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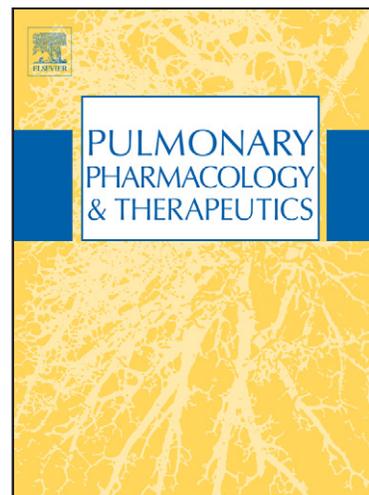
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Abstract

The objectives of this study were to determine the effect of single and repeat dosing with oral ondansetron, a 5-HT₃-specific receptor blocker, on the degree and duration of bronchodilation induced by inhaled ipratropium bromide in patients with COPD. Five clinics and university medical centers in four countries participated in the study; forty seven patients with COPD were randomized to treatment; 44 completed all treatments. Patients had a baseline (pre-bronchodilator) FEV₁ > 1 liter and post-bronchodilator (200 mcg salbutamol) FEV₁ < 90% of predicted, with FEV₁ reversibility (to 80 mcg inhaled ipratropium bromide and 400 mcg salbutamol) of at least 12% or 200 ml over baseline. The study was divided into two parts. In Part A, each patient received in a random order, four-way cross-over manner, single doses of ondansetron placebo (oral) plus ipratropium bromide placebo (inhaled), ondansetron placebo plus ipratropium bromide 40 mcg inhaled via MDI, ondansetron 24 mg oral plus ipratropium bromide placebo and ondansetron 24 mg plus ipratropium bromide 40 mcg. In Part B, each patient received in a random order, two-way crossover manner, ipratropium bromide 40 mcg tid via MDI plus ondansetron 8 mg oral, qid, for two days; on day 3 patients received a single dose of ipratropium bromide 40 mcg plus 8 mg oral ondansetron. Alternatively, patients received ipratropium bromide via MDI and oral ondansetron placebo, as described above. Statistically significant differences in weighted mean FEV₁ (0-6 hours), peak FEV₁ and FEV₁ determined 6 hours post-dose were noted comparing ipratropium bromide to placebo. Similar positive results were observed for sGaw and FVC. Addition of ondansetron to ipratropium bromide did not significantly modify values obtained with ipratropium alone. Ipratropium bromide induced a marked bronchodilation, compared to placebo. Addition of ondansetron (single or repeated doses) did not significantly increase the degree or duration of

bronchodilation induced by ipratropium alone. sGaw was consistently more sensitive than FEV1 in measuring extent and duration of bronchodilation.

Keywords: Drug combination, combination bronchodilator, COPD, bronchodilation, ondansetron, 5-HT3, ipratropium bromide.

1. Introduction

COPD has been recognized as a major health problem for about 50 years (1). In contrast with other leading chronic diseases, its prevalence and disease-related morbidity and mortality are increasing (2-6). Bronchodilators are typically prescribed for maintenance therapy of the reversible obstructive component of the disease. In patients with minimally reversible or irreversible obstruction, symptom improvement observed following bronchodilator therapy may be related to the degree of reduction in gas trapping and dynamic hyperinflation, which, in turn, may result in reduction in the overall work of breathing (7, 8). The bronchodilators most commonly used are inhaled beta2-adrenoceptor agonists and inhaled anticholinergics (2-5, 9); current international guidelines recommend combination therapy for patients not well controlled by monotherapy (2-6), since anticholinergics and beta2-adrenoceptor antagonists achieve their bronchodilating effects via different mechanisms (9). A number of studies have indeed demonstrated that, in patients with stable COPD, the combination is more effective than either agent alone (9-13).

Dominant autonomic control of the airways is provided by the parasympathetic nerves, which control a variety of airway functions (14, 15). Acetylcholine, released from the parasympathetic nerves, stimulates muscarinic receptors, causing bronchoconstriction and mucus secretion. The effect of acetylcholine in the airways is mediated mainly through three muscarinic receptor subtypes, designated M1, M2 and M3 (16). M1 receptors facilitate neurotransmission through the cholinergic ganglia; M2 receptors are found on pre and postganglionic parasympathetic nerves and inhibit release of acetylcholine, while M3 receptors are present in airway smooth muscle (ASM) and submucosal glands and are responsible for mediating bronchoconstriction and mucus secretion (16, 17). Inhibition of acetylcholine release by M2 receptors may be decreased or lost due to M2 receptor dysfunction in asthma and in COPD (18, 19), resulting in unopposed activity at the M3 receptors. This excessive M3 receptor stimulation may contribute to the bronchoconstriction and mucus hypersecretion observed in inflammatory airways diseases.

Serotonin (5-HT) has also been reported to have effects on airway smooth muscle contraction through interactions with multiple receptor subtypes. Most data has been generated in in vitro experiments. In isolated rat bronchi 5-HT induced contraction of airway smooth muscle (ASM) directly, by activating airway smooth muscle 5-HT2 receptors, and indirectly, by activating 5-HT2 receptors on parasympathetic nerve endings, leading to release of acetylcholine (20,21).

Studies in human airways have shown that cholinergic contraction induced in vitro following electrical stimulation was increased by the presence of 5-HT; this facilitation of cholinergic contraction could be blocked completely by tropisetron, a 5-HT₃ and 5-HT₄ receptor blocker, and partially by ondansetron, a 5-HT₃ receptor blocker (22). In subjects with asthma, plasma levels of 5HT are elevated and correlate with clinical severity rating and FEV₁ (23). One possible source of 5-HT are the endocrine cells of the lung (24); an increase in the number of endocrine cells (and presumably 5-HT) has been described in bronchiectatic lungs, lung containing neoplasms and lungs of subjects exposed to hypoxia (25). In a small group of subjects with COPD reversible to albuterol, administration of inhaled or of intravenous ketanserin, a 5-HT₂ antagonist, induced a small degree of bronchodilation that was statistically significantly different from placebo, 30 minutes following administration of the drug (26). Combination therapy has become standard in the treatment of airway disease; this allows the targeting of diverse mechanisms that participate in the disease process. Identification and characterization of these mechanisms utilizing specific inhibitors may improve our understanding of the disease and could help in the development of optimal treatment. The objective of this study was to determine the short term effect of single and repeat dosing with ondansetron, a 5-HT₃- specific receptor blocker, on the degree of bronchodilation induced by inhaled ipratropium bromide in patients with stable COPD. Three endpoints were evaluated in the determination of bronchodilation: FEV₁ and FVC, measured by spirometry, and sGaw, determined by plethysmography.

2. Materials and Methods

2.1 Study Design

This was a double-blind, randomized, placebo controlled, crossover, two part study comparing the effect on pulmonary function of inhaled ipratropium bromide (Atrovent®, Boehringer Ingelheim, 27), 40 mcg (single dose or tid), given by metered-dose inhaler, ondansetron (Zofran®, GlaxoSmithKline, 28), 24 mg single dose or 8 mg tid, given orally, and their combination.

The study was carried out in five centers in four countries (2 centers in the US, one center each in Belgium, The Netherlands and Germany). The study was approved by the appropriate Ethics Committee/Institutional Review Board at each site and was conducted according to the principles of good clinical practice.

The study was divided into two parts and a screening visit. At screening, baseline measurements were performed and the eligibility of patients to participate in the study was determined. Part A of the study (four-way crossover) was conducted within 2 weeks of the screening visit; patients were randomized to receive, in a cross-over manner, single doses of ondansetron placebo plus ipratropium bromide placebo, ondansetron placebo plus ipratropium bromide 40 mcg via MDI, ondansetron 24 mg oral plus ipratropium placebo, and ondansetron 24 mg oral plus ipratropium

bromide 40 mcg via MDI. Patients received single doses of each study medication in the clinic; spirometry and plethysmography were performed 30 minutes before and 0.5, 1, 2, 3, 5 and 6 hours following administration of study medication. Dosing days were separated from each other by at least 48 hours.

Part B of the study was conducted at least 48 hours following the last administration of study medication in Part A. Part B was a randomized, double-blind, placebo-controlled, two-period crossover study. Patients were randomized to receive ipratropium bromide 40 mcg tid via MDI plus ondansetron placebo qid for two days; on day 3 patients received a single dose of ipratropium bromide 40 mcg via MDI plus ondansetron placebo. Alternatively, patients received ipratropium bromide 40 mcg tid via MDI plus ondansetron 8 mg qid orally, for two days; on day 3 patients received a single dose of ipratropium bromide 40 mcg via MDI plus ondansetron 8 mg orally. The two study periods were separated from each other by at least 48 hours. Patients remained in the clinic for about 7 hours following administration of study medication on day 3 of each crossover period; spirometry and plethysmography were determined as before, 30 minutes prior to and 0.5, 1, 2, 3, 5 and 6 hours following administration of study medication, on day 3 of each crossover period. A follow-up visit was conducted 7 to 14 days after the last dosing with study medication.

2.2 Patients

Inclusion criteria included the following: male and female patients, age ≥ 40 to ≤ 75 years old, who gave written informed consent, with a diagnosis of COPD according to the American Thoracic Society guidelines (2); current or former (discontinued smoking for > 1 yr) smokers (smoking history ≥ 10 packs/year); pre-bronchodilator FEV1 > 1 liter, post-bronchodilator (180 mcg albuterol/200 mcg salbutamol via MDI) FEV1 $< 90\%$ of predicted; FEV1/FVC < 0.7 ; an increase in FEV1 of at least 12% or 200 ml over baseline after 80 mcg inhaled ipratropium bromide and 360 mcg albuterol/400 mcg salbutamol. Entry criteria are similar to those of other publications (13, 29, 30, 31, 32) except that only one (29) included a reversibility criterion for entry (an increase in FEV1 of 15% over baseline following bronchodilator). The other studies did not include a reversibility requirement; on the other hand, in all studies FEV1 increased by 200 mL or more over baseline following the administration of a single dose of bronchodilator.

Exclusion criteria included: a diagnosis of asthma; an acute COPD exacerbation that required treatment with oral corticosteroids or hospitalization, or upper respiratory tract infection, within one month of screening; need for short or long-term oxygen therapy; use of oral corticosteroids at doses > 10 mg/day; change in the dose of inhaled or oral corticosteroids within 6 weeks of screening.

2.3 Efficacy parameters

The primary efficacy variable was the weighted mean FEV₁ (0-6 hours) for single doses or the last dose of the repeat-dose period. Secondary efficacy variables were weighted mean sGaw (0-6 hr), peak values for FEV₁, FVC, FEV₁/FVC ratio and sGaw (peak refers to the maximum value in 0-6 hours), and FEV₁, FVC, FEV₁/FVC ratio and sGaw determined 6 hours post-dosing. Spirometry and plethysmography were performed following standard procedures (3, 4, 5). Pulmonary function determinations were performed at the same time of day in order to minimize daytime variability of measurements. Rescue inhalations with short-acting bronchodilator were to be avoided for at least 4 hours prior to dosing to at least 6 hours post-dosing. Subjects abstained from long-acting beta₂-agonists, long-acting anticholinergics (tiotropium) and xanthines for two weeks prior to the first dose to the end of the study.

2.4 Safety variables

Safety was assessed using adverse event reporting, electrocardiograms, vital signs and clinical laboratory evaluations.

2.5 Statistical Analysis

The primary comparison of interest was weighted mean FEV₁ (0-6 hours) in the single dose crossover phase, comparing ondansetron (24mg) and ipratropium (40mcg) vs. ipratropium (40mcg) and ondansetron placebo. This comparison was repeated for weighted mean sGaw (0-6 hours); peak FEV₁, FVC, FEV₁/FVC ratio and sGaw and for FEV₁, FVC, FEV₁/FVC ratio and sGaw determined 6 hours post-dosing.

Unless otherwise specified, all analyses were performed using SAS software (version 8.2). This was a multicentre study; for the purpose of this study, centre and/or country differences were not assessed due to the small number of centres in each country and the small number of patients at each site.

Actual sample times were used to calculate the weighted means and peak endpoints. The weighted mean parameters were calculated by dividing the area under the curve (AUC) by time. The AUC was calculated using the linear trapezoidal method.

In order to evaluate the primary outcome (weighted mean FEV1 0-6 hours) a mixed effects model was fitted, with fixed effects for period, treatment and baseline FEV1 (as a covariant) and random effects for subjects. Baseline FEV1 was fitted as a continuous variable; baseline FEV1 was the pre-dose value of FEV1 on the appropriate dosing day (Study Part A-single dose). Least square (LS) means for each treatment, differences in LS means and the 95% confidence intervals for the difference are presented. The same model was used to evaluate this outcome for Part B of the study (repeat dose) using baseline as the pre-dose value of FEV1 on Day 1. sGaw data was log transformed for analysis., treatment ratios were calculated by taking the difference between least square means and the 95% confidence interval was calculated for the difference and anti-logged.

Information from previous studies comparing ipratropium plus beta2-agonist vs ipratropium , following administration of bronchodilator (10, 13) has provided estimates of within subject standard deviation for weighted mean FEV1 of 0.15 L and shown differences of 0.06 L and 0.08 L. In order to power the study based on these differences, a sample of more than 60 subjects would have been required. Due to logistics and resources, the subject number was limited to 40: with 40 subjects completing and a within subject standard deviation of 0.15L, differences in FEV1 weighted means of 0.096L and 0.111L can be detected with 80% and 90% power, respectively. All calculations were 2-sided and assumed a significance level of 5%.

3. Results

Forty seven patients were randomized to treatment; forty four completed all treatments and three were discontinued prematurely. One patient was withdrawn because of a protocol violation, after undergoing all single-dose treatments and one repeat-dose treatment; one patient withdrew consent after receiving one single-dose treatment (placebo), and one patient was withdrawn because of lack of compliance with the protocol, after receiving all single-dose treatments.

A summary of demographic and baseline data is presented in Table 1. Following administration of bronchodilator, 45 patients had an increase in FEV1 of > 200 mL and two had an increase of 200 mL, while 17 patients had increases of > 12% over baseline. There were no differences in the responses to bronchodilator between all patients and those taking corticosteroids. Concomitant

medications at baseline included the following bronchodilators: salbutamol/albuterol (43% of patients), ipratropium bromide (17%), the combination of ipratropium bromide and albuterol, Combivent[®] (6%). 38.2% of the patients were on inhaled corticosteroids and 2% on oral corticosteroids (7.5 mg/day). The bronchodilator reversibility as percent increase from baseline was 25.0 % (mean value, range from 6.1 to 50.0%). Xanthines, inhaled long-acting beta2-agonists, and tiotropium bromide were discontinued two weeks before administration of the first dose of study medication and for the duration of the study.

The combination of ipratropium and ondansetron appeared to be well tolerated. There were no withdrawals due to adverse experiences. A statistically significant difference in weighted mean FEV₁ (0 – 6 hours) between treatments was noted in the comparison of ipratropium bromide vs placebo (Tables 2, 3, Figure 1). Treatment with ipratropium bromide (compared to placebo) also resulted in a statistically significant increase in peak FEV₁ and in FEV₁ determined 6 hours post-dose (Table 4). However, dosing with ondansetron and ipratropium together was no more effective than dosing with placebo and ipratropium bromide in increasing the weighted mean of FEV₁ (0-6 hours), peak FEV₁ and FEV₁ 6 hr. This was observed for both the single dose and the repeat-dose parts of the study.

Similarly, statistically significant increases in weighted mean sGaw, and in peak values and values determined 6 hours post-dosing for FVC and sGaw were observed after dosing with ipratropium, compared to placebo. As was observed for FEV₁, there was no significant increase in FVC and sGaw after dosing with both ipratropium and ondansetron compared with ipratropium alone. Results for the repeat-dose part of the study were similar to results from single dose administration (Table 4, Figure 2).

The only statistically significant change observed after dosing with ondansetron was an increase in FVC 6 hours post-dosing with a single 24 mg dose, in the presence of ipratropium placebo. When compared with ondansetron placebo/ ipratropium placebo, this treatment resulted in a statistically significant increase in FVC 6 h of 0.132 L (95% confidence interval: 0.021, 0.242 L). This increase was similar to that seen with ipratropium 40 mcg compared with placebo (treatment difference 0.224 L; 95% confidence interval: 0.113, 0.335 L). Following co-administration of ondansetron 24 mg and ipratropium 40 mcg, FVC was not significantly different to FVC after administration of ipratropium 40 mcg alone. In order to compare changes in sGaw and FEV₁, effect size was calculated by dividing treatment differences by the standard deviation; sGaw was consistently more sensitive than FEV₁, particularly at peak value and 6 hours post-dose (Table 5).

4. Discussion

The comparison of ipratropium bromide 40 mcg + ondansetron 24 mg with ipratropium bromide 40 mcg + placebo showed that there was no improvement in weighted mean FEV₁ (0-6 hours), peak FEV₁ or FEV₁ determined 6 hours post-dosing when patients received ondansetron, compared

with placebo. Similar lack of improvement was observed for FVC, FEV1/FVC ratio and sGaw. Therefore, results of this randomized, double-blind, placebo-controlled, crossover study indicate that dosing with oral ondansetron in addition to ipratropium is not effective in improving pulmonary function in patients with COPD.

When ipratropium bromide was compared with placebo, statistically significant increases in weighted mean FEV1 (0-6 hours), peak FEV1 and FEV1 6 hours were observed. Similar positive results were determined for FVC and sGaw. The comparison of ondansetron 24 mg with placebo showed a statistically significant improvement in FVC determined 6 hours post-dosing, but no other variable showed a statistically significant change. Results obtained from a limited repeat-dose administration were similar to those observed following single doses. However since we have not corrected for multiple comparisons, this increase could be a false-positive finding.

As expected, ipratropium bromide induced a marked bronchodilation compared to placebo, as determined by spirometry (FEV1). This was accompanied by increases in sGaw (weighted mean, peak value and sGaw determined 6 hours post-dose); sGaw was consistently more sensitive than FEV1, particularly in determinations at peak and 6 hours post-dose. Similar results have been observed with ipratropium bromide (12) and other bronchodilators (29,33) in patients with COPD (12,29) and in normal healthy volunteers (33). In a recent publication, spirometry, plethysmography and impulse oscillometry were compared in their ability to measure bronchodilation induced by inhalation of increasing doses of salbutamol in patients with COPD. For the lower doses of salbutamol, plethysmography (sGaw) and impulse oscillometry were more sensitive than FEV1 in detecting bronchodilation; on the other hand, sGaw was the most variable measurement, followed by oscillometry parameters, with spirometry (FEV1) being the least variable (34). Plethysmography measures airway resistance, conductance and lung volumes while impulse oscillometry measures airway resistance and lung reactance (35). Unlike spirometry, these tests do not require effort dependent forced expiration. In patients with COPD experiencing bronchodilation induced by increasing doses of salbutamol, the shape of the dose-response curves was different for sGaw compared to other measurements; there was an initial sharp improvement in sGaw at low doses of salbutamol, after which the gradient of the curve was similar to other readings (34). This initial rapid improvement in airway conductance may explain the increased sensitivity of plethysmography compared with the other methods at low bronchodilator doses. For the purposes of detecting small physiological effects in COPD (34) or asthma (36), this may be a potential advantage (e.g. measuring physiological changes at 12 or 24 hours after administration of a bronchodilator).

Serotonin (5-HT) has been reported to have effects on airway smooth muscle contraction through interactions with multiple receptor subtypes. Conversely, blockers of 5-HT receptor subtypes have been shown to reduce constriction or induce bronchodilation. In *in vitro* studies in human airways, tropisetron, a 5-HT3 and 5-HT4 receptor blocker, and ondansetron, a 5-HT3 receptor blocker, were able to completely or partially, respectively, reduce the facilitation of contraction induced by

electrical stimulation in the presence of 5-HT (22). In a small group of subjects with COPD reversible to albuterol, administration of inhaled or of intravenous ketanserin, a 5-HT₂ antagonist, induced a small degree of bronchodilation that was statistically significantly different from placebo (26). In contrast, in this study, addition of a 5HT₃ receptor blocker (ondansetron) did not improve the effect of ipratropium in inducing bronchodilation in patients with COPD.

In conclusion, results obtained in this study suggest that the participation of serotonin in establishing pulmonary tone or inducing bronchoconstriction may be mediated through interaction with 5-HT subtype receptors other than 5-HT₃. *In vitro* data suggests that blocking several 5-HT receptors (5-HT₃ and 5-HT₄; 22) may have been more effective than blocking a single type of receptor. This suggests that tropisetron may have been a better choice than ondansetron. In addition, although both compounds have a high 5-HT₃ binding affinity, tropisetron has a considerably longer half life than ondansetron (8-10 hrs and 3.5 hrs, respectively) (36). On the other hand, one goal of this study was to identify receptors involved in the disease process; this required specific receptor blockers. As additional mechanisms involved in airway diseases are identified and the number of drugs used in treatment increases, this type of study, conducted in a small number of patients for a short period of time, may be of value in the identification of useful drug combinations (38, 39). This study also suggests that determination of sGaw may be a useful complement to the determination of FEV₁ in establishing both peak bronchodilatory activity and duration of effect.

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Table 1.
Summary of Demographic and Baseline Data of ITT Population (n=47)

Variables	Data
Age, yr; mean (SD), range	59.6 (7.8), 43-75
Sex, No. (%)	
male	42 (89)
female	5 (11)
Race, No. (%)	
White	42 (89)
Black	4 (9)
American-Hispanic	1 (2)
Concomitant Medications	
Inhaled corticosteroids	18 (38.2%)
Oral Corticosteroids	1 (2%)
FEV ₁ before albuterol/salbutamol (all patients), L	1.70 (0.49)
FEV ₁ before albuterol/salbutamol, L (patients taking corticosteroids)	1.72 (0.53)
FEV ₁ before albuterol/salbutamol, % Predicted (all patients)	49.0 (12.1)
FEV ₁ after albuterol/salbutamol (all patients), L	2.09 (0.52)
FEV ₁ after albuterol/salbutamol (patients taking corticosteroids), L	2.1 (0.51)
Reversibility	
Delta FEV ₁ : increase over baseline (all patients), L	0.39 (0.17)
Delta FEV ₁ : increase over baseline (patients taking corticosteroids), L	0.38 (0.11)
Delta FEV ₁ : % increase over baseline (all patients)	25.0 (12.1)
Delta FEV ₁ : percent of predicted value (all patients)	11.3 (4.6)

Table 2

Summary of derived parameters: Weighted Mean 0-6 h FEV1 (L)

Treatment	N	n	Mean (SD)	Median (range)
Single dose (Part A)				
Ondansetron pbo + ipratropium pbo	47	47	1.683 (0.4995)	1.608 (0.75 2.96)
Ondansetron pbo + ipratropium 40 mcg	46	46	1.849 (0.5243)	1.704 (0.84 3.18)
Ondansetron 24 mg + ipratropium pbo	46	46	1.702 (0.5141)	1.659 (0.72 2.99)
Ondansetron 24 mg + ipratropium 40 mcg	46	46	1.858 (0.5288)	1.743 (0.89 3.23)
Repeat dose (Part B)				
Ipratropium 40 mcg qid + Ondansetron pbo tid	45	44	1.795 (0.5245)	1.725 (0.75 3.14)
Ipratropium 40 mcg qid + ondansetron 8 mg tid	45	43	1.761 (0.5168)	1.643 (0.81 3.05)

Table 3
 Summary of Results for Weighted Mean 0 – 6 h FEV₁ (L) - Single Dose Difference Between
 Combinations of Study Medications

Treatment Comparison	Difference	95 % Confidence Interval
Ondansetron 24 mg + ipratropium 40 mcg vs Ondansetron pbo + ipratropium 40 mcg	0.001	-0.044, 0.046
Ondansetron 24 mg + ipratropium pbo vs Ondansetron pbo + ipratropium pbo	0.011	-0.033, 0.055
Ondansetron pbo + ipratropium 40 mcg vs Ondansetron pbo + ipratropium pbo	0.149	0.105, 0.194

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Table 4

Summary of Results for FEV1, FVC and sGaw.

Ipratropium Bromide vs Placebo – Single Dose				
Differences of Least Square Means for FEV1 and FVC				
Variable	Least Square Means		Test – Reference Treatment	
	Test Treatment	Reference Treatment	Difference	95% CI
Weighted Mean FEV1 0-6 hr.	1.84	1.69	0.149	(0.105, 0.194)
Peak FEV1, L	1.98	1.80	0.173	(0.123, 0.223)
FEV1 6 hr post-dose	1.73	1.65	0.078	(0.017, 0.138)
Peak FVC, L	3.70	3.38	0.324	(0.228, 0.420)
FVC 6 hr post-dose	3.29	3.07	0.224	(0.113, 0.335)

Ipratropium Bromide vs Placebo – Single Dose				
Ratio of Geometric Least Square Means for sGaw				
Variable	Geometric Least Square Means		Ratio of Geometric Means	
	Test Treatment	Reference Treatment	Test / Reference Treatment Ratio	95% CI
Weighted Mean sGaw 0-6 hr.	0.574	0.420	1.368	(1.179, 1.588)
Peak sGaw	0.721	0.493	1.463	(1.265, 1.692)
sGaw 6 hr post-dose	0.454	0.383	1.184	(1.008, 1.392)

Table 5
Treatment effect (Treatment Difference / Standard Deviation) – Single Dose

Parameter	effect size	(treatment difference/ standard deviation)
1) FEV1 wm (0-6h)	1.400	(0.149/0.1064)
2)FEV1 peak (0-6h)	1.455	(0.173/0.1189)
3)FEV1 6h	0.054	(0.078/0.1447)
4)sGaw wm(0-6h)	1.436	(0.313/0.2182)
5)sGaw peak (0-6h)	1.786	(0.381/0.2130)
6)sGaw 6h	0.717	(0.169/0.2361)

The effect size is equal to the treatment difference divided by the standard deviation; treatment differences for sGaw are on the log scale.
wm=weighted mean

Figure 1

Weighted mean FEV1 determined for six hours following single-dose administration

Figure 2

Geometric mean sGaw determined for six hours following single-dose administration

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Figure 1. Weighted mean FEV₁ determined for six hours following single and last dose (of the repeat dose, ▲ o) administration

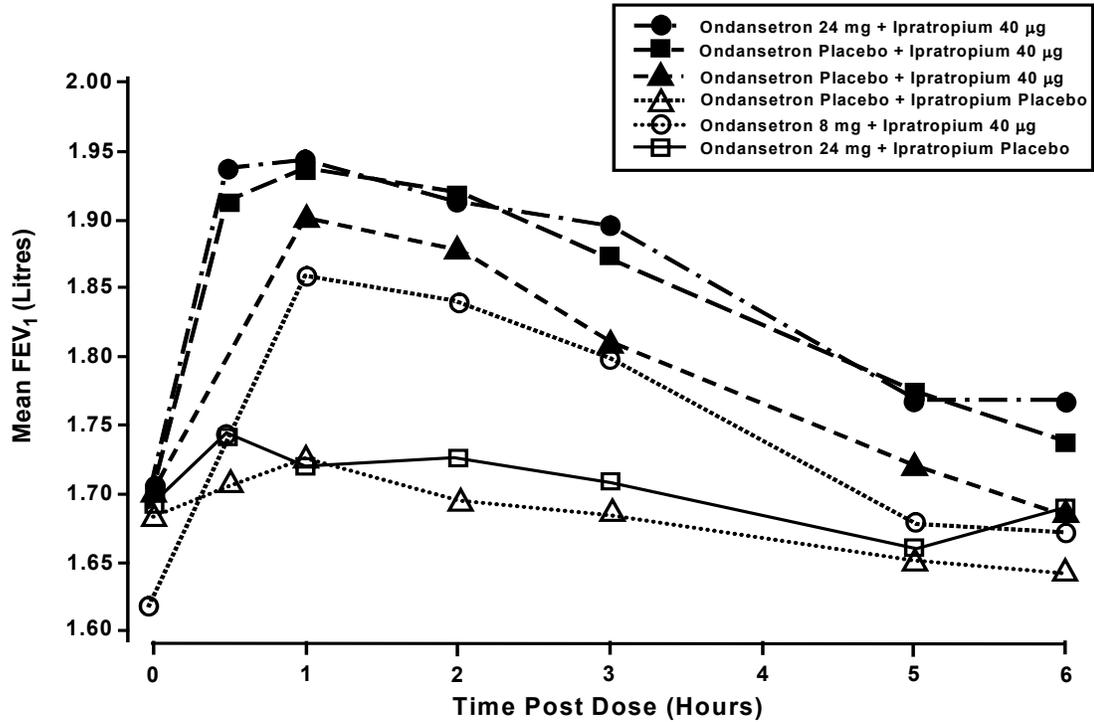


Figure 2. Geometric mean sGaw determined for six hours following single and last dose (of the repeat dose, ▲ o) administration.

