A single administration of glucocorticoid increases exercise capacity in men with stable chronic obstructive pulmonary disease

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ABSTRACT

INTRODUCTION: Oral use of glucocorticoids is a well-described therapy in the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD). Patients with COPD occasionally report subjective benefits of glucocorticoids in terms of fewer symptoms and better exercise performance, even when they do not experience exacerbation. This study investigated whether a single high therapeutic dose of oral glucocorticoid improves short-term exercise tolerance in patients with moderate-to-very severe COPD.

METHODS: In a double-blinded crossover design, patients were randomised to either 100 mg of prednisolone or placebo. The study consisted of a baseline visit and two study visits, each seven days apart. The primary endpoint was time to exhaustion (TTE) on an ergometer bike using a submaximal exercise test on 70% of the maximal workload. On every study visit, spirometry, the COPD Assessment Test, maximal inspiratory/expiratory pressure and maximal voluntary contraction of the quadriceps muscle were measured. A total of 14 male patients with grade C/D COPD were randomised.

RESULTS: The mean TTE was significantly longer at the prednisolone visit (p = 0.019), whereas no differences were seen on other parameters such as lung function, respiratory symptoms or muscle strength.

CONCLUSION: Our finding suggests that COPD patients experience improvements in exercise tolerance from a single high dose of glucocorticoid even in the stable phase of their disease.

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Globally, chronic obstructive pulmonary disease (COPD) is a common disease, and it is now the third leading cause of death worldwide [ ]. The main focus of COPD treatment is to reduce progressive decline in lung function, to preserve and/or improve the patient's quality of life and level of physical activity while avoiding exacerbations [2]. Evidence for using either oral or intravenous glucocorticoids in acute exacerbations of COPD (AECOPD) has been described in several studies, and a dose of 30-60 mg prednisolone per day for 10-14 days has been standard treatment, often initiated with a higher intravenous bolus dose if the patient is hospitalised [3]. However, in stable COPD, the use of long-term inhaled or systemic corticosteroids has been debated for some years [4]. A Cochrane review concluded that the short-term beneficial outcomes of systemic corticosteroids in AECOPD as well as in stable disease include improvement in lung function, increased exercise capacity (stable COPD) and a lower risk of early relapse (AECOPD); however, in both cases, the improvements are accompanied by a higher risk of drug-related adverse events than with placebo [5]. Due to the well-known side effects of systemic steroids such as osteoporosis, hyperglycaemia, decreased strength of respiratory muscles and even a higher mortality rate [6], low doses of oral steroids for a long period are not recommended in stable COPD.

Corticosteroids enhance performance during endurance activity among athletes and have been on the World Anti-Doping Agency's list of prohibited drugs for several years. A beneficial effect of 60 mg prednisolone daily for seven days, measured on time to exhaustion at 70-75% of the maximum oxygen uptake (VO_2-max), has been shown in a group of healthy, recreationally trained men [7]. The same authors found no effect on exercise performance in a comparable study of a single administration of 20 mg prednisolone [8]. However, it remains unknown whether acute administration of a high dose of systemic corticosteroid improves exercise capacity in patients with stable COPD. The principal objective of this study was therefore to evaluate if a single administration of oral corticosteroids had an effect on exercise capacity, muscular power and symptoms in stable male COPD patients.

METHODS

Design

The study was a randomised, double-blind, placebo-controlled, cross-over trial, where patients were randomised to treatment with either 100 mg prednisolone or placebo, administered orally. The study was conducted at the Respiratory Research Unit, Bispebjerg Hospital, Denmark, and all patients were recruited

from the respiratory outpatient clinic. There were a total of three visits at a seven-day interval. Baseline values were measured at visit 1, including an incremental exercise test on an ergometer bike. At visits 2 and 3, the patients were instructed to take study medication (either 100 mg prednisolone or placebo) 3 h before the visit. The study medication (active and placebo) was prepared by the pharmacy at Glostrup Hospital. The packages were neutral and the tablets indistinguishable. At the baseline visit, all patients gave their written informed consent to participate in the study, which was conducted according to the principles of Good Clinical Practice (GCP). The trial was monitored by the GCP unit at Copenhagen University. The Protocol was approved by the local ethics committees (R. no. H-3-2012-142), and prior to the study the Danish Health and Medicines Authority inspected the study site and approved study procedures and settings (EudraCT 2012-004503-13).

Patients

Male patients with a forced expiratory volume in the 1st sec. (FEV1) < 70% of the predicted value and FEV1/forced vital capacity < 70% were enrolled. Patients were between 40 and 75 years of age and had a smoking history of > 20 pack-years and were able to perform a cycling test. The exclusion criteria were: daily use of oral glucocorticoid, exacerbation of COPD or any type of infectious disease within six weeks of study entry or during the study period, concomitant pulmonary disease such as asthma, cystic fibrosis, interstitial lung disease, alpha 1-antitrypsin deficiency, clinically significant osteoporosis or Type 2 diabetes, history of malignancy within the previous five years and treatment with beta- blockers or cardiovascular diseases that would impair exercise performance.

All patients were allowed to use their regular inhaled COPD medication (long- and short-acting beta-2-agonists and anticholinergics as well as inhaled corticosteroids either in combination with long-acting beta-2-agonists or as monotherapy). Theophyllines and roflumilast were also allowed. The patients were encouraged to use the same dose and administration of regular medication on the days of receiving the study medication as on any other day.

Baseline characteristics
At the first visit, all subjects had their height, weight and lung function measured, and medical history and tobacco consumption were recorded.

Questionnaire
At every study visit, the patients filled out the COPD Assessment Test (CAT), which is a questionnaire assessing the symptom burden.

Dynamic lung function
Spirometry was measured using maximum expiratory flow volume according to the standards specified by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) 2005 guidelines, using Easy-One (Spiropharma).

Static lung function and diffusion capacity
Measurement of total lung capacity and diffusion capacity was performed using Jaeger MasterScreen, and residual volume was calculated as a subtraction of slow vital capacity from total capacity according to the standards specified by the ERS and ATS 2005 guidelines.

Muscle strength
Maximal inspiratory/expiratory pressure (MIP/MEP) was measured according to the ATS/ERS Statement on Respiratory Muscle Testing (2002) using the RPM micro (Carefusion). Maximal voluntary contraction (MVC) on the quadriceps muscle was measured using a handheld muscle tester (Lafayette instrument) and measured in lbs.

Exercise testing
The incremental cycle test was performed after 10 min. of warming up on 10 W followed by a 5-min. break to apply the oxycon mask. The patients then started pedalling at 70-80 rotations/min., initiating the test at 30 W with an increase of 10 W per min. The W-max for each patient was determined as the greatest workload reached in a 20-sec. period. The Simulated Mission Endurance Test (SMET) was defined as described by the ERS task force of clinical exercise testing [9] by performing a 5-min. warm-up at 10% of W-max followed by 20 min. of 40% of W-max. After 5 min. of rest, the patients then performed the SMET on 70% of W-max measured as the maximum exercise capacity recorded in the incremental test. Time to exhaustion (TTE) was measured in sec.

Subjective measurement of shortness of breath
Exertional dyspnoea and leg discomfort (BORG CR10 scale) [10] were measured immediately after TTE.

Statistics
In the cycling test, it is expected that the trial subjects can cycle for 360 sec. ($\pm$ standard deviation (SD) 50). By assuming an improvement in W-max of 40 sec. after administration of oral prednisolone and adjustment for the cross-over design, it was calculated that a sample size of nine patients was sufficient (at a power of 0.8 and ($\alpha = 0.05$).

Data were analysed in SPSS statistical software version 20 (IBM software, Chicago, Illinois, USA).

For the primary and secondary endpoints, we used a paired t-test. Analyses with the Wilcoxon signed-rank test (non-parametric testing) yielded the same result.

Baseline characteristics were analysed as mean ($\pm$ SD). The conventional level of statistical significance ($p < 0.05$) was used for all analyses.

Trial registration: EudraCT 2012-004503-13.

RESULTS

Baseline characteristics

Among 16 screened patients, 14 were randomised and completed the study. The baseline demographics and clinical characteristics of all randomised patients are shown in **Table 1**. The mean age was 66 years, seven had very severe COPD (FEV1 < 30% of the predicted value), six had severe COPD (FEV1 30-50% of the predicted value) and one patient suffered from moderate disease (FEV1 50-80% of the predicted value) COPD. The mean FEV1 ($\pm$ SD) was 35% ($\pm$ 10.8) of the predicted value. The mean ($\pm$ SD) W-max for the incremental work test at screening was 83.6 W ($\pm$ 25.6).

Spirometry and respiratory parameters

No differences were found in FEV1 between the placebo and prednisolone visit; FEV1 was 1.14 l ($\pm$ 0.5) and 1.16 l ($\pm$ 0.53), respectively, p = 0.47. Other respiratory parameters were unchanged (**Table 2**) with exception of ventilation per min. at TTE with placebo 41.14 l/min. ($\pm$ 10.30), prednisolone 44.21 l/min. ($\pm$ 11.63), p = 0.008 (Table 2).

Time to exhaustion and muscle strength

Prednisolone was statistically significantly superior to placebo with respect to TTE (p = 0.019). The mean value in the placebo group was 298.86 sec. ($\pm$ 189.58) and in the prednisolone group 393.64 sec. ($\pm$ 273.36) with a mean difference of 94.78 sec. (**Figure 1**). MIP, MEP and MVC were unchanged prior to and after the TTE test at both visits (Table 2).

Symptom scores

No differences were seen on the BORG dyspnoea scale; placebo: 5.23 ($\pm$ 0.58), prednisolone: 5.67 ($\pm$ 0.65), (p = 0.36) or leg discomfort; placebo: 4.46 ($\pm$ 2.83), prednisolone: 4.14 ($\pm$ 2.2), (p = 0.52) at TTE. The CAT score was equally symptomatic: 12.57 ($\pm$ 7.93) at the placebo visit and 13.43 ($\pm$ 7.37) at the prednisolone visit, p = 0.08 (Table 2).

DISCUSSION

The most important finding of the present study is that 100 mg of orally administered prednisolone significantly improved exercise tolerance measured as TTE in male patients with severe COPD. Furthermore, the TTE

TABLE 1

	Mean $\pm$ SD
FEV1, l	1.1 $\pm$ 0.5
FEV1, %	35 $\pm$ 10.8
FVC, l	2.4 $\pm$ 0.6
FVC, %	56.9 $\pm$ 11.6
FEV1/FVC, %	45.8 $\pm$ 10.9
RV, l	4.8 $\pm$ 1.8
RV, %	171.0 $\pm$ 31.1
TLC, l	7.6 $\pm$ 0.94
TLC, %	113 $\pm$ 15.5
RV/TLC, %	56 $\pm$ 6.5
DL_{CO}/SB, mmol/min/kPa	7.8 $\pm$ 9.1
DL_{CO}/VA, mmol/min/kPa/l	1.1 $\pm$ 0.3
BMI, kg/m^2	25.2 $\pm$ 4.9
Pack years	46.3 $\pm$ 18.7
CAT score	14.3 $\pm$ 6.0
Age, yrs	66.2 $\pm$ 6.9
MVC, %	61.6 $\pm$ 12.2
VO$_2$max, l/min	17.8 $\pm$ 4.7
Wmax, watt	83.6 $\pm$ 25.6

Baseline characteristics of the included patients (N = 14).

CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; DL$_{CO}$ = diffusing capacity of the lung for CO; FEV1 = forced expiratory volume in 1st sec.; FVC = forced vital capacity; MVC = maximal voluntary contraction; RV = residual volume; SB = single breath; SD = standard deviation; TLC = total lung capacity; VA = alveolar volume; VO$_2$max = maximal O$_2$ consumption; Wmax = maximal work load at the incremental test.

TABLE 2

	Placebo	Prednisolone	p-value
FEV1, l	1.1 ($\pm$ 0.5)	1.2 ($\pm$ 0.5)	0.47
FEV1, %	36.3 ($\pm$ 11.9)	36.8 ($\pm$ 12.4)	0.57
FVC, l	2.5 ($\pm$ 0.7)	2.5 ($\pm$ 0.8)	0.72
FVC, %	61.4 ($\pm$ 12.1)	61.2 ($\pm$ 13.4)	0.91
FEV1/FVC, %	45.6 $\pm$ (11.7)	46.0 ($\pm$ 11.3)	0.66
Pre-cycling			
MIP, cmH$_2$O	78.5 ($\pm$ 21.8)	75.7 ($\pm$ 20.0)	0.33
MEP, cmH$_2$O	120.7 ($\pm$ 38.4)	117.5 ($\pm$ 26.1)	0.57
Post-cycling			
MIP, cmH$_2$O	78.3 ($\pm$ 21.2)	76.6 ($\pm$ 20.5)	0.46
MEP, cmH$_2$O	117.4 ($\pm$ 35.6)	118.4 ($\pm$ 33.2)	0.77
CAT score	12.6 ($\pm$ 7.9)	13.4 ($\pm$ 7.4)	0.08
At TTE			
VE, l/min.	41.1 ($\pm$ 10.3)	44.2 ($\pm$ 11.6)	0.008
BF/min.	28.6 ($\pm$ 6.4)	29.9 ($\pm$ 5.8)	0.35
VO$_2$, l/min	1,263.8 ($\pm$ 237.3)	1,325.9 ($\pm$ 246.1)	0.65
VCO$_2$, l/min	1,147.8 ($\pm$ 294.8)	1,196.3 ($\pm$ 278.1)	0.87

Mean values ($\pm$ standard deviation) after 100 mg prednisolone or placebo (N = 14).

BF = breathing frequency; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1st sec.; FVC = forced vital capacity; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; TTE = time to exhaustion; VCO$_2$ = maximal CO$_2$ expiration; VE = maximal min. ventilation; VO$_2$max = maximal O$_2$ consumption.
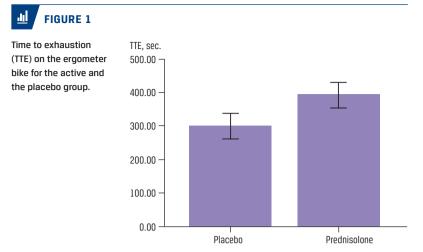
FIGURE 1

Time to exhaustion (TTE) on the ergometer bike for the active and the placebo group.

was not facilitated by improvement in any respiratory parameters measured in the study. Prednisolone did not seem to affect the peak muscle force of the quadriceps muscle, which is the main muscle group involved in this exercise testing. The driving force of the increased exercise tolerance therefore necessarily stems from other factors than muscle strength and lung function. We do not have a precise explanation for our finding. A previous study suggested that decreased eosinophilic airway inflammation following a short prednisolone course had a positive effect on shuttle walk distance [11]. However, a subsequent study with the same kind of treatment could not differentiate patients into groups of corticosteroid responders or non-responders [12]. Whether the difference in TTE found in the present study is of clinically significant importance can be questioned since the mean difference between the two treatment visits ($\approx$ 95 sec.) was marginally lower than the $\approx$ 100 sec. specified by Puente-Maestu et al. to be the estimated minimum clinical improvement difference (MCID) [13]. However, this value was established in COPD patients with better lung function than those participating in the present study.

Only one study from 1985 has investigated a similar hypothesis using an incremental cycling test, and the authors found no effect on VO2 consumption or W-max [14]. In COPD trials where improvements in exercise tolerance have been a primary outcome, studies of long- and short-acting bronchodilators in particular have found increasing lung function and reduced dynamic hyperinflation, suggesting that improvement in respiratory parameters is the main mechanism enhancing exercise performance [15, 16]. However, one study demonstrated that a budesonide/formeterol combination had a better effect on exercise tolerance than formeterol alone 1-6 h after intake [17]. The mechanism was suggested to be a non-genomic action of budesonide on cells and vasculature, but no further in-

formation regarding possible factors enhancing exercise endurance was provided.

COPD patients often suffer from impaired muscle strength in the lower extremities associated with decreased exercise capacity and functional capacity [18]. In healthy subjects, corticosteroids have been suggested to inhibit fatigue by preventing an overreaction of the immune system that might lead to exercise-induced muscle damage [19]. None of the patients in this trial reported any sign of muscle pain or soreness after the study visits, indicating that no significant exercise-induced muscle inflammation occurred. Glucocorticoids also increase the availability of metabolic substrates such as increased glycogen synthesis, lipolysis and plasma-free fatty acids levels, but in patients with severe degrees of airflow obstruction, the exercise-limiting factor is mainly due to imbalance between the ventilatory capacity and requirements and not to a lack of metabolic substances [20].

There are several limitations to the present study, e.g., the BORG was not measured at fixed intervals during cycling, which would have made it possible to estimate the level of dyspnoea and leg fatigue at isotime. Furthermore, we used the CAT score, which is not validated for detection of symptom variations when visits are this close. A different questionnaire specifying these aspects could probably illuminate daily symptoms or mood changes in a more precise manner. The small sample size is also a limitation, and type I statistical error thus cannot be ruled out. Furthermore, the results are not applicable to COPD patients in general and, more importantly, only reflect a short-term treatment effect. Strengths of this study include the randomised double-blinded cross-over design and that every measurement was standardised and performed in the same manner on each study visit (visits 2 and 3). However, the crossover design also introduces a limitation since it is possible that the patients who were given prednisolone first and placebo later experienced a short-term positive effect on TTE and a negative long-term effect. This would skew the results compared with those who were given placebo first and then prednisolone.

CONCLUSION

A single administration of 100 mg prednisolone provides significant improvement in exercise tolerance in men with severe COPD, and this might explain why some COPD patients are taking corticosteroids "off the record" even when not experiencing an exacerbation. The study failed to identify the driving factor for the improved exercise tolerance, but it did not seem to be owed to increased muscle strength, lung function, improvements in symptoms or any other respiratory parameters measured in this study.

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