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Tiotropium Bromide

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Contents

Abstract

▲ Tiotropium bromide is an anticholinergic bronchodilator that antagonises muscarinic M_1, M_2 and M_3 receptors. It dissociates more slowly from M_1 receptors and, importantly, from M_3 receptors (which are located in bronchial smooth muscle) than from M_2 receptors and subsequently has a long duration of action permitting once-daily administration.

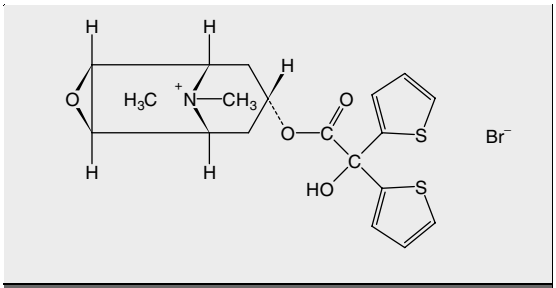
▲ In patients with chronic obstructive pulmonary disease (COPD), tiotropium 18μg once daily significantly improved lung function compared with placebo and ipratropium 40μg four times daily in 1-year trials or salmeterol 50μg twice daily in a 6-month study.

▲ The incidence of COPD exacerbations decreased and use of rescue medication was lower with tiotropium compared with placebo or ipratropium. There was no evidence of tachyphylaxis during 1-year treatment with tiotropium.

▲ Compared with placebo, salmeterol and ipratropium, tiotropium produced significant improvements in patients' perception of dyspnoea and health-related quality of life.

▲ Tiotropium is generally well tolerated; dry mouth is the most common drug-related adverse event, occurring in about 10 to 16% of patients in clinical trials.

Features and properties of tiotropium bromide (BA 679 BR)	
Indications	
Chronic obstructive pulmonary disease	
Mechanism of action	
Anticholinergic bronchodilator	Muscarinic receptor antagonist; slowly dissociates from M_1 and M_3 receptors
Dosage and administration	
Usual dosage in clinical trials	18μg
Route of administration	Inhalation
Frequency of administration	Once daily
Pharmacokinetic profile (tiotropium base 18μg via inhalation-driven dry powder inhaler)	
Peak and trough plasma concentrations	16 ng/L; 4 ng/L
Time to peak and trough plasma concentrations	5 minutes; <1 hour
Elimination	≈7% of the delivered dose recovered unchanged in urine
Elimination half-life	5 to 6 days
Adverse events	
Most frequent	Dry mouth



Tiotropium bromide

Vagally mediated bronchoconstriction is thought to be the major reversible component of airway obstruction in patients with chronic obstructive pulmonary disease (COPD). As such, current guidelines for the management of COPD recommend the use of bronchodilator therapy with anticholinergics and β_2-agonists, alone or in combination, at all stages of the disease process in patients with symptoms.[1-3]

Muscarinic receptors are intimately involved in controlling smooth muscle function in human airways.[4] Three muscarinic receptor subtypes (M_1, M_2 and M_3) have been identified in human airways, and each of these subtypes serves a different physiological function.[4] M_1 receptors facilitate cholinergic neurotransmission through parasympathetic ganglia. M_2 receptors are located on postganglionic cholinergic nerves and provide negative feedback modulation of acetylcholine release. Inhibition of M_2 muscarinic receptors results in increased acetylcholine release and bronchoconstriction. M_3 receptors located on bronchial smooth muscle and in mucous glands mediate the contractile response in airways smooth muscle and mucus secretion in response to acetylcholine.[4]

Tiotropium bromide is a member of the quaternary ammonium class of anticholinergic bronchodilators that dilate bronchial smooth muscle through antagonism of muscarinic receptors located in airway smooth muscle. Tiotropium bromide binds with similar affinity to muscarinic subtype M_1, M_2 and M_3 receptors; however, the drug dissociates much more slowly from M_1 and M_3 receptors than from M_2 receptors.[5] Consequently, tiotropium bromide has a long duration of action allowing once-daily administration in patients with COPD.

This article reviews current evidence supporting the use of tiotropium bromide in the management of patients with COPD. In clinical trials, the dry powder formulation was labelled according to the quantity of tiotropium base in each capsule for inhalation (20μg tiotropium bromide = 18μg tiotropium base). When these trials are discussed, the drug is referred to as 'tiotropium'.

1. Pharmacodynamic Profile

Receptor Binding Studies

- In Chinese hamster ovary cells transfected with human muscarinic subtype (Hm) DNA, the apparent binding affinity (K_D) of tiotropium bromide for Hm_1, Hm_2 and Hm_3 muscarinic receptors was similar to that of ipratropium bromide.[6] However, kinetic studies (at 23°C) showed that [^{3}H]tiotropium bromide dissociates ≈100 times more slowly than [^{3}H]ipratropium bromide from Hm_1 [dissociation half-life ($t_{½dis}$) 14.6 *vs* 0.11 hours, respectively] and Hm_3 ($t_{½dis}$ 34.7 *vs* 0.26 hours) receptors.[6] Dissociation of [^{3}H]tiotropium bromide and [^{3}H]ipratropium bromide from Hm_2 receptors was more rapid ($t_{½dis}$ 3.6 *vs* 0.035 hours).[6]

- Tiotropium bromide was ≈10-fold more potent than ipratropium bromide in displacing [^{3}H]*N*-methylscopolamine (NMS) from muscarinic receptors in human peripheral lung membranes.[5] Compared with ipratropium bromide, the protective effect (>70% inhibition) of tiotropium bromide against NMS binding was sustained ($t_{½dis}$ 212 *vs* 11.4 minutes).[5]

- Autoradiographic mapping of [^{3}H]tiotropium bromide in isolated human lung and trachea showed dense and uniform labelling on alveolar walls and submucosal glands.[5] There was no evidence of specific labelling of airway smooth muscle or endothelium in either specimen.[5] Pirenzipine 100 nmol/L (M_1-selective) and 4-diphenylacetoxy-*N*-methylpiperidine 10 nmol/L (M_1- and M_3-selective) were effective in displacing [^{3}H]tiotropium

bromide binding sites in alveolar walls and submucosal glands, but methoctramine 100 nmol/L (M_2-selective) had no inhibitory effect in either tissue.[5] This evidence further substantiates the kinetic selectivity of tiotropium bromide for M_1 and M_3 receptors over M_2 receptors.

In Vitro and *In Vivo* Studies

• In isolated human bronchi, tiotropium bromide inhibited contraction induced by electrical field stimulation in a concentration-dependent manner, with an IC_{50} (concentration required to inhibit cholinergic neural responses by 50%) value ≈23-fold more potent than atropine (0.24 *vs* 5.5 nmol/L, respectively).[7] The onset of action for tiotropium bromide was slower compared with atropine ($t_{½}$ onset 43.5 *vs* 6.8 minutes, respectively).[7] However, tiotropium bromide had a longer duration of action than atropine after washout of these two antagonists ($t_{½}$ offset >300 *vs* 64 minutes, respectively).[7]

• Tiotropium bromide aerosol provided a longer duration of action against acetylcholine-induced bronchoconstriction than an equipotent dose of aerosolised ipratropium bromide in anaesthetised dogs (6 *vs* 1.8 hours, respectively).[6] Increasing the ipratropium bromide dose by a factor of 10 (from 1 to 10 g/L) improved the percent inhibition of bronchospasm from 58 to 100%, but only extended the duration of action of the drug from 78 to 107 minutes. In contrast, increasing the tiotropium bromide dose from 0.1 to 1 g/L provided 85 to 100% inhibition lasting for up to 6 hours.[6]

In Patients with Chronic Obstructive Pulmonary Disease

• Significant improvements ($p < 0.05$ *vs* placebo) in forced expiratory volume in 1 second (FEV_1) were reported 1 to 4 hours after administration of a single dose of tiotropium 18, 36 and 72μg in 33 patients with COPD [FEV_1 <65% predicted and <70% of forced vital capacity (FVC)].[8]

• After adjustment for a significant carry-over effect on FEV_1 following single doses of tiotropium ≥18μg in this study, statistically significant ($p < 0.05$ *vs* placebo) increases in mean peak FEV_1 (0.325, 0.347 and 0.38L) were reported for the tiotropium 18, 36 and 72μg groups, respectively, compared with an increase of 0.237L in the placebo group.[8] FEV_1 values remained above the baseline value (1.34L) for up to 72 hours. Increases in peak FEV_1 were dose dependent in this randomised, double-blind, crossover study.[8]

• Timing of tiotropium administration does not affect outcome. The nocturnal decline in FEV_1 was attenuated with tiotropium 18μg administered either in the morning (9am) or evening (9pm) in a placebo-controlled trial of 121 patients with stable COPD.[9] Average FEV_1 (measured every 3 hours for 24 hours after 6 weeks of treatment) was significantly ($p < 0.01$) improved in both the morning and evening tiotropium groups compared with placebo (mean average FEV_1 1.11, 1.06 and 0.9L, respectively) by the end of this randomised, 6-week double-blind study, reported as an abstract.[9]

• In a preliminary report, tiotropium 18μg once daily for 3 weeks (n = 18) produced a greater depth of aerosol particle penetration than placebo (n = 19) into the bronchial tree [measured by a penetration index (PI) obtained from planar gamma camera imaging and by alveolar deposition at 48 hours after administration (AD_{48})]. There was a 12% improvement from baseline FEV_1 with tiotropium ($p < 0.0005$ *vs* placebo), in parallel with 29 and 24% improvements in PI and AD_{48} ($p < 0.003$ *vs* placebo for both comparisons).[10]

• In the above double-blind randomised trial, ^{81m}Kr imaging did not demonstrate significantly improved effect with tiotropium than with placebo on large airways lung function. However, the change in ^{81m}Kr score was greater in patients with poor than in those with higher peak flow ($p = 0.03$).[11]

• Oxygen desaturation during REM sleep was improved during 4 weeks' therapy with tiotropium (dose not stated in the abstract) given in the morning (+2.31%) or the evening (+2.13%, both $p < 0.05$ *vs* placebo) in a randomised double-blind trial

in 49 evaluable patients. Objective sleep quality did not change significantly, although all patients in the trial experienced some sleep disturbance.[12]

2. Pharmacokinetic Profile

Since tiotropium acts locally and plasma concentrations of the drug when administered by inhalation are low or undetectable, only limited pharmacokinetic information is available.

- Approximately 20% of an orally inhaled dose of tiotropium is deposited in the lung.[13] Tiotropium is rapidly absorbed into the systemic circulation after oral inhalation: maximal plasma tiotropium concentrations (C_{max}) are achieved within 5 minutes (t_{max}) and subsequently decline to low concentrations in less than 1 hour.[13]

- At steady state, C_{max} values were 16.2 and 19.0 ng/L, respectively, after 50 and 92 days' administration of tiotropium 18μg once daily in patients with stable COPD.[14] Minimum plasma concentrations (C_{min}) were 4.2 and 4.3 ng/L, respectively, on these days.[14] There was no evidence of drug accumulation once steady state was achieved.[14]

- Approximately 7% of the delivered dose of tiotropium is excreted unchanged in the urine.[14] Mean 24-hour urinary excretion of the drug was 1205.3, 1169.6 and 1253.7ng, respectively, after 50, 92 and 178 days of treatment with tiotropium 18μg once daily in patients with COPD.[14] The mean plasma elimination half-life was 5 to 6 days at steady state.[13]

3. Therapeutic Profile

Tiotropium has been evaluated in a number of large, randomised, double-blind, controlled trials. Tiotropium has been compared with ipratropium in two 1-year trials.[15] A placebo arm was included in a 4-week dose-ranging study,[16] two 1-year trials without an active comparator,[17] and a 6-month study of tiotropium versus salmeterol.[18]

Some interim results or individual data from the separate studies are available for the similarly-designed 1-year comparisons versus placebo[19-23] or ipratropium.[24,25] However, combined results from the individual trials have been fully published for the ipratropium[15] and placebo-controlled studies.[17] The combined data are cited in this review in preference to individual results from these trials, supplemented by additional information from abstracts[26-30] where appropriate. The salmeterol study is also fully published.[18]

Where stated, patients in these trials were aged ≥40 years (mean of about 63 to 65 years), had a smoking history of ≥10 pack-years and a diagnosis of COPD. Mean baseline FEV_1 was ≤65% of predicted, and ≤70% of FVC. Patients continued to use short-acting β_2-agonist bronchodilators on an as-needed basis. Inhaled or low-dose oral corticosteroids and theophylline were continued throughout the study if the dose was stable prior to randomisation.[15,17,18]

Trough FEV_1, a primary efficacy endpoint, was measured 1 hour before, and just prior to, the next scheduled tiotropium dose.[15,17,18] Other variables included peak FEV_1 (the highest observed measurement 0 to 3 hours after a dose) and average FEV_1, as well as peak, average and trough FVC, morning and evening peak expiratory flow rates (PEFR) and use of rescue medication.[15-18] Health-related quality of life (QOL), COPD exacerbations and dyspnoea were also investigated.[15,17,18]

Tiotropium was administered once daily via a dry powder capsule inhaler (HandiHaler®). *In vitro* studies have shown that this device delivers drug at inspiratory flow rates as low as 15 L/min.[31] In one small study involving 26 patients with mild to severe COPD (FEV_1 ≤65 to ≤27% of predicted), all patients generated sufficient inspiratory flow rates (ranging from 20.4 to 45.6 L/min) to effectively operate the HandiHaler®.[31] Ipratropium[15] and salmeterol[18] were administered via metered-dose inhaler.

Dose-Ranging Study

- Mean trough FEV_1 values were increased significantly in all four tiotropium groups relative to the placebo group after 1 week of treatment in 165 patients, and these changes were sustained throughout 4 weeks of treatment.[16] Mean trough

FEV_1 increased by 0.12, 0.09, 0.13 and 0.17L, respectively, in the tiotropium 4.5, 9, 18 and 36μg groups and decreased by 0.02L in the placebo group (baseline mean FEV_1 1.08L).[16] Significant increases ($p < 0.05$ *vs* placebo) in peak FEV_1 and FVC compared with baseline were achieved within 6 hours following the first dose of tiotropium.[16]

• Increases in mean trough and average FVC were also greater with tiotropium 4.5 and 18μg than with placebo throughout the study ($p < 0.05$). Trough and average FVC responses were consistently improved with the 9 and 36μg doses throughout the study but did not differ from placebo at study end, except for the average FVC response with the 9μg dose ($p < 0.05$).[16] All doses of tiotropium produced significantly greater morning, noon and evening PEFR than placebo ($p < 0.05$).[16]

• After discontinuation of tiotropium, FEV_1 and PEFR values gradually returned to baseline during a 3-week observation period, which is indicative of the long duration of action of the drug.[16] There was no evidence of rebound bronchoconstriction during this period.[16]

Comparisons with Other Bronchodilators and Placebo

Lung Function

• In the two 1-year trials[17] comparing tiotropium 18μg once daily (n = 550) with placebo (n = 371), tiotropium increased mean trough FEV_1 by 11 to 13% ($p < 0.01$ *vs* placebo), mean trough FVC by 12 to 13% (no p-value given), and morning and evening PEFR by 12 to 13% ($p < 0.05$ *vs* placebo). There was no evidence of tachyphylaxis over 1 year. Tiotropium was superior to placebo regardless of age[27] and gender.[28]

• Pooled 1-year results indicated that the superior efficacy of tiotropium (n = 356) compared with ipratropium (n = 179) was sustained throughout the treatment period ($p < 0.001$ for trough FEV_1 and $p < 0.05$ for trough FVC at all time points) [figure 1]. Mean baseline FEV_1 was 1.19L.[15] At one year, mean trough FEV_1 and FVC remained 9.6 and 11.6%, respectively, above baseline values in the tiotropium group, compared with ipratropium which reduced trough FEV_1 by 2.5% and increased trough FVC by 4.2%.[15] Morning and evening PEFR improved to a greater extent in the tiotropium than the ipratropium group ($p < 0.01$ at all time points).[15]

• Tiotropium improved FEV_1 at the end of the 1-year period more than ipratropium ($p < 0.05$) in all three categories of disease severity (mild, moderate and severe).[26]

• Tiotropium 18μg once daily (n = 209) increased mean trough FEV_1, FVC and PEFR to a significantly greater extent than salmeterol 50μg twice daily (n = 213) in a placebo-controlled 6-month study.[18] Both active drugs were superior to placebo (n = 201; $p < 0.01$).[18] Mean trough FEV_1 responses were higher with tiotropium than with salmeterol (by 52ml, $p < 0.01$), as were peak FEV_1

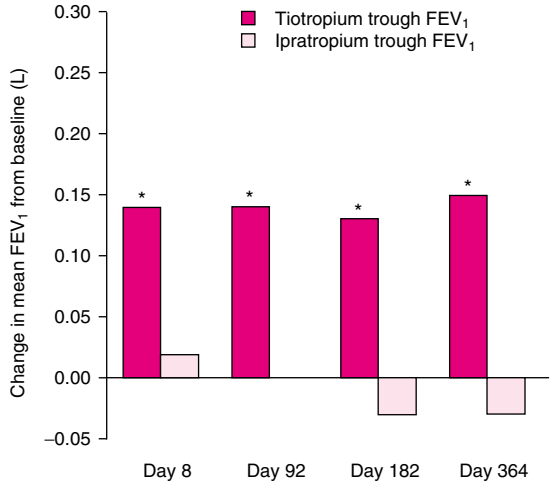


Fig. 1. Comparative efficacy of tiotropium and ipratropium. Mean change in trough forced expiratory volume in 1 second (FEV_1) after one year's treatment with tiotropium 18μg once daily via dry powder inhaler (Handihaler®) [n = 356] and ipratropium 40μg four times daily via metered-dose inhaler (n = 179). Results are combined for two randomised, double-blind multicentre trials. Mean baseline FEV_1 was 1.19L.[15,29] * $p < 0.001$ *vs* ipratropium.

responses (by 83ml, $p < 0.01$), average FEV_1 responses (by 77ml, $p < 0.01$) and trough FVC responses (by 112ml, $p < 0.01$). Increases in PEFR in the morning ($p < 0.001$ except weeks 15 and 16) and evening ($p < 0.05$) were larger with tiotropium (11 and 13%) than with salmeterol (9 and 6%).

Dyspnoea

- Dyspnoea, as measured by the Transition Dyspnea Index (TDI), improved further with tiotropium than with placebo at all time points according to pooled data ($p < 0.001$).[17] Forty-two to 47% of tiotropium versus 29 to 34% of placebo recipients ($p < 0.01$) achieved a clinically important change (score of ≥1) in TDI focal score, which is a summation of three domains (magnitude of task, magnitude of effort, and functional impairment). Shortness of breath and wheezing ($p < 0.05$), but not cough and chest tightness, were improved more with tiotropium than with placebo.[17]

- Increases in the TDI focal score were significant in the tiotropium versus the ipratropium group after 1 week of treatment and were sustained throughout the duration of these studies (difference of 0.9 points, $p < 0.01$ *vs* ipratropium on day 364).[15] Thirty-one percent of the tiotropium versus 18% of the ipratropium group experienced clinically meaningful improvement ($p = 0.004$).[15]

- TDI focal score was also increased to a greater extent with tiotropium than with salmeterol (by 0.78 units, $p < 0.05$) or placebo (by 1.02 units, $p = 0.01$) at 6 months. The increase was clinically significant in 42, 35 and 26% of patients in these groups, respectively ($p < 0.01$ for tiotropium *vs* placebo).[18]

Exacerbations

- In the placebo-controlled trials, fewer tiotropium than placebo recipients had at least one COPD exacerbation (36 *vs* 42%, $p < 0.05$). The time to first exacerbation was increased ($p = 0.011$) and the number of exacerbations overall decreased with tiotropium versus placebo (0.76 *vs* 0.95 events • patient/year, $p = 0.045$).[17]

- In the tiotropium group there were fewer hospitalisations because of exacerbations (0.086 *vs* 0.161 events • patient/year, $p = 0.019$), fewer patients were hospitalised for exacerbations (5.5 *vs* 9.4%, $p < 0.05$) and fewer days were spent in hospital because of exacerbations (0.6 *vs* 1.2 days • patient/year, $p = 0.023$).[17]

- Similarly, compared with ipratropium after 1 year's treatment, tiotropium significantly reduced the incidence of COPD exacerbations (35 *vs* 46%, $p = 0.014$), the number of exacerbations (0.73 *vs* 0.96 events • patient/year, $p = 0.006$) and the number of exacerbation days (10.8 *vs* 17.7 days • patient/year, $p = 0.002$).[15]

- Tiotropium treatment also lengthened the time to first exacerbation ($p = 0.008$) and time to first hospitalisation for exacerbation ($p = 0.048$) compared with ipratropium. There was a nonsignificant tendency with tiotropium toward a decrease in the proportion of patients hospitalised and number of hospitalisations.[15]

- There was a tendency for fewer patients in the tiotropium group to have COPD exacerbations (36.8%) than those in the salmeterol (38.5%) or placebo groups (45.8%), but these differences were not significant.[18]

Other Assessments

- Use of rescue salbutamol was approximately one dose per day lower with tiotropium than with placebo in the last week of the trials (3.2 *vs* 4.1 doses per day, $p < 0.01$).[17] Tiotropium recipients administered approximately four fewer inhalations of salbutamol per week than ipratropium recipients ($p < 0.05$ for 40 of 52 weeks).[15] Both tiotropium and salmeterol groups used fewer salbutamol puffs per day than placebo ($p < 0.0001$).[18]

- Physician's global evaluation scores favoured tiotropium over placebo at all assessment points ($p < 0.01$).[17]

- Compliance assessment of tiotropium via HandiHaler® showed that >85% of patients took the drug at least 90% of the time, as assessed by punctured capsule counts in the placebo-controlled trials.[30]

Health-Related Quality of Life

The efficacy of tiotropium in improving health-related QOL, as measured by responses to the disease-specific St George's Respiratory Questionnaire (SGRQ),[32] was demonstrated in comparisons with placebo,[17] ipratropium[15] and salmeterol.[18] The SGRQ is a validated QOL instrument that was developed for use in patients with chronic airflow limitation.[32] It consists of an overall total score and three domains, including symptoms (frequency and severity), activity (activities that cause or are limited by breathlessness), and impacts (social functioning and psychological disturbances resulting from respiratory disease).[32] The generic Short Form 36 (SF-36) questionnaire was also used to evaluate health status.

St George's Respiratory Questionnaire

- Tiotropium 18μg once daily produced significantly greater improvements than placebo in SGRQ total and impacts scores after 6, 9 and 12 months ($p < 0.05$) in the combined analysis of the placebo-controlled trials.[17] More patients in the tiotropium (49%) than the placebo group (30%) had clinically meaningful improvements in total SGRQ (a decrease of ≥4 units) [$p < 0.05$].[17]

- Tiotropium improved total SGRQ score (difference of 3.3, $p < 0.05$) and impacts scores (difference of 4.28, $p = 0.001$) further than ipratropium at 1 year. Clinically meaningful improvements in total SGRQ were more common with tiotropium than with ipratropium at 9 months (54 *vs* 42% of patients, $p < 0.05$) and 12 months (52 *vs* 35%, $p = 0.001$).[15]

- Tiotropium 18μg once daily, but not salmeterol 50μg twice daily, improved SGRQ total and impacts scores significantly more than placebo after 6 months' therapy ($p < 0.05$).[18] The percentage of patients with an SGRQ total score improvement of ≥4 was higher ($p < 0.05$) with tiotropium (51%) than with salmeterol (40%) and placebo (42%).[18]

Short Form 36 Questionnaire

- Use of the SF-36 questionnaire showed tiotropium to improve physical health but not mental health domains relative to placebo ($p < 0.05$) at all assessment times.[17] Tiotropium and ipratropium had similar effects on SF-36 domains, except for a greater improvement in physical health summary with tiotropium ($p < 0.015$ *vs* ipratropium).[15]

4. Tolerability

- With the exception of dry mouth, the overall tolerability profile of tiotropium appears similar to that of placebo.[17] Dry mouth was the most common event reported with tiotropium according to the combined results of the two 1-year placebo-controlled trials (16 vs 2.7%, $p < 0.05$).[17]

- Dry mouth occurred in 12.1% of tiotropium recipients and 6.1% of ipratropium recipients ($p = 0.03$),[15] and in 10% of the tiotropium group in the comparison with salmeterol (no other values given).[18] Dry mouth was generally of mild intensity, resolved with continued treatment in most patients, and did not necessitate treatment cessation.[15]

- The number of patients discontinuing treatment due to adverse events was 9.6% for tiotropium and 13.7% for placebo groups in the combined analysis of 1-year placebo-controlled trials,[17] and 10.1% for tiotropium and 12.8% for ipratropium in the other analysis of 1-year trials.[15] There were no clinically significant changes in vital signs, 12-lead ECG or laboratory values during one year's treatment with tiotropium.[15]

- There were no dose-dependent increases in the incidence or severity of any adverse effect with tiotropium in dosages of 4.5, 9, 18 or 36μg once daily for 4 weeks in a dose-ranging trial, although the highest dose was associated with the highest incidence of events (50%).[16]

5. Dosage and Administration

In clinical trials tiotropium was administered via inhalation in a dosage of 18μg once daily by dry powder inhaler (HandiHaler®). Time of administration (morning versus evening) did not alter the efficacy of the drug.

6. Tiotropium Bromide: Current Status

Tiotropium is a long-acting anticholinergic bronchodilator that is administered once daily by inhalation. It is presently in the late stages of clinical development. Well controlled clinical trials in patients with COPD have shown greater efficacy with tiotropium than with placebo and ipratropium 40μg four times daily for 1 year and greater increases in lung function than salmeterol 50μg twice daily for 6 months. The drug is well tolerated, with dry mouth the most common adverse event.

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