Effects of formoterol (Oxis® Turbuhaler®) and ipratropium on exercise capacity in patients with COPD

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Abstract Although long-acting inhaled β_2-agonists improve various outcome measures in COPD, no double-blind study has yet shown a significant effect of these drugs on exercise capacity. In a randomized, double-blind, placebo-controlled, crossover study, patients received formoterol (4.5, 9, or 18 µg b.i.d. via Turbuhaler®), ipratropium bromide (80 µg t.i.d. via pMDI with spacer), or placebo for 1 week. Main endpoint was time to exhaustion (TTE) in an incremental cycle ergometer test. Secondary endpoints were Borg dyspnoea score during exercise, lung function, and adverse events. Thirty-four patients with COPD were included, mean age 64.8 years, FEV_1 55.6% predicted, reversibility 6.1% predicted. All doses of formoterol, and ipratropium significantly improved TTE, FEV_1, $FEF_{25-75\%}$, FRC, IVC, RV and sGAW compared with placebo. A negative dose–response relationship was observed with formoterol. Ipratropium increased time to exhaustion more compared with formoterol, 18 µg, but not with formoterol, 4.5 and 9 µg. No changes in Borg score were found. There was no difference in the adverse event profile between treatments. In conclusion, 1 week of treatment with formoterol and ipratropium significantly improved exercise capacity and lung function compared with placebo. However, a negative dose–response relation for formoterol was unexpected and needs further investigation. © 2002 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

Dyspnoea on exertion is an important feature of chronic obstructive pulmonary disease (COPD). Bronchodilators are routinely prescribed to symptomatic patients with COPD with the aim of reducing bronchial obstruction and symptoms and improving exercise capacity. In the GOLD guidelines on COPD (1), bronchodilators are recommended either as needed or on a regular basis to prevent or reduce symptoms. The guidelines suggest that long-acting inhaled bronchodilators are the most convenient therapy, and some studies have suggested that inhaled long-acting β_2-agonists are more effective than

anticholinergics in improving lung function in patients with stable COPD (2,3). However, the effects of long-acting β_2-agonists on exercise capacity in COPD have not been intensively investigated. There have been three double-blind studies investigating the effects on exercise capacity of salmeterol (4–6), but there are no published reports about the effects of formoterol on exercise capacity in COPD.

We investigated the effects of 1 week maintenance treatment with three different doses of formoterol fumarate dihydrate (4.5, 9, and 18 µg b.i.d) via Turbuhaler®, ipratropium (80 µg t.i.d.) via pMDI and spacer, and placebo on exercise capacity, Borg dyspnoea score and lung function in patients with COPD. We hypothesized that formoterol would give a dose-dependent increase in exercise time, significantly greater than with placebo and similar to that with ipratropium. The primary efficacy outcome variable was time to exhaustion (TTE), defined

as the total cycling time during an incremental bicycle ergometer test. Secondary outcome variables were lung function parameters assessed before the exercise test and dyspnoea (measured by Borg score) while cycling.

PATIENTS AND METHODS

Study design

Four centres participated in this randomized, double-blind, placebo-controlled, crossover study, comprising five 1-week study periods, each separated by a 6–12 day wash-out period. During the wash-out period, patients were allowed to use only terbutaline sulphate (500 µg/dose, Bricanyl® Turbuhaler®, AstraZeneca Pharmaceutical Productions, Sweden) on demand. In the study week, they used one of the following study medications for exactly 7 days: formoterol fumarate dihydrate (delivered dose of 4.5 µg, 9, or 18 µg b.i.d., corresponding to 6, 12, and 24 µg metered dose, Oxis® Turbuhaler®, AstraZeneca Pharmaceutical Productions), ipratropium bromide (80 µg t.i.d. Atrovent® aerosol, Boehringer Ingelheim, Germany) inhaled via a spacer (Aerochamber®, Boehringer Ingelheim, Germany), or placebo, employing a double-dummy technique. The protocol was approved by the Medical Ethics Committee at each centre and all patients gave written informed consent.

Patients

Inclusion criteria: Patients in a stable phase of COPD were enrolled. Men or women aged ≥ 50 years were enrolled if they had a clinical diagnosis of COPD, with symptoms for at least the past 2 years. All patients were current or ex-smokers with a smoking history of at least 10 pack-years. After a run-in period of 6–12 days (visit 2), in which no bronchodilator medication except terbutaline was allowed, the pre-bronchodilator forced expiratory volume in one second (FEV_1) was established. This had to be 40–70% predicted and > 0.7 l. Also, the FEV_1/FVC ratio had to be $< 88\%$ predicted for men and $< 89\%$ for women (7).

Exclusion criteria: Patients having diseases other than COPD limiting their performance in an exercise test were excluded. Also excluded were patients with a history of asthma or seasonal allergic rhinitis with a disease onset before 40 years of age, or other respiratory diseases which might have influenced the results of the study. Patients experiencing an exacerbation of their COPD requiring oral corticosteroids or antibiotics 30 days prior to enrollment, or those using oxygen therapy at home, were also excluded. Patients were withdrawn from the study if they experienced more than one exacerbation requiring oral corticosteroids or antibiotics during the study.

Medication at enrollment and during the study

Patients were not allowed to use β-blockers (including eyedrops), antihistamines, leukotriene antagonists, or medication containing ephedrine. Inhaled or oral steroids had to be kept at a constant dosage from at least 30 days prior to enrollment and during the study. The highest allowed daily dose of oral corticosteroids was 10 mg prednisolone, 8 mg methylprednisolone, or 1 mg betamethasone. Mucolytics had to be kept constant 14 days prior to visit 1. Patients were allowed to use terbutaline as rescue medication in the treatment and wash-out periods.

Study protocol

At visit 1, participants underwent a physical examination, blood and urine analyses, electrocardiography, and performed a progressive cycle ergometry (PCE) test for practice purposes. At visit 2, after a run-in period of 6–12 days, baseline spirometry and body plethysmography were done with pre-bronchodilator. Reversibility was assessed 15 min after administration of inhaled terbutaline sulphate, 1 mg, and was calculated as the difference between pre- and post-bronchodilator FEV_1 % predicted (8). This was followed by a second PCE for practice purpose. Patients were then randomized and began using the study medication for the first period. Patients attended the outpatient clinic once every 2 weeks (visits 3–7) at the same time of the day (within 1 h). Study medication was taken at home 2–3 h before the spirometry tests. Spirometry and body plethysmography were performed at each visit, followed by a PCE test.

MEASUREMENTS

Spirometry

No rescue medication was allowed within 6 h prior to measurements. Spirometry was performed according to the guidelines of the ERS (7). After 15 min of rest, the patients performed three acceptable forced expiratory measurements, sitting in an upright position and wearing a nose-clip. The highest FEV_1, FVC and inspiratory vital capacity (IVC) were taken. The forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25-75\%}$) was derived from the manoeuvre that gave the largest sum of FVC and FEV_1. Predicted values were calculated according to the European Community for Steel and Coal, as described by Quanjer (7).

Body plethysmography

After 1 min of quiet breathing, lung volumes (total lung capacity [TLC], residual volume [RV], and functional re-

sidual capacity [FRC]), and airway resistance (Raw) were measured. Raw was obtained at inspiratory and expiratory flows of 0.5 l/s at a respiration rate of 0.5 Hz. Means of three measurements were recorded. Specific airway conductance (sGAW) was calculated on the basis of these values.

Progressive cycle ergometer (PCE) test

The symptom-limited maximum exercise test was performed on an electronically braked bicycle ergometer. Patients cycled at a rate of 60 rpm, starting at 10 W for 1 min and increasing by 10 W each minute. Patients were asked to cycle as long as possible until limited by dyspnoea or exhaustion. PCE tests performed at visits 1 and 2 were for training purposes only, to minimize learning effects. TTE was measured with a stopwatch as being the time from the start of exercise to the moment patients were unable to cycle any longer (maintaining 60 rpm). Borg dyspnoea scores (9) were performed at baseline, every 2 min while cycling, and when the patient stopped cycling.

Treatment compliance

At enrollment, patients were carefully instructed how to use both the Turbuhaler® inhaler and the pMDI with Aerochamber® to ensure the correct inhalation technique. During each visit, inhalation techniques were verified using empty inhalers.

During each period, patients kept track of their medication use in a diary. The investigator checked the diary for completeness at each clinic visit.

STATISTICS

Descriptive data are presented as means and standard deviations (SD). Outcome variables were analysed with analysis of variance (ANOVA) using patient, treatment, and period as covariates. The results are shown as adjusted means and standard errors of the mean (SEM) as derived from the ANOVA model. A P-value of < 0.05 was considered statistically significant. Laboratory results, blood pressure and ECG were obtained at the first and last visit for safety reasons only. Since patients received one of five different treatments immediately before the last visit, results were not analysed statistically.

RESULTS

Patient characteristics

Forty-seven patients were enrolled in the study. Twelve subjects did not meet the selection criteria at visit 2, thus 35 patients were randomized to treatment. Two of the 35 patients did not complete the study; one patient discontinued because of a trauma to the right arm (this patient missed one period and was included in the results for the other four treatment periods) and one patient was erroneously included. Four patients deviated from the protocol and did not follow the randomized treatment order, one because of an exacerbation and three because of missed dose(s) of medication 24 h prior to a visit. The faulty periods were repeated directly after study period 5 and the faulty study period was ignored in the analyses. The data from 34 patients were used in the statistical analyses. Baseline characteristics of these patients are displayed in Table I.

Progressive cycle ergometer test (PCE test)

The three doses of formoterol and ipratropium 80 μg t.i.d. increased TTE significantly compared with placebo (Table 2). The mean increases in TTE with formoterol 4.5 μg, 9 μg, 18 μg and ipratropium compared with placebo were 0.73, 0.57, 0.38 and 0.77 (SEM. 0.17) min, respectively. Though all doses of formoterol were significantly better than placebo, there was a negative dose–response relationship for the three doses of formoterol, the lowest dose corresponding to the longest exercise time. The TTE with ipratropium was significantly longer (P=0.02) than with formoterol 18 μg, but not longer than with either formoterol 4.5 or 9 μg (Table 2).

TABLE I. Baseline characteristics

Variable	Mean (SD)
Age (Years)	64.8 (8.4)
FEV_1 (l)	1.69 (0.47)
FEV_1 (% pred)	55.6 (8.9)
IVC (l)	3.55 (0.96)
FEV_1 / IVC (%)	47.5 (7.3)
FEV_1 /IVC (% pred)	62.9 (9.8)
FVC (l)	3.51 (1.00)
FEV_1 reversibility (l)	0.19 (0.15)
FEV_1 reversibility (% pred)	6.1 (4.42)
Smoking history	N (%)
Past-smoker	21 (62)
Current smoker	13 (38)
Pack-years	
10–20	7 (21)
21–30	3 (9)
31–40	10 (29)
>40	14 (41)
Sex	
Male	28 (82)

FEV_1 = forced expiratory volume in l sec. FVC = forced vital capacity; IVC = inspiratory vital capacity, SD = standard deviation.

TABLE 2. Effects of treatment on exercise capacity (mean bicycle exercise time) and Borg score

Treatment	Time to exhaustion (min)	Borg dyspnoea score
Formoterol 4.5 μg b.i.d.	10.94***	7.61
Formoterol 9 μg b.i.d.	10.78**	7.64
Formoterol 18 μg b.i.d.	10.59*, †	7.41
Ipratropium 80 μg t.i.d.	10.98***	7.64
Placebo	10.21	7.64
s.e.m. (ANOVA)‡	0.12	0.45

All data are period-adjusted means after 1 week of treatment.
*$P < 0.05$, **$P < 0.01$, and ***$P < 0.0001$ compared with placebo treatment,
†$P < 0.05$ compared with ipratropium; SEM = standard error of the mean.
‡See Methods for explanation of single SEM).

Borg dyspnoea score

There were no significant differences in end-exercise Borg dyspnoea scores between the different treatments (Table 2). Nor were there differences in the mean values of dyspnoea, calculated as the area under the Borg dyspnoea score curve during exercise divided by the total exercise time, as a measure of the mean experienced dyspnoea.

Lung function

All doses of formoterol and ipratropium significantly improved FEV_1 ($P < 0.0001$) compared with placebo (Table 3). The mean increase in FEV_1 with formoterol 4.5, 9, 18 μg and ipratropium compared with placebo was 0.19, 0.24, 0.38 and 0.20 (SEM 0.04) l, respectively. FVC, IVC, FRC, sGAW and RV also improved significantly for all doses of formoterol and ipratropium compared with placebo. Although there was a trend for a greater improvement in FEV_1 and sGAW with 9 and 18 μg formoterol

compared with 4.5 μg, these trends were not statistically significant. There were no significant differences between ipratropium and the three doses of formoterol in any of these lung function parameters. $FEF_{25-75\%}$ improved significantly compared with placebo with all three doses of formoterol ($P < 0.05$), but not with ipratropium ($P = 0.23$).

SAFETY

There were two adverse events categorized as serious. One patient, while in the wash-out period after formoterol 9 μg, developed acute glaucoma; another patient, while on ipratropium, injured her arm in an accident and missed the last visit. Neither serious adverse event was deemed related to the investigational products. There was no significant difference between the treatments in the number or profile of adverse events. The number of side-effects commonly associated with β_2-agonists (headache, palpitation, tremor, etc.) was low in

TABLE 3. Lung function parameters during treatment with formoterol 4.5, 9, and 18 μg b.i.d., ipratropium 80 μg t.i.d., and placebo

Treatment	FEV₁ (l)	IVC (l)	FVC (l)	FEF₂₅₋₇₅% (l)	sGAW ((s kPa)⁻¹)	FRC (l)	RV (l)	TLC (l)
Formoterol 4.5 μg b.i.d.	1.80****	3.81****	3.68	0.62*	0.82****	4.81**	3.55***	7.25
Formoterol 9 μg b.i.d.	1.85****	3.77****	3.73	0.66***	0.81****	4.73***	3.36****	7.06
Formoterol 18 μg b.i.d.	1.87****	3.81****	3.73	0.66***	0.79****	4.77**	3.45***	7.20
Ipratropium 80 μg t.i.d.	1.81****	3.82****	3.74	0.59	0.82****	4.78**	3.43***	7.12
Placebo	1.61	3.5	3.45	0.56	0.54	5.07	3.81	7.19
SEM‡ (ANOVA)	0.04	0.05	0.05	0.03	0.04	0.09	0.10	0.09

All data are period-adjusted means after 1 week of treatment.
FEV_1 = forced expiratory volume in one second, IVC = inspiratory vital capacity, FVC = forced vital capacity, $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of vital capacity; sGAW = specific airway conductance, FRC = functional residual capacity, RV = residual volume, TLC = total lung capacity; SEM = standard error of the mean of ANOVA (Analysis of variance, ‡ see Methods for explanation of single s.e.m.). ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$ compared with placebo treatment.

TABLE 4. Heart rates

Treatment	Heart rate before exercise	Increase in heart rate after exercise
Formoterol 4.5 µg b.i.d.	77.4 (12.5)	50.5 (21.9)
Formoterol 9 µg b.i.d.	80.1 (17.5)	46.6 (17.9)
Formoterol 18 µg b.i.d.	79.9 (15.3)	47.4 (21.0)
Ipratropium 80 µg t.i.d.	78.3 (13.8)	48.8 (18.6)
Placebo	79.1 (18.8)	47.3 (22.7)

Data are presented as means (SD).

all treatment groups—tremor, for example, was reported by only one patient, using formoterol 18 µg b.i.d. No significant differences were noted in heart rates before or after exercise in any of the treatment groups compared with placebo (Table 4). All doses of formoterol were well tolerated.

DISCUSSION

Formoterol 4.5, 9, 18 µg b.i.d., and ipratropium 80 µg t.i.d. all gave significant improvements in exercise capacity and lung function compared with placebo without a significant change in Borg dyspnoea score. There was a negative dose–response relationship for the three doses of formoterol, the lowest dose of formoterol corresponding to the longest exercise time.

We found a small, but significant, improvement of 0.73 min for formoterol 4.5 µg in an incremental cycle ergometer test. Even though significantly different from placebo, intuitively, this result seems a very small difference. Unfortunately, there are no data defining the minimal clinically signficant improvement in the incremental cycle ergometer test. Our study was designed some time ago, and many authors would currently advocate an endurance test at sub-maximal exercise level (10–11). Only a few studies have actually compared the different exercise modes with bronchodilator interventions. Such a study was performed by Oga *et al*. in which oxitropium was found to yield significant improvements in a 6-min walking test, a progressive cycle ergometer test, and a cycle endurance test at 80% of maximal workload (11). The 7% improvement we found in the progressive cycle ergometer test is at least as good as the 3.5% improvement found in their study (which corresponded to a 19% improvement in endurance time (11). Our result would, by extrapolation, be expected to translate to similar improvements in endurance time as those found by O'Donnell (10). Therefore, the relatively small improvement in our study was not only significant, but also within the ranges found by others to be clinically relevant.

To the best of our knowledge, this is the first double-blind study to demonstrate an increase in exercise capacity with long-acting β$_2$-agonists in patients with COPD.

Boyd and colleagues (5) investigated the effects of salmeterol 50 and 100 µg b.i.d. for 16 weeks on symptoms, lung function and exercise capacity with a 6-min walking distance test. They found no improvement in exercise capacity for either of the doses of salmeterol. Grove *et al.* (4) evaluated the effect of salmeterol 50 µg b.i.d. for 4 weeks, and also found no effect in the 6-min walking distance test or in adaptation capacity measured with a cycle-ergometer test. Mahler *et al.* (6) compared treatment with salmeterol 50 µg b.i.d for 12 weeks *vs* placebo, again without a significant difference in the 6-min walking test.

These studies and the present one differ in a number of aspects. Firstly, the patients in the present study had less severe airway obstruction, i.e. a mean FEV$_1$ of 1.69 l compared with 1.28, 1.17 and 1.29 l in the studies by Boyd, Grove, and Mahler, respectively. Patients with reversibility of airway obstruction were excluded from the studies by Boyd *et al.* (5) and Grove *et al.* (4), in contrast to our study. Nine out of the 34 patients in our study had a significant reversibility to a short-acting β$_2$-agonist, defined as an FEV$_1$ increment of 9% of the predicted normal value. However, all results remained significant when we re-analysed our data without the nine subjects with significant reversibility. Furthermore, we used an incremental cycle ergometer test, whereas Boyd, Grove, and Mahler used the 6-min walking distance test to determine exercise capacity. The 6-min walking distance test is self-paced, time-limited, tests at sub-maximal load, and has no incremental resistance, unlike an incremental cycle-ergometer test , which tests maximal load and exercise time. Thus, the cycle ergometer measures other aspects of exercise. Many studies with short-acting β$_2$-agonists have used the 6- and 12-min walking tests (4,12–20). Approximately, half of these studies found a significant increase in exercise capacity after β$_2$-agonist use, with the suggestion of more significant results when using the 12 min rather than the 6-min walking distance test. As an additional test, Grove *et al.* used a cycle test, with physiological strain as the outcome variable (4); maximal exercise capacity was estimated from sub-maximal exercise data, according to the theory of the adaptation capacity (21). However, this *extrapolated* maximal exercise capacity is difficult to compare with our *measured* maximal exercise capacity. Furthermore, the
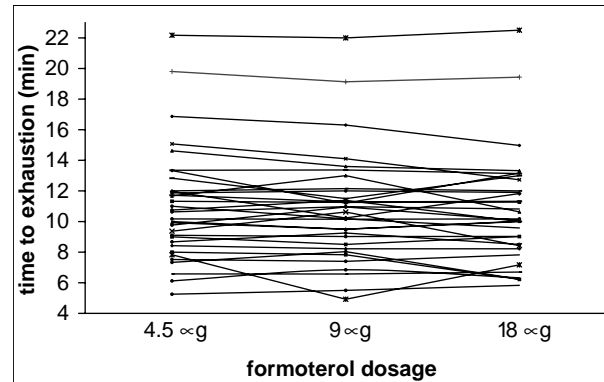
difference in results could be due to the long-acting β_2-agonist used, since the negative studies used salmeterol, which is a partial agonist, whereas we used the full agonist formoterol. The difference between a full and a partial agonist could theoretically be important in a situation with high endogenous catecholamine levels such as during exercise (although our results provide no proof for this since we tested formoterol only). Finally, Patakas *et al.* (22) performed a single-blind study, with a single dose of 50 μg of salmeterol in patients with an FEV_1 less than 1l, finding a significant improvement in walking distance at the maximal Borg dyspnoea score.

The negative dose–response relationship for the three doses of formoterol was an unexpected finding, which was not reflected in a negative dose–response in lung function parameters (which, in fact, showed a positive dose–response relationship). There are both intra- and extra-pulmonary explanations that could account for this.

An intra-pulmonary explanation could be a dose-dependent deterioration in the existing ventilation–perfusion mismatch in COPD, due to dose-dependent vasodilation caused by β_2-stimulation of the pulmonary vasculature (23) in combination with bronchodilation. An increasing mismatch at higher doses of formoterol could be responsible for a poorer increase in exercise capacity compared with lower formoterol doses.

Possible extra-pulmonary explanations for smaller effects on exercise capacity with higher doses of formoterol include an increase in side-effects, especially tremor. However, we did not observe a difference in the number or profile of adverse events between the three doses of formoterol, ipratropium and placebo. Tremor was reported in only one patient receiving formoterol 18 μg b.i.d. Other known muscle effects of β_2-agonists are those on skeletal muscle force. β_2-agonists 'muscle type' in a dose dependent fashion increase the contraction force of the fast-contracting muscle type, which is important for PCE. Holmberg and Waldeck (24) have demonstrated that, after maintenance treatment of guinea pigs with terbutaline for less than 1 week, a marked tolerance develops for isoprenaline- or terbutaline-induced increases in force generation of the fast-contracting muscle type by transmural stimulation *ex vivo* (24). It can be envisaged that such downregulation or uncoupling of skeletal muscle β_2-receptors also occurs after maintenance formoterol treatment, in a dose-dependent fashion, and may lead to fewer functional β_2-receptors being available to endogenous catecholamines released during exercise. Muscle performance may also be influenced by the increase in serum lactate concentration induced by β_2-agonists (25).

All β_2-agonists can have dose-dependent chronotropic and inotropic effects. These are considered to be mediated predominantly via a direct effect on cardiac β_2-receptors and via a reflex mechanism, secondary to

peripheral vasodilatation caused by stimulation of vascular β_2-receptors. The chronotropic and inotropic effects of higher doses of β_2-agonists suggest a potential for increased myocardial oxygen consumption. However, we found no significant difference in heart frequencies pre- or post-peak exercise for any treatments compared with placebo. This result is in line with the findings of Grove and Lipworth (26). Overall, the results suggest that possible negative effects of formoterol on myocardial function in our study are too small to explain the negative dose-response relationship. Finally, although the overall dose–response relation was negative for the group as a whole, it was certainly not invariably present, as indicated by the individual dose–response curves presented in Fig. 1.

We analysed changes in Borg dyspnoea score during exercise in several different ways and could not detect a significant change with either formoterol or ipratropium. This is in contrast to the studies by Grove (4) and Boyd (5), but is in line with the study by Mahler (6).

Our study confirms the significant effects of long-acting β_2-agonists on lung function parameters in COPD reported previously (4–6,27). Spirometric and plethysmographic tests such as $FEF_{25-75\%}$ and sGaw also demonstrated significant improvements after all doses of formoterol. Maesen *et al.* recently showed that this correlates with a decreased work of breathing in patients with apparently poorly reversible lung function (28). In our study, we additionally found a significant reduction in RV and FRC. The lowest dose of formoterol (4.5 μg) was sufficient for the greatest part of the effect on lung function parameters.

Ipratropium was given in a moderately high dose of 80 μg t.i.d., and significantly improved TTE and lung function parameters compared with placebo and to a similar extent to formoterol 4.5 μg. TTE with ipratropium was significantly longer than with formoterol 18 μg b.i.d. Regarding ipratropium and incremental exercise tests, only single-dose studies have been performed so far (29–31).

These used maximum workload and maximum oxygen consumption at a PCE as outcome measures. The improvements found in the single dose studies are in line with our results, after 1 week of treatment. The significant but small improvements in exercise capacity with formoterol and ipratropium are fully in line with other studies testing bronchodilators with progressive cycle ergometry in COPD (29,30,32,33).

In the present study, ipratropium at a moderately high dose gave the same effect as the low dose of formoterol. Thus, while ipratropium and the long-acting inhaled β_2-agonist formoterol can be used alternatively in patients with moderate COPD, yielding similar improvement in exercise capacity, this result is in line with the GOLD guidelines suggesting that long-acting inhaled bronchodilators are more convenient (1). From our results we cannot deduce whether treatment with formoterol and ipratropium together would have given better responses in lung function parameters and exercise capacity than each treatment separately.

We conclude that formoterol significantly improves exercise capacity and lung function in patients with COPD. The effects of low-dose formoterol (4.5 μg b.i.d.) are comparable to those of ipratropium 80 μg t.i.d. The finding of a negative dose–response relationship between formoterol and exercise time is unexpected and needs further investigation.

Acknowledgements

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