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Effect of adjunct fluticasone propionate on airway physiology during rest and exercise in COPD

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KEYWORDS
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Dyspnea;
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Summary
Rationale: Combination therapy with corticosteroid and long-acting β_2-agonists (LABA) in a single inhaler is associated with superior effects on airway function and exercise performance in COPD compared with LABA monotherapy. The physiological effects of adding inhaled corticosteroid monotherapy to maintenance bronchodilator therapy (long-acting anticholinergics and LABA singly or in combination) in COPD are unknown.
Methods: This was a randomized, double-blind, placebo-controlled, crossover study (NCT00387036) to compare the effects of inhaled fluticasone propionate 500 μg (FP500) twice-daily and placebo (PLA) on airway function during rest and exercise, measured during constant work rate cycle exercise at 75% of maximum incremental cycle work rate, in 17 patients with COPD ($FEV_1 \leq 70\%$ predicted).
Results: After treatment with FP500 compared to PLA, there were significant increases in post-dose measurements of FEV_1 (+115 mL, $P = 0.006$) and the FEV_1/FVC ratio (+2.5%, $P = 0.017$), along with decreases in plethysmographic residual volume (−0.32L; $P = 0.031$), functional residual capacity (−0.30L, $P = 0.033$), and total lung capacity (−0.30L, $P = 0.027$) but no changes in vital capacity or inspiratory capacity (IC). Post-treatment comparisons demonstrated a significant improvement in endurance time by 188 ± 362 s with FP500 ($P = 0.047$) with no concomitant increase in dyspnea intensity. End-inspiratory and end-expiratory lung volumes were reduced at rest and throughout exercise with FP500 compared with PLA ($P < 0.05$).
Conclusion: Inhaled FP500 monotherapy was associated with consistent and clinically important improvements in FEV_1, static lung volumes, dynamic operating lung volumes, and exercise endurance when added to established maintenance long-acting bronchodilator therapy in patients with moderate to severe COPD.

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Introduction

Treatment with an inhaled corticosteroid (ICS) is indicated for the prevention of exacerbations in patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are prone to exacerbations.[1,2] ICS monotherapy is associated with modest improvements in trough FEV_1 but their long term use has not been shown to delay the rate of decline of FEV_1 over time.[3–5] In contrast to the effects of bronchodilators in COPD, improvement in airway function with ICS monotherapy is more gradual and of lesser magnitude. The underlying mechanisms are unknown but are postulated to be linked to reduced airway mucosal inflammation and edema.[6,7]

A number of studies have shown that when ICS and long-acting β_2-agonists (LABA) are delivered as fixed combination in a single inhaler, their effect on airway function and respiratory symptoms is superior to the LABA component alone.[8–10] Worth et al.[11] recently reported that one week treatment with combined budesonide/formoterol (320/9 μg *b.i.d.*) therapy was associated with greater cycle exercise endurance time (by 69 s) compared with formoterol alone in patients with moderate to severe COPD. Similar improvement trends were seen in a study by our group which conducted a secondary analysis on the comparative effects of fluticasone/salmeterol (250/50 μg *b.i.d.*) and salmeterol alone on pulmonary function and exercise endurance.[12] That study was primarily designed to examine physiological differences between fluticasone/salmeterol combination and placebo and was not sufficiently powered to compare the effects of the combination vs. salmeterol. However, it is evident from these two studies that when ICS is added to LABA in a single combination inhaler, bronchodilation and lung deflation is amplified and exercise tolerance is improved as early as 2 h after dosing.

It is not known if the additive effects of ICS are restricted to the ICS/LABA combination or whether similar improvements are seen when ICS is added to other bronchodilator classes such as inhaled long-acting anticholinergics. Moreover, the mechanisms of improved airway function when ICS is added to a bronchodilator are also unknown. Potential but unproven mechanisms of improved airway function proposed in asthma are: 1) the non-genomic effects of corticosteroids on the airway vasculature and 2) inhibitory effects on airway smooth muscle contraction.[13,14] In the study of Worth et al.,[11] differences in reduction of resting lung hyperinflation between the combination treatment and the LABA alone were not significant and the small improvements in dynamic inspiratory capacity recorded during exercise seem unlikely to account for all of the increased exercise tolerance. The question arises whether other physiological effects of ICS previously described in asthma (but not in COPD) during exercise, such as improved arterial oxygenation,[15] contribute to improved exercise tolerance. The present study is the first to evaluate the effects of an ICS on airway physiology during rest and exercise in patients established on a maintenance long-acting bronchodilator regimen.

The main purpose of the current study was therefore to increase our understanding of the short term physiological effects of ICS monotherapy when added to regular foundation treatment with long-acting anticholinergic or β_2-agonists bronchodilators (singly or in combination). We wished to determine if added ICS therapy was associated with additional improvement in dyspnea intensity during standardized exercise tests and to identify potential underlying mechanisms. We hypothesized that adjunct short term treatment with inhaled fluticasone propionate would be associated with a reduction in exertional dyspnea ratings and that this in turn would be related to improvements in dynamic respiratory mechanics. We therefore conducted a crossover study in 17 patients with moderate to severe COPD who were randomized to FP500 or placebo (PLA) for a 2 week period. We undertook within-subject comparisons of dyspnea intensity ratings at a standardize endurance time (primary outcome), resting pulmonary function tests, exercise endurance, breathing pattern, operating lung volumes, cardio-metabolic and pulmonary gas exchange parameters after treatment with active drug or PLA.

Methods

Subjects

Subjects included clinically stable COPD patients $\geq$40 years of age with a clinical diagnosis of COPD for at least 1 year, a cigarette smoking exposure $\geq$20 pack-years, an $FEV_1 \leq 70\%$ predicted, an $FEV_1/FVC \leq 0.7$, FRC $\geq$ 120% of predicted and moderate to severe chronic activity-related dyspnea as evidenced by a modified Baseline Dypspnea Index focal score $\leq$6.[16] Patients were excluded if they had a history of asthma or any condition other than COPD that might contribute to dyspnea or exercise intolerance, if they were hospitalized or had signs of a lower respiratory tract infection 4 weeks prior to the first experimental visit, or if they had an oxygen saturation $\leq$80% during exercise on room air.

Study design

This double-blind, placebo-controlled crossover comparison study (ClinicalTrials.gov registration number: NCT00387036) received ethical approval from the University and Hospital Human Research Ethics Board (ID#: DMED-949-06) and all subjects gave informed written consent prior to participating. On visit 1, subjects underwent screening procedures to determine eligibility including complete pulmonary function testing and an incremental cardiopulmonary exercise test on a cycle ergometer to determine peak exercise work rate. On visit 2, subjects performed pulmonary function tests and a constant-load cycling test at 75% of peak work rate (as determined from visit 1) for familiarization purposes. Patients meeting all eligibility requirements entered the active treatment period of the study where they received, in a double-blind manner, inhaled fluticasone propionate 500 μg (FP500) or matching PLA added twice-daily to their normal daily drug regimen for 2 weeks. At the beginning of each treatment period (visits 3 and 5), subjects performed baseline pulmonary function tests followed by a constant-load exercise test

(pre-treatment). At the end of each treatment period (visit 4 and 6), subjects performed pulmonary function tests before (post-treatment, pre-dose) and 2 h after receiving study treatment (post-treatment, post-dose), followed by a constant-load exercise test (post-treatment, post-dose). Between treatment periods, all subjects underwent a single-blind placebo washout phase for 2 weeks. Patients were required to refrain from using all systemic steroids (for at least 2 months) or inhaled corticosteroids (for at least 2 weeks) prior to visit 1 until the study was completed. All subjects maintained their use of short- and long-acting bronchodilators throughout the duration of the study. Prior to each visit, short-acting bronchodilators and short- and long-acting theophyllines were withdrawn for at least 6, 24, and 48 h, respectively. Patients also withheld the study medication on the morning of all visits to facilitate the timing of post-dose procedures following witnessed in-clinic dosing. Subjects avoided caffeine, heavy meals, alcohol and strenuous exercise prior to each visit.

The primary endpoint of this study was the modified Borg dyspnea score measured at a standardized time during constant-load exercise. Secondary endpoints included cycle endurance performance, spirometric parameters, and static and dynamic lung volumes.

Pulmonary function

Spirometry, constant-volume body plethysmography, single-breath diffusing capacity for carbon monoxide and maximal mouth pressures were performed according to recommendations[17–21] using an automated testing system (Vs62j Body Plethysmograph and Vmax229d; SensorMedics, Yorba Linda, CA). All measurements are expressed as percentages of predicted normal values.[22–27] Predicted inspiratory capacity was determined as the difference between predicted total lung capacity and predicted functional residual capacity.

Cardiopulmonary exercise testing

Symptom-limited exercise tests were performed on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics) using the Vmax229d Cardiopulmonary Exercise Testing System (SensorMedics) according to recommended guidelines[28] and as previously described.[29] The incremental exercise test on visit 1 consisted of steady-state rest, a 1 min warm-up, and 10 W stepwise increases in work rate every 1 min until symptom-limitation (i.e., peak exercise). Maximal work rate was defined as the highest work rate that could be sustained for 30 s. Constant-load exercise tests involved a period of steady-state rest, a 1 min warm-up and an immediate increase in work rate corresponding to 75% of maximal work (as determined on visit 1) until symptom limitation. Constant-load endurance time was defined as the duration of loaded pedaling.

Measurements

Subjects rated the intensity of their "breathing discomfort" and "leg discomfort" at rest and throughout exercise by pointing to a modified 10-point Borg scale. The scale's endpoints were anchored such that '0' represented "no breathing/leg discomfort" and '10' represented "the most severe breathing/leg discomfort ever experienced or imagined." At exercise cessation, subjects verbalized their main reason for stopping exercise. Arterial oxygen saturation by pulse oximetry, heart rate by electrocardiography, and blood pressure by auscultation were measured at rest and throughout exercise. Minute ventilation (V'E), oxygen consumption ($V'O_2$), carbon dioxide production ($V'CO_2$), partial pressure of end-tidal CO_2 ($PETCO_2$), tidal volume (V_T), and breathing frequency were measured breath-by-breath and averaged over 30 s epochs. Changes in operating lung volumes were derived from dynamic inspiratory capacity measurements.[30] Assuming that TLC remains constant throughout exercise,[31] changes in IC reflect changes in end-expiratory lung volume ($EELV = TLC - IC$), and changes in inspiratory reserve volume ($IRV = IC - V_T$) reflect changes in end-inspiratory lung volume ($EILV = TLC - IRV$). IC maneuvers were performed during the final 30 s of each 2 min exercise period. All breath-by-breath ventilatory and metabolic data were analyzed over the first 30 s period of each second minute during exercise and was linked with symptom ratings and IC measurements obtained during the final 30 s of each second minute. This was done to avoid contamination of averaged breath-by-breath data surrounding an IC maneuver.

Statistical analysis

The sample size of 17 provides the power (80%) to detect a significant difference in dyspnea intensity measured at a standardized time during exercise based on a ± 1 Borg unit difference, a standard deviation based on values established in our laboratory from a similar group of COPD patients ($n = 105$), and a two-tailed test of significance. Primary analysis was performed on post-dose measurements. Possible carry-over and period effects were assessed according to recommended guidelines for cross-over trials.[32] Treatment responses were compared using paired *t*-tests. Exercise responses were compared at isotime (i.e., the highest equivalent time achieved in all constant-load exercise tests) and at peak exercise and also as slopes derived from linear regression analysis of data sets from each individual during exercise. Reasons for stopping exercise and descriptors of breathlessness were analyzed using Fisher's exact test. Pearson's correlation was performed using the difference in endurance time (FP500 vs. PLA) at isotime as the dependent variable and differences in selected measurements as independent variables. A $P < 0.05$ significance level was used for all analysis. Results are reported as mean $\pm$ SD unless otherwise specified.

Results

Seventeen subjects with moderate to severe COPD and significant chronic activity-related dyspnea completed this study and are described in Table 1. Exercise capacity during the incremental exercise test was reduced primarily due to severe dyspnea; i.e., 76% stopped exercise due to

breathing discomfort ($n = 7$) or a combination of breathing and leg discomfort ($n = 6$). Treatment order was balanced such that 8 subjects (47%) were randomized to FP500 first. All subjects were on baseline inhaled long-acting bronchodilators. At the time of testing, 13/17 (76%) were on both a long-acting anticholinergic and a long-acting β_2-agonist, 2/17 (12%) were on a long-acting anticholinergic medication alone and 2/17 (12%) were on a long-acting β_2-agonist alone. Four of the 17 patients were naive to ICS therapy. All patients that were not naive stopped their ICS treatment at least 2 weeks prior to the first visit. All patients had a short-acting bronchodilator to use as needed and 2/17 (12%) also had a short-acting inhaled anticholinergic to use as needed.

Table 1 Subject Characteristics.

Measurement	Value
Males:females (n)	12:5
Age (years)	67.2 ± 6.9
Height (cm)	171 ± 7
Mass (kg)	76 ± 11
BMI (kg/m^2)	26.0 ± 3.0
Smoking history (pack-years)	54 ± 31
Duration of COPD (years)	6.6 ± 6.9
BDI (focal score)	5.1 ± 1.1
FEV_1 (L)	1.45 ± 0.51
FEV_1 (% predicted)	54 ± 11
FEV_1/FVC (%)	40 ± 6
FVC (L)	3.66 ± 1.20
FVC (% predicted)	94 ± 18
IC (L)	2.71 ± 0.90
IC (% predicted)	92 ± 19
TLC (L)	7.51 ± 1.17
TLC (% predicted)	120 ± 11
FRC (L)	4.80 ± 0.84
FRC (% predicted)	144 ± 25
RV (L)	3.58 ± 0.88
RV (% predicted)	158 ± 38
sRaw (cm H_2O s)	21.0 ± 9.3
sRaw (% predicted)	487 ± 203
DL_{CO}/V_A (mL/min/mmHg/L)	2.24 ± 0.73
DL_{CO}/V_A (% predicted)	60 ± 19
Medications:	
Salbutamol	$n = 17$
Ipratropium	$n = 2$
Salmeterol	$n = 9$
Formoterol	$n = 4$
Tiotropium	$n = 15$
Fluticasone	$n = 1$
Salmeterol/Fluticasone	$n = 10$
Budesonide/Formoterol	$n = 3$

Data are presented as mean ± SD. BMI, body mass index; BDI, modified baseline dyspnea index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; sRaw; specific airways resistance; DL_{CO}, single-breath diffusing capacity of the lung for carbon monoxide; VA, alveolar volume.
* Inhaled corticosteroids withdrawn ≥ 2 weeks prior to study.

Pulmonary function

Post-dose comparisons demonstrated that FP500 resulted in a significant increase in FEV_1 and FEV_1/FVC and a reduction in TLC, FRC and RV following 2 weeks of treatment relative to PLA (Table 2). There were no pre-dose vs. 2 h post-dose differences in pulmonary function parameters following treatment for both PLA and FP500.

Exercise endurance

Endurance time during the constant-load cycling test was not different between pre- and post-treatment PLA (604 ± 430 vs. 583 ± 381 s, respectively, $P > 0.05$). Post-treatment comparisons of constant-load cycling demonstrated a significant improvement in endurance time by 188 ± 362 s ($P = 0.047$) following FP500 compared with PLA (Table 3). Fig. 1 shows the change in endurance time in individual subjects. The majority of subjects ($n = 13$) increased their endurance time (range: 28–890 s) with 11 reaching the minimal clinically important difference of ~100 s.[33] Four subjects had variable reductions in endurance time (range: 8–635 s). Two subjects had unusual increases in endurance time by 890 and 819 s and one had a significant reduction in endurance time by 635 s. Removal of these three outliers reduced the observed mean improvement in performance from 188 s to 152 s but improved statistical significance from a $P = 0.047$ to $P = 0.013$. Improvements in endurance time were not related to improvements in resting pulmonary function.

Sensory responses

Ten patients had a ≥1 Borg unit reduction in dyspnea at isotime (range 1–4 Borg units), 3 patients had no change in dyspnea rating, and 4 patients had a ≥1 Borg unit increase in dyspnea ratings (range 1–2.5 Borg units). As a group, there were no statistically significant changes in breathing or leg discomfort during exercise (Fig. 2) but FP500 allowed subjects to tolerate similar levels of dyspnea for a longer duration. Dyspnea/V'E slopes were not different following treatment between PLA and FP500 (0.42 ± 0.44 vs. 0.34 ± 0.22, respectively, $P > 0.05$). There was a modest correlation between change in dyspnea isotime rating and change in endurance performance between PLA and FP500 ($r = -0.44$) but this was not statistically significant ($P = 0.07$). Primary reasons for stopping exercise with PLA [breathing ($n = 8$); legs ($n = 4$); combination ($n = 5$); other ($n = 0$)] were not significantly different from FP500 [breathing ($n = 5$); legs ($n = 5$); combination ($n = 6$); other ($n = 1$)].

Physiological responses during exercise

Ventilatory and physiological data at isotime and peak exercise following treatment are shown in Table 3. There was a trend for breathing frequency to decrease (Fig. 3, $P = 0.06$) and ΔIC (from rest) to decrease (Table 3, $P = 0.08$) at isotime following FP500 treatment. Operating lung volumes (i.e., EELV and EILV) were consistently

Table 2 Post-treatment and post dose pulmonary function tests.

Measurement	Placebo	Fluticasone
FEV_1 (L)	1.50 ± 0.56	1.61 ± 0.58*
FEV_1/FVC (%)	39 ± 6	42 ± 5*
FVC (L)	3.78 ± 1.24	3.84 ± 1.22
PEF (L/sec)	5.14 ± 1.47	5.24 ± 1.46
FEF_{25-75} (L/sec)	0.43 ± 0.19	0.46 ± 0.17
IC (L)	2.71 ± 0.95	2.71 ± 0.92
TLC (L)	7.46 ± 1.46	7.16 ± 1.38*
FRC (L)	4.76 ± 0.89	4.45 ± 0.93*
RV (L)	3.42 ± 0.88	3.10 ± 0.86*
sRaw (cm H_2O s)	19.8 ± 8.0	18.5 ± 8.4

Data are presented as mean ± SD. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF_{25-75}, mean forced expiratory flow between 25% and 75% of FVC; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; sRaw; specific airways resistance. There were no pre- to post-dose differences for either placebo or fluticasone. *$P < 0.05$, post-dose placebo vs. post-dose fluticasone.

reduced at rest and throughout exercise when expressed as a percentage of predicted TLC (Fig. 4) or when expressed in absolute terms (Table 3). At peak exercise, there was a trend for a higher heart rate ($P = 0.06$) following FP500 (Fig. 5 and Table 3) with no significant differences in oxygen saturation (Fig. 5).

Discussion

The novel finding of this study was that the addition of FP500 to regular long-acting bronchodilator therapy was not associated with an improvement in standardized dyspnea ratings during exercise but was associated with

Table 3 Post-dose cardio–respiratory and perceptual responses during constant-load exercise at the end of each 2-week treatment period.

Measurement	Isotime		Peak	
	Placebo	Fluticasone	Placebo	Fluticasone
Time (min)	444 ± 390	444 ± 390	583 ± 381	771 ± 596[a]
Dyspnea (Borg)	4.6 ± 2.6	3.9 ± 2.1	5.9 ± 2.2	6.5 ± 2.7
Leg Discomfort (Borg)	5.3 ± 2.9	4.8 ± 2.1	6.5 ± 2.6	7.2 ± 2.5
HR (beats/min)	118 ± 17	117 ± 18	120 ± 16	124 ± 17[b]
O_2 pulse (ml/beat)	10.5 ± 3.5	10.3 ± 3.2	10.7 ± 3.3	10.4 ± 3.2
$V'O_2$ (L/min)	1.24 ± 0.47	1.21 ± 0.43	1.28 ± 0.43	1.29 ± 0.43
$V'CO_2$ (L/min)	1.25 ± 0.48	1.23 ± 0.45	1.29 ± 0.43	1.30 ± 0.43
V'E (L/min)	43.9 ± 14.6	43.0 ± 13.9	45.4 ± 12.9	46.0 ± 13.1
$V'E/V'CO_2$	36.4 ± 1.4	36.2 ± 1.5	36.2 ± 1.3	36.4 ± 1.5
f_R (breaths/min)	29.5 ± 4.5	27.9 ± 4.1[b]	31.1 ± 4.2	30.6 ± 4.0
V_T (L)	1.49 ± 0.43	1.53 ± 0.41	1.47 ± 0.42	1.51 ± 0.41
T_I (sec)	0.82 ± 0.18	0.88 ± 0.17[b]	0.76 ± 0.13	0.77 ± 0.13
T_E (sec)	1.28 ± 0.28	1.32 ± 0.23	1.23 ± 0.20	1.23 ± 0.24
T_I/T_{TOT} (%)	38.9 ± 4.3	39.7 ± 4.9	38.5 ± 4.2	38.8 ± 4.1
IC (L)	2.21 ± 0.67	2.26 ± 0.66	2.18 ± 0.69	2.14 ± 0.64
ΔIC from rest (L)	−0.51 ± 0.40	−0.42 ± 0.31[b]	−0.54 ± 0.41	−0.54 ± 0.38
IRV (L)	0.69 ± 0.42	0.73 ± 0.41	0.68 ± 0.41	0.63 ± 0.37
EELV (L)	5.33 ± 1.08	4.90 ± 1.04[a]	5.36 ± 1.09	5.02 ± 1.06[a]
EILV (L)	6.85 ± 1.32	6.44 ± 1.21[a]	6.86 ± 1.28	6.53 ± 1.23[a]
P_{ETCO2} (mmHg)	34.8 ± 3.8	35.8 ± 4.8	34.8 ± 3.7	35.3 ± 4.5
SpO_2 (%)	92.9 ± 3.8	93.0 ± 3.7	91.9 ± 4.3	92.5 ± 3.6

Data are presented as mean ± SD. HR, heart rate, $V'O_2$, oxygen uptake; $V'CO_2$, carbon dioxide production; RER, respiratory exchange ratio; V'E, minute ventilation; fR, breathing frequency; V_T, tidal volume; T_I, inspiratory time; T_E, expiratory time; T_{TOT}, total time, T_I/T_{TOT}, inspiratory duty cycle; IC, inspiratory capacity; ΔIC, change in inspiratory capacity from rest (i.e., magnitude of dynamic lung hyperinflation); IRV, inspiratory reserve volume; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; $PETCO_2$, partial pressure of end-tidal CO_2; oxyhemoglobin saturation measured by pulse oximetry.

[a] $P < 0.05$, post-dose placebo vs. post-dose fluticasone.

[b] $P \leq 0.08$, post-dose placebo vs. post-dose fluticasone.

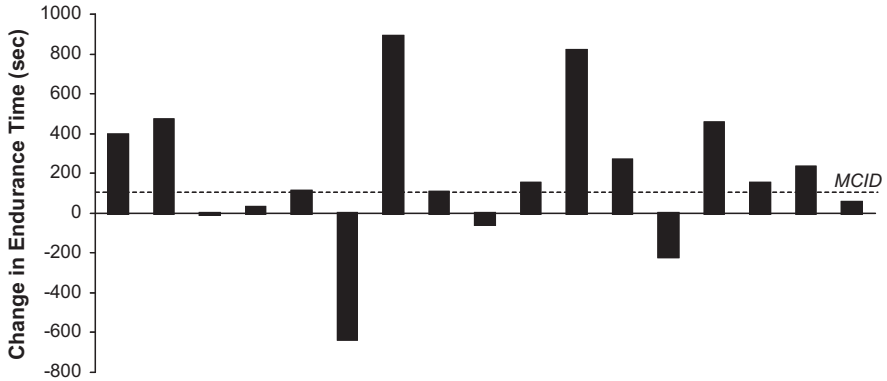

Figure 1 Change in constant-load endurance performance in all subjects (i.e., the difference between post-treatment placebo and post-treatment fluticasone). Horizontal dashed line represents the minimum clinically important difference (MCID) of ~100 s.[33]

significant improvements in spirometry, lung hyperinflation and exercise tolerance when compared with PLA in stable patients with moderate to severe COPD.

Study patients experienced moderate to severe activity-related dyspnea despite regular foundation treatment with long-acting bronchodilators. Peak oxygen uptake and work rate were reduced by 31 and 47% of predicted normal values, respectively, mainly as a result of critical ventilatory constraints and attendant dyspnea. During the course of the study, all patients continued their usual bronchodilators as prescribed by their physician: the majority (76%) received both a long-acting anticholinergic and β_2-agonist; the remainder received a long-acting anticholinergic alone (12%) or a long-acting β_2-agonist alone (12%).

Adjunct treatment with FP500 over a 2 week period was associated with consistent reductions in all lung volume components: RV, FRC, and TLC were reduced by approximately 0.3 L. Unlike previous studies that examined bronchodilator efficacy in patients of similar COPD severity, reductions in RV and FRC following ICS were not associated with significant reciprocal increases in VC and IC, respectively.[34,35] Thus, there was a net reduction in TLC and the FEV_1/FVC ratio improved. This contrasts with the results of studies of single long-acting bronchodilators where the FEV_1/FVC ratio is unchanged.[35,36] The improvement in FEV_1 (by 115 ml) after FP500 compared with PLA is surprisingly large, particularly since this occurred in the setting of baseline dual long-acting bronchodilators in the majority. We were not able to determine the differential effects of adjunct ICS on small and large airway function or the precise biologic mechanisms of improvement in this study. However, the consistent reduction in lung volume components with ICS vs. PLA points to improvements in airway conductance and in the mechanical time constant for emptying of heterogeneously distributed alveolar units.

When ICS is given as sole therapy (without bronchodilators) small improvements in airway function have been reported compared with PLA after 2 weeks of treatment.[37] In a systematic review of several clinical trials, Sin et al.[38] noted an average increase in baseline trough FEV_1 of only 45 ml in the first 6 months of ICS monotherapy. Another meta-analysis of 12 placebo-controlled trials demonstrated that ICS induced a mean increase in FEV_1 by 96 ml after 1–6 months and 51 ml after 1–3 years.[39] Specific clinical trials such as the ISOLDE trial[3] showed that FEV_1 with ICS was higher than placebo by at least 70 ml at each time point throughout the 36 month trial. In the TRISTAN[8] and TORCH[40] trials, ICS monotherapy increased post-bronchodilator FEV_1 by approximately 45 ml compared with placebo. In the present study where patients received baseline bronchodilator therapy, larger effects were seen after only 2 weeks of ICS treatment. The improvements in airflow rates and lung hyperinflation could represent an additive or synergistic bronchodilation effect which has been reported when ICS and long-acting β_2-agonist treatment are combined in a single device.[8–10] A number of theoretical mechanisms could explain this. For example, ICS may enhance the bronchodilation of LABA by DNA transcription thus increasing adrenergic receptor gene expression. Alternatively, or in addition, ICS may act acutely by direct

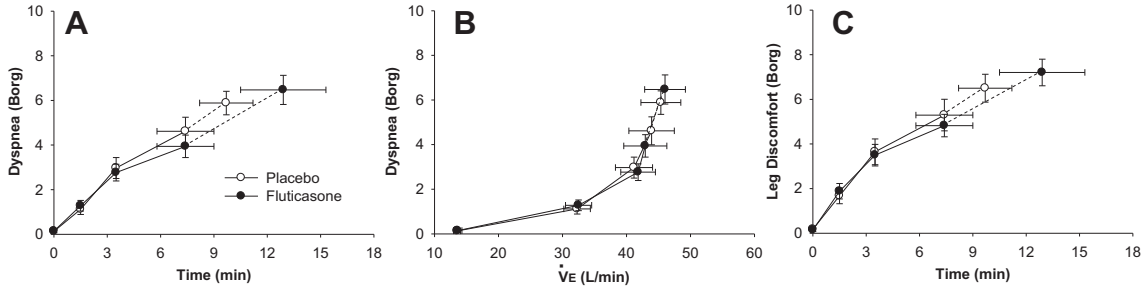

Figure 2 Post-treatment and post-dose sensory responses to constant-load cycle exercise. V'E, minute ventilation. Data are presented as mean ± SE.

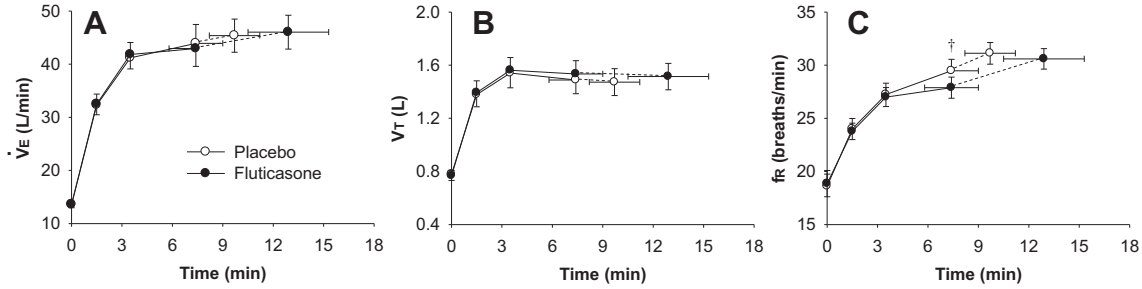

Figure 3 Post-treatment and post-dose ventilatory and breathing pattern response to constant-load cycle exercise. V'E, minute ventilation; V_T, tidal volume; f_R, breathing frequency. Data are presented as mean ± SE. †$P = 0.06$.

inhibition of extraneuronal catecholamine transporter which may result in enhanced availability and action of norepinephrine with consequent greater bronchodilation.[41] Other non-genomic actions of ICS which have been shown in asthma are enhancement of norepinephrine-induced bronchial vasoconstriction which may act to reduce mucosal edema.[6,7] Thus, it is conceivable that ICS may enhance the action of bronchodilators by reducing their clearance from the airways.[42] However, one previous study found no evidence of either increased bronchial blood flow or vasoconstriction with inhaled budesonide in COPD.[43]

The primary outcome was not met: FP500 treatment was not associated with improved submaximal dyspnea ratings. However, adjunct ICS was associated with a significant improvement in exercise endurance time by an average of 188 s which exceeds current estimates of the minimal clinically important difference for constant-load cycle tests at 75% of maximum work rate (i.e., ~100 s).[33] The high intensity constant work rate protocol used here has been shown to be reproducible and responsive in the multicenter trial setting.[44] However, in this study the change in endurance time across patients in association with FP500 tended to be more variable (Fig. 1). This large variability in endurance performance was unexpected and difficult to explain but may be related to both methodological and physiological factors. For example, it is possible that the peak incremental work rate was underestimated in some subjects resulting in longer than average constant-load durations at work rates below the individual's critical power, which may have contributed to an increase in baseline endurance variability. The variability may also have been attributable to individual responses to FP500 due to potential differences in airway inflammation (eosinophilic vs. neutrophilic) although this was not specifically assessed in the present study and every effort was made to exclude asthmatic patients. The lack of correlation between improved endurance time and pulmonary function makes this latter possibility less likely. Despite the variability in endurance performance, the majority (13/17) showed improvement with 11 reaching a clinically meaningful increase (Fig. 1). Removal of three outliers (with an unusually large decrease or increase in exercise performance) reduced the mean improvement to 152 s but increased the overall level of statistical significance. This improvement is broadly comparable to that reported in two previous studies that compared combination ICS/LABA in a single inhaler to PLA.[11,12]

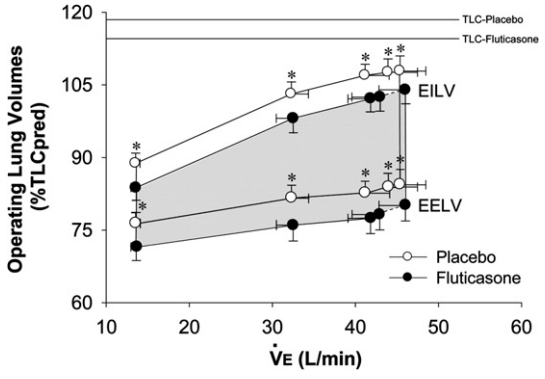

Figure 4 Post-treatment and post-dose operating lung volumes vs. minute ventilation during constant-load cycle exercise. TLCpred, predicted total lung capacity; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; V'E, minute ventilation. Data are presented as mean ± SE. *$P < 0.05$.

Improvement in exercise tolerance following bronchodilator treatment alone or in combination with ICS has been linked to improvements in resting and exercise IC with consequent greater V_T expansion and a delay in reaching critical mechanical constraints and the attendant intolerable dyspnea.[12,34,35] By contrast, in this study there was no significant improvement in resting IC, breathing pattern or ventilation with the addition of FP500, and submaximal dyspnea intensity ratings were not significantly reduced at a given time or ventilation. Moreover, improvements in pulmonary function were not correlated with increases in endurance time. With FP500 treatment, patients were able to meet the increased ventilatory requirements of exercise by breathing at a lower absolute lung volume than with PLA: EELV was diminished at rest and throughout exercise by an average of ~0.35 L. It is possible therefore that an improvement in operating length of the respiratory muscles (particularly the diaphragm) together with improved airway conductance, contributed to the ability of our patients to exercise for a longer duration without a significant increase in dyspnea. It is also possible, but unproven, that topical FP500 (via genomic or non-genomic mechanisms) can modulate respiratory sensation, independent of changes in airway function, by altering afferent activity from sensory receptors in the airway mucosa, as has been postulated in asthma.[45,46]

Havercamp et al.[15] have described consistent improvements in arterial oxygenation in asthmatics following ICS

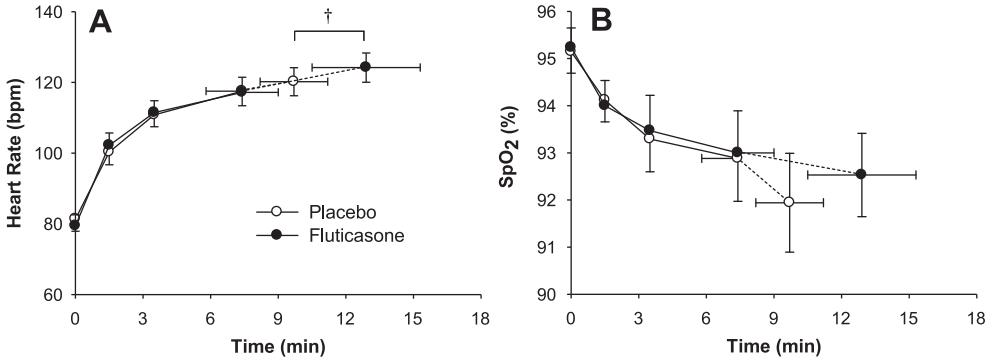

Figure 5 Post-treatment and post-dose heart rate and arterial oxygen saturation response to constant-load cycle exercise. SpO_2, pulse oximetry derived arterial oxygen saturation. Data are presented as mean ± SE. †$P = 0.06$.

monotherapy which contributed to improvements in exercise performance. In the current study, this mechanism is unlikely to be important as indices of pulmonary gas exchange were comparable during FP500 and PLA. Interestingly, arterial O_2 desaturation was not significantly increased during FP500 treatment despite the longer exercise duration, suggesting possible minor improvements in ventilation—perfusion relations at higher ventilations.

Limitations

This study was an exploratory physiological study with a relatively small sample size. The study was powered to detect a difference in on our primary endpoint (i.e., standardized dyspnea rating) but the current sample size may have been insufficient to detect possible differences in some physiological variables. It is also important to acknowledge that the small sample size makes it difficult to generalize our findings to the COPD population as a whole. Furthermore, the present study examined only the short-term impact of FP500 on airway function beyond that achieved by usual maintenance long-acting bronchodilators of different classes. It is therefore unclear whether the enhancement of bronchodilator effects is the result of a unique interaction with LABA or occurs regardless of the baseline bronchodilator choice.

In summary, this is the first study to examine the additional short term sensory and physiological effects of FP500 on airway function when added to regular maintenance treatment with long-acting bronchodilators in stable COPD patients. Following 2 weeks of FP500 therapy, we observed no consistent improvement in dyspnea intensity ratings at a standardized exercise time or ventilation but did show clinically important improvements in secondary outcomes which included spirometry, static lung volumes and dynamic operating lung volumes during exercise compared with PLA. Improvements in exercise endurance, though statistically significant, were highly variable and the mechanism of improvement is not fully understood.

Current guidelines suggest that ICS should be prescribed for prevention of acute exacerbations in patients with moderate to severe COPD. The current study provides new evidence that the addition of ICS monotherapy to maintenance bronchodilator therapy has the potential to provide additional physiological benefits which may have positive clinical implications.

Conflicts of interest

Jordan Guenette, Natya Raghavan, Veronica Harris-McAllister, Megan E. Preston, and Katherine A. Webb have no conflicts of interest to report. Denis O'Donnell, via Queen's University, has received research funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Nycomed and Pfizer; and has served on speakers bureaus, consultation panels, and advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Nycomed and Pfizer.

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