FVC). Predicted normal values were based on the tables for standardized lung function tests of the European Coal and Steel Community [16]. Patients were studied during a stable phase of the disease, and were required to have a smoking history of more than 10 pack-years, and to be 40 yrs of age or older. Airway reversibility - increase of at least 15% from baseline - to inhaled ipratropium bromide (metered-dose inhaler (MDI) two puffs of 20 µg) was an inclusion criterion. Patients with a history of asthma, allergic rhinitis, or atopy, or a blood eosinophil count above 400 per µL were excluded.

Thirty three of the 35 randomized patients completed the study and were included in the efficacy analyses; their demographic data are summarized in table 1. One patient discontinued on test day 1, 3 h after inhaling placebo, because he had to be hospitalized with severe dyspnoea. A second patient discontinued the study

Table 1. – Characteristics of patients

Patient No.	Sex	Age yrs	Pred L	FEV₁ Baseline L	% pred	Reversibility* Post L	% change from baseline
1	M	68	2.67	0.99	37	1.33	34
2	M	55	3.78	2.17	57	2.51	16
3	M	74	2.46	1.42	58	1.82	28
4	M	68	3.07	0.94	31	1.15	22
5	M	53	3.93	0.90	23	1.28	42
6	M	70	3.02	1.25	41	1.45	16
7	M	65	3.49	1.06	30	1.36	28
8	M	67	2.99	0.85	28	1.24	46
9	M	52	3.21	2.01	63	2.66	32
10	F	64	2.48	1.41	57	1.74	23
11	M	62	3.14	1.59	51	2.10	32
12	M	63	3.33	1.14	34	1.59	40
13	M	52	3.43	2.15	63	2.74	27
14	F	66	1.67	0.99	59	1.26	27
15	M	68	3.07	0.91	30	1.22	34
16	M	66	3.12	1.22	39	1.58	30
17	F	69	1.84	1.19	65	1.39	17
18	M	66	3.34	0.86	26	1.00	16
19	M	49	3.62	1.34	37	1.70	27
20	M	61	3.50	1.90	54	2.25	18
21	M	60	3.42	1.42	42	1.85	30
22	M	68	3.11	1.29	42	1.73	34
23	M	71	2.55	1.06	42	1.33	26
24	M	54	4.08	1.24	30	1.92	55
25	M	74	2.79	1.26	45	1.75	39
26	M	70	3.31	1.21	37	1.43	18
27	M	54	4.11	2.28	56	2.78	22
28	M	71	2.99	1.73	58	2.01	16
29	M	65	2.72	1.01	37	1.20	19
30	M	68	3.07	1.00	33	1.23	23
31	M	65	2.94	1.65	56	1.99	21
32	M	74	2.81	1.08	38	1.44	33
33	M	69	2.83	1.59	56	1.83	15
Mean		64	3.09	1.34	44	1.69	28
±SD		7	0.54	0.40	12	0.48	10

*: following two puffs of 20 µg ipratropium bromide. M: male; F: female; pred: predicted value; FEV_1: forced expiratory volume in one second.

between test days 3 and 4 because of dyspnoea, requiring the use of rescue medication before inhalation of test drug on test day 4.

Study design

The trial was designed as a five period, double-blind, randomized, placebo-controlled, crossover study, and it was conducted in one centre. There was a 72 h washout period between the treatments. Patients were treated according to a classical randomization table.

Procedure

Patients were selected in five Dutch departments of pulmonary diseases (Heerlen, Hengelo, Zutphen, Hoorn and The Hague). Those who satisfied the inclusion and exclusion criteria were enrolled into the trial using a study facility in the vicinity of the De Wever Hospital, Heerlen. On the five study days, tiotropium bromide 10, 20, 40, 80 µg or placebo, as a lactose powder, were inhaled using the Inhalator Ingelheim (FO_2). Pulmonary function measurements (FEV1, FVC, peak expiratory flow rate (PEFR) and forced mid-expiratory flow (FEF25–75%) were performed using a Dry Rolling Seal Spirometer, system 2130/922 Sensor Medics. Prior to the test drug (between 8.00 and 9.00 a.m.) and 15, 30, 60 and 90 min and 2, 3, 4, 6, 8, 10, 12, 15, 19, 23, 24, 26, 28, 30 and 32 h after test drug administration, the flow-volume curve was registered. The best value of three, body temperature, barometric pressure and saturated with water vapour (BTPS) corrected, was employed. Safety parameters included vital signs (measured just prior to each pulmonary function test), 12-channel electrocardiographic (ECG) recording, laboratory safety tests and recording of adverse events, which were assessed according to KARCH and LASAGNA [17].

A washout was required for all bronchodilators prior to the start of pulmonary function testing. Inhaled short-acting bronchodilators were excluded for at least 8 h, long-acting for at least 24 h, and xanthines for at least 48 h. Inhaled corticosteroids were allowed if the patient's dosage was stabilized for at least 4 weeks prior to the preadmission visit, and was stable throughout the entire study period. If the FEV1 deteriorated during the test period, inhaled salbutamol (two puffs of 100 µg) was allowed. The study was performed according to the rules of the declaration of Helsinki, and was approved by the Medical Ethics Committee of the De Wever Hospital. All patients gave written consent to participate in the study.

Statistics

The data were analysed using analysis of variance (ANOVA) suitable for crossover studies. The terms in the ANOVA model included patients, visits and treatments. The term "adjusted" means is used to indicate the use of least-squares means, which enabled the means at each treatment level to be adjusted to account for the other terms in the statistical model. Since the data showed clear evidence of carry-over effects, an additional analysis was conducted after excluding data from visits following 20, 40 or 80 µg doses of tiotropium bromide. The primary efficacy variable was FEV1. The main focus was on peak FEV1 (defined as peak improvement in FEV1 above test-day baseline) and average improvement in FEV1 (defined as the area under the FEV1 time profile above test-day baseline divided by the length of the time interval) evaluated over the first 8, 12, 24 and 32 h after drug inhalation. In addition, the following time intervals were analysed: 12–24 and 24–32 h. Secondary efficacy endpoints included FVC, PEFR and FEF25–75%.

The within-patient standard deviation was assumed to be 0.2 L for the peak FEV1 on the grounds of our previous study [13]. In order to recognize a difference of 0.15 L in the mean peak FEV1 at the 5% level between placebo and the therapeutic dose of tiotropium bromide with a power of 90%, it was found that 20 subjects would be adequate as calculated by the two-sided paired t-test. The decision was, however, made to allow 35 patients to participate.

Results

The mean increase in FEV1 from baseline for the four tiotropium doses and placebo is shown in figure 1. There was a nearly immediate response to tiotropium bromide. The bronchodilator effect was dose-dependent, the 10 µg dose producing about half the change in FEV1 brought about by the 80 µg dose. Thirty two hours following inhalation, there was still a clear dose-dependent response, but at this time the 10 µg tiotropium bromide dose produced only a very slight increase in FEV1 in comparison to placebo. In contrast, the 20, 40 and 80 µg doses produced a dose-dependent response with higher doses responding more strongly in terms of increasing FEV1 over baseline. During the 32 h observation period, more patients required rescue medication when they were on placebo (13 out of 33) (table 2). Following tiotropium bromide treatments, rescue medication was needed by seven (10 µg), eight (20 µg), and five (40 and 80 µg) out of the 33 patients. As these patients had their last recorded values used as an endpoint value for their remaining (missing) observations, this may introduce a larger bias in the placebo than in the tiotropium bromide treatment data.

Only 14 out of the 33 patients (43%) satisfied the protocol requirement that the predose FEV1 on test days 2–5 had to be within 15% of that on test day 1. A highly significant difference was found between the predose FEV1 on the first test day and that on subsequent test days (p=0.001). Moreover, there appeared to be a significant effect from the treatment at the previous visit on the predose FEV1 of the subsequent test day (p=0.024) (table 3). Although only the 80 µg dose seemed to have a significantly greater carry-over effect than placebo, in order to exclude confounding by higher order carry-over
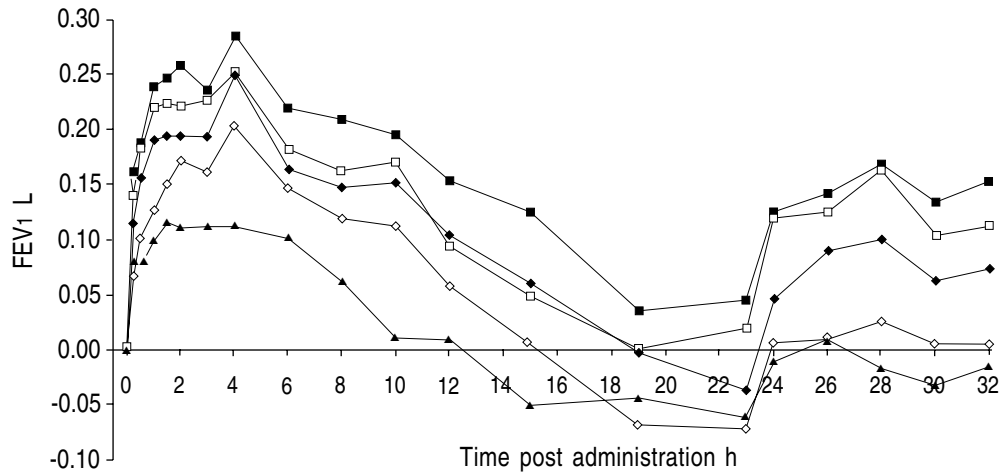
Fig. 1. – Increase in adjusted mean improvment in FEV1 from test-day baseline. ━■━ : 80 µg tiotropium bromide; ━□━ : 40 µg tiotropium bromide; ━◆━ : 20 µg tiotropium bromide; ━◇━ : 10 µg tiotropium bromide; ━▲━ : placebo. FEV1: forced expiratory volume in one second.

Table 2. – Number of patients not requiring rescue medication following test drug inhalation at different time points by treatment

Treatment	Patients not needing rescue medication n				
	Starting	6 h	12 h	24 h	32 h
Placebo	33 (12)	32 (11)	28 (7)	22 (6)	20 (6)
Tiotropium bromide 10 µg	33 (14)	33 (14)	32 (13)	26 (10)	26 (10)
Tiotropium bromide 20 µg	33 (21)	33 (21)	31 (19)	27 (15)	25 (15)
Tiotropium bromide 40 µg	33 (21)	33 (21)	31 (20)	29 (19)	28 (18)
Tiotropium bromide 80 µg	33 (17)	32 (17)	30 (16)	29 (15)	28 (15)

Values in brackets refer to number of patients on those test days which do not follow a tiotropium bromide 20, 40 or 80 µg dose.

Table 3. – Effect of treatment on previous test day on predose FEV1 of the subsequent test day*

Previous treatment	Subsequent test days (Preceded by placebo, tiotropium bromide 10, 20, 40 or 80 µg)					
	Test day 1	Placebo	Tiotropium bromide 10 µg	Tiotropium bromide 20 µg	Tiotropium bromide 40 µg	Tiotropium bromide 80 µg
Adjusted mean predose FEV1 L	1.405 (0.025)	1.458 (0.028)	1.506+ (0.028)	1.481+ (0.027)	1.448 (0.028)	1.580+ (0.029)

Values are presented as mean and SEM in parenthesis. *: the standard errors of difference (SED) were in the range 0.037–0.041 L. Adjusted means which are more than approximately twice the SED value apart are significantly different (p<0.05). +: versus test day 1, p<0.05. FEV1: forced expiratory volume in one second.

effects, two series of analyses were performed for peak improvement in FEV1 and average improvement in FEV1 over differing time periods: one ignoring carry-over effects and another after excluding data of the test day following 20, 40 or 80 µg doses of tiotropium bromide. Figure 2 shows the mean increase in FEV1 for the various treatment groups after excluding the data following 20, 40 and 80 µg doses of tiotropium bromide to eliminate carry-over effects. It is apparent that, in this case, there is a greater separation between tiotropium bromide doses and placebo.

Peak FEV1 response

Analysis of the peak bronchodilatory response, ignoring carry-over effects, revealed that there were significant differences (p=0.0007) among the five treatments (table 4). The increase in peak FEV1 was greater for all tiotropium bromide treatments compared to placebo, which ranged 19–26% of test-day baseline for tiotropium bromide compared to 16% for placebo; the standard error for the difference in mean was 3%. There was an apparent dose-response to tiotropium bromide
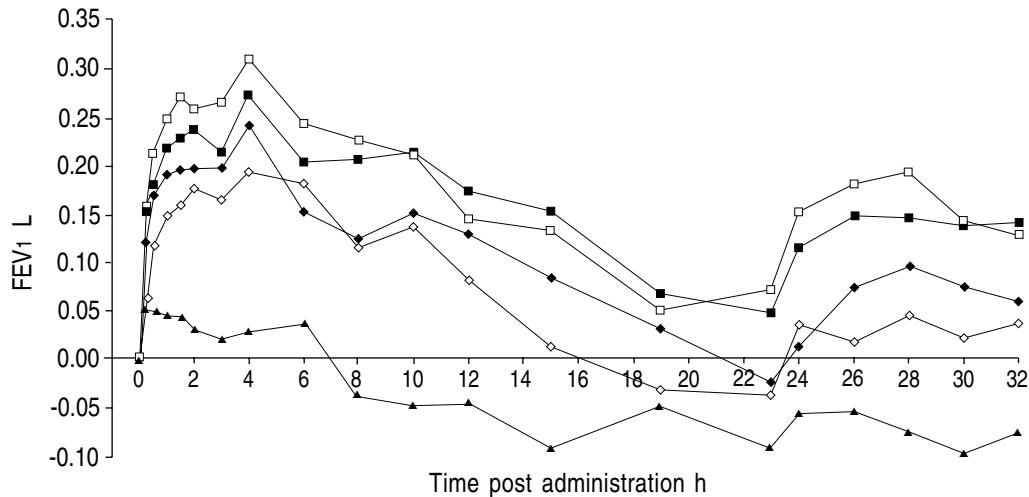
Fig. 2. – Increase in adjusted mean improvement in FEV1 from test-day baseline, excluding test days which follow tiotropium bromide 20, 40 and 80 µg. ─■─ : 80 µg tiotropium bromide; ─□─ : 40 µg tiotropium bromide; ─◆─: 20 µg tiotropium bromide; ─◇─: 10 µg tiotropium bromide; ─▲─ : placebo. FEV1: forced expiratory volume in one second.

Table 4. – Adjusted means for peak improvement in FEV1*

Treatment	Placebo	Tiotropium bromide 10 µg	Tiotropium bromide 20 µg	Tiotropium bromide 40 µg	Tiotropium bromide 80 µg
Adjusted mean peak FEV1 L	0.237 (0.025)	0.280 (0.025)	0.325+ (0.025)	0.347+ (0.025)	0.380+ (0.025)

Values are presented as mean and SEM in parenthesis. *: the standard errors of difference (SED) between treatments was 0.035 L. Adjusted means which are more than approximately twice the SED value apart are significantly different ($p < 0.05$). +: versus placebo, $p < 0.05$. Response to doubling of dose: 0.032 (SEM 0.011) L. FEV1: forced expiratory volume in one second.

with larger increases for those treatment groups receiving higher doses. The peak response obtained following 20, 40 and 80 µg doses of the active drug differed significantly ($p < 0.05$) from the peak response on the placebo test day. When formally tested, there was a significant difference between the placebo-treated patients and the four treatments in which tiotropium bromide was administered ($p = 0.038$; the 80 µg dose being significantly better than the 10 µg dose), and the slope of the linear regression on the log dose-response for peak FEV1 was also significant ($p = 0.004$).

The results of the analysis involving only the results of the test days which did not follow 20, 40 or 80 µg doses of tiotropium bromide showed a similar trend. The peak FEV1 ranged 20–25% of test-day baseline for tiotropium bromide doses compared to only 11% for placebo; the standard error for the difference in mean was about 4%.

Average FEV1 over a specific time period

A highly significant effect of the treatments ($p < 0.001$) was found for all time periods from the test drug administration over 8, 12, 24 or 32 h. The effect of the treatment on the time periods 12–24 h ($p = 0.004$) and 24–32 h ($p < 0.001$) was also highly significant. The mean

FEV1 response ranged 5–11% above test-day baseline following 20–80 µg doses of tiotropium bromide 32 h after treatment. No change was noticed for the 10 µg dose or placebo. The dose response is evident from table 5 and appears to increase with time. This may be because the higher dose levels were all producing the maximum possible response shortly after inhalation, whereas at a later stage of the observation period the lower doses were having a reduced effect.

When data for those test days which followed a tiotropium bromide dose of 20, 40 or 80 µg were excluded, the means for the placebo group were smaller but the standard errors of differences were larger and more variable. This reduction was caused by the exclusion of quite a large amount of data. However, the results were less likely to be biased by any carry-over effects. The results to doubling the dose were very similar to the analysis ignoring carry-over effects.

The secondary pulmonary function variables FVC, PEFR and FEF25–75% showed comparable results and were in agreement with the FEV1 findings.

Drug tolerability

All 35 patients who entered the study and received at least one dose of investigational drug were included in

Table 5. – Adjusted means of average improvement in FEV1 (L) over a specific time period*

Time period	Placebo	Tiotropium bromide 10 µg	Tiotropium bromide 20 µg	Tiotropium bromide 40 µg	Tiotropium bromide 80 µg	SED	Response to doubling of dose
0–8 h	0.099 (0.022)	0.150 (0.022)	0.183 (0.022)	0.203 (0.022)	0.232 (0.022)	0.031	0.026
0–12 h	0.074 (0.022)	0.134 (0.022)	0.169 (0.022)	0.186 (0.022)	0.218 (0.022)	0.032	0.027
0–24 h	0.018 (0.023)	0.054 (0.023)	0.097 (0.023)	0.111 (0.023)	0.151 (0.023)	0.032	0.031
0–32 h	0.010 (0.024)	0.044 (0.024)	0.093 (0.024)	0.017 (0.024)	0.151 (0.024)	0.033	0.035
12–24 h	-0.039 (0.025)	-0.027 (0.025)	0.025 (0.025)	0.037 (0.025)	0.085 (0.025)	0.035	0.035
24–32 h	-0.015 (0.031)	0.014 (0.031)	0.083 (0.031)	0.132 (0.031)	0.15 (0.031)	0.044	0.046

Values are presented as mean and SEM in parenthesis. *: adjusted means which are more than about twice the standard error of difference (SED) value apart are significantly different ($p < 0.05$). FEV1: forced expiratory volume in one second.

the analyses. All adverse events experienced by the patients were classified by the investigators as doubtful. Dyspnoea, as a result of a worsening of the patient's COPD symptoms, was the adverse event most frequently reported for all treatment groups: 15 out of 35 patients (43%) with placebo; 8 out of 34 patients (24%) with 10 µg tiotropium bromide; 9 out of 34 patients (27%) with 20 µg of drug; 6 out of 34 patients (18%) with 40 µg; and 5 out of 34 patients (15%) with the 80 µg drug dose (see also table 2). One patient reported back pain after placebo on day three, after 40 µg tiotropium bromide on day four, and after 80 µg tiotropium bromide on day five. Another patient reported headache and nausea when receiving 10 µg tiotropium bromide, and one other experienced an upper respiratory tract infection on test day five (after 80 µg tiotropium bromide). On the previous test days, this patient reported cough after placebo (on day three) and malaise on day four (this day he received 40 µg tiotropium bromide). With the exception of dyspnoea, the incidence of adverse events for all body systems was similar in all treatment groups, with no evidence of potentiation of adverse events in the patients given tiotropium bromide.

There were no clinically significant changes from baseline in ECG recordings, in any of the mean values of the laboratory parameters, and the differences in mean changes from baseline in blood pressure and pulse rate were not significantly different.

Discussion

The present study has clearly demonstrated and confirmed that inhaled tiotropium bromide has a long bronchodilator activity in patients with COPD. In comparison to placebo, tiotropium bromide produced significant improvement in lung function as assessed by FEV1, FVC, PEFR and FEF25–75%. The prolonged pharmacological action of tiotropium bromide was further supported by two findings: even 72 h after inhaling high doses (20, 40 and 80 µg) the FEV1 had not returned to baseline

values; and there was a decrease in the use of rescue medication (beta-agonist) particularly with the higher doses. In a recent study conducted in mild asymptomatic asthmatic patients, O'CONNOR et al. [14] demonstrated that inhaled tiotropium bromide provided complete protection against methacholine-induced bronchoconstriction for 72 h.

The onset of action of this long-acting bronchodilator seems to be comparable to that observed with other quaternary compounds, such as ipratropium bromide and oxitropium bromide. The peak bronchodilator effect is slightly delayed (1–4 h) compared to other quaternary compounds (0.5–1 h) [18–20]. Both the peak effect and duration of action are dose-dependent. The 80 µg dose had a duration of action of 32 h compared to placebo, whereas it was considerably shorter with 10 µg tiotropium bromide. It is of interest to note that the time response curves of the FEV1 and the secondary parameters showed an obvious diurnal rhythm, consisting of a decrease during the night (15–19 h) followed by an increase above placebo baseline in the early morning (23–32 h). It is well documented that diurnal variation of lung function is influenced by cholinergic activity [21–22]. The fact that the night dip was only partly reversed by tiotropium bromide suggests that other mechanisms may be involved, or that higher doses are needed to completely block the cholinergic tone at night [23–25].

Several studies have shown that long-term treatment with short-acting antimuscarinic bronchodilators is effective and safe in patients with COPD and that tachyphylaxis does not develop [4, 7–11, 26]. The safety profile of quaternary antimuscarinic bronchodilators is superior to that of beta-agonists, particularly regarding cardiovascular side-effects [27, 28]. Ventilation-perfusion abnormalities are often present in COPD patients with advanced disease as well as in acute exacerbations; beta-agonists increase hypoxaemia, whereas antimuscarinic bronchodilators have no deleterious effects [29]. In contrast there is evidence that long-term treatment with inhaled short-acting beta-agonists, at least in asthmatics, induces tachyphylaxis [30–34], and increases airway

responsiveness [35–37]. Worsening of the disease has also been reported [38–39]. The efficacy and safety of long-term treatment with inhaled beta-agonists in COPD is not well-documented, but some studies suggest that long-term therapy in patients with COPD decreases the duration of bronchodilatation [4, 40]. Although the bronchodilator action of long-acting beta-agonists, such as salmeterol, both in stable and nocturnal asthma is well-established [41–42], an increase in airway responsiveness has been observed following long-term treatment with inhaled salmeterol [43]. There is some evidence that the systemic activity, particularly cardiovascular, of salmeterol is higher than that of the short-acting beta-agonist salbutamol [44].

The long-lasting bronchodilatory effect of tiotropium bromide opens up new prospects not only for the maintenance treatment of COPD but also for the treatment of nocturnal asthma. The full therapeutic potential and safety profile of this long-acting antimuscarinic bronchodilator can only be established in long-term studies.

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