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Strength and endurance of the respiratory and handgrip muscles after the use of flunisolide in normal subjects

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Peripheral muscle

Summary
Objective: To evaluate the effects of the inhaled flunisolide upon the strength and endurance of the respiratory and peripheral muscles of normal subjects.
Design: A randomized, double blind and placebo-controlled study.
Setting: A university-affiliated teaching hospital.
Participants: Thirteen normal volunteers selected from a graduation course.
Intervention: Subjects were randomly allocated to receive a placebo or corticosteroid (flunisolide) to be inhaled twice a day for 4 weeks. After 2 weeks of a washout period, subjects who were receiving the placebo, received flunisolide and vise versa for another 4-week period.
Measurements and results: Spirometry was used to define the volunteers as being normal in terms of pulmonary function. During the study, subjects performed tests of respiratory muscle function (strength and endurance), measurements of handgrip strength and endurance and anthropometric measurements. Muscle strength was measured each week while muscle endurance was measured every 2 weeks. There was no significant difference in the maximal inspiratory and expiratory pressure and handgrip strength during weeks 1–4 when the subjects used either flunisolide or placebo. However, we observed an increase in the endurance time of the respiratory and handgrip muscles in the 4th week of both flunisolide and placebo use, what may be considered due to a learning effect.

Abbreviations: AC: arm circumference; AMC: arm muscular circumference; BMI: body mass index; FEV_1: forced expiratory volume in the 1 s; FVC: forced vital capacity; KgF: Kgforce; $P_{E_{max}}$: maximal expiratory pressure; $P_{I_{max}}$: maximal inspiratory pressure; SD: standard deviation; TCST: triceps cutaneous skinfold thickness

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Conclusion: Inhalation of flunisolide by normal subjects for 1 month does not cause any acute or clinically perceived effect in the peripheral or respiratory muscles.

Introduction

Steroid-induced myopathy is defined as a muscular weakness which occurs in subjects being treated with corticosteroids without any other previous neuromuscular disease.[1] In a study of two groups of patients with chronic obstructive pulmonary disease (COPD), comparable in respect to their degree of bronchial obstruction, sex and age, Decramer and Koenraad[2] demonstrated that the group with corticosteroid myopathy presented accentuated weakness of the quadriceps and general muscular atrophy. Muscular biopsy demonstrated that the atrophy was predominant in the types IIa and IIb fibers.

Studies in animals have demonstrated that the decrease in diaphragmatic force is directly proportional to the loss of its muscular mass and to alterations in the energy production metabolism.[3–5] In patients with asthma or collagen diseases, treatment with corticosteroids reduces the muscle strength.[6]

Due to the systemic effects of the systemic use of glucocorticoids, both in the muscles and other organs, inhalatory administration has been considered as ideal for delivering these medications in patients with chronic obstruction airflow. This form of application allows the administration of relatively small doses of the drug, which produce the same beneficial effects in the airways as the systemic use of corticosteroids.[7]

Although we have already demonstrated that inhaled flunisolide does not cause alterations in the bone and suprarenal metabolisms of asthmatics,[8] others have demonstrated that a systemic absorption of the inhaled corticosteroid may occur with the subsequent appearance of adverse effects.[9] These effects may be dependent upon the dose, the sensitivity of the organ or of the individual. In COPD patients, for instance, it has been shown that inhaled triamcinolone (1200 mcg dose) decreases the bone mineral density faster than with the use of placebo.[10] Skin bruises after using inhaled fluticasone (1000 mcg/day) has also been referred as a side effect in COPD patients which demonstrate the systemic absorption of inhaled corticosteroid.[11] Currently high doses of inhaled corticosteroids have been proposed for a group of COPD patients with stable disease.[10] This could have a negative systemic effects on these COPD patients. However, as far as we know, there is no any controlled, randomized double blind study that has analyzed the possibility of an adverse effect with the inhalation of corticosteroid upon the respiratory or peripheral muscles.

The objective of this study was to analyze the effects of topical flunisolide upon the respiratory and peripheral muscles function of normal subjects.

Patients and methods

Sample size considerations

A sample size of 12 patients would permit a power of 80% to detect a clinically relevant treatment difference on PI_{max} (assuming the true difference between the treatments being 25 cm H_2O) with a two-sided 5% significance level (*P* value).[12–14] The within-patient standard deviation of the maximal inspiratory pressure for this estimate was 20.0 cm H_2O, according to the Brazilian reference values.[15]

Volunteers

Thirteen male post-graduate students were recruited for the study with the following criteria: normal spirometry, no history or evidence of respiratory, cardiac, allergic, neuromuscular, rheumatological or endocrinal disease and no upper respiratory infections or use of any medication during the 3 weeks proceeding the study.

Study plan

A randomized, double blind, cross-over and placebo-controlled study was carried out. Subjects were randomly allocated to receive an inhaled placebo or the inhaled corticosteroid (flunisolide, 1000 mcg/day, divided in two doses) for 4 weeks. The metered dose inhalers had exactly the same appearance, except by an identification code, which was kept in secret to avoid bias until the end of the data collection and analysis period. After a 2-week washout period the process was reinitiated, but in reverse, and the placebo aerosol was used for a further 4 weeks. Before the initiation of the study, the subjects performed spirometry and measurements of strength and endurance of the respiratory and handgrip muscles as well as a nutritional evaluation (body mass index, triceps cutaneous skinfold thickness and arm muscle circumference). The subjects signed an informed consent form and the study was approved by the Committee of Research Ethics of the Intuition.

Spirometry

Spirometry was performed to define the volunteers as normal in terms of their pulmonary function. A VITATRACE VT 130SL spirometer (Brazil)) was utilized following the criteria of the American Thoracic Society.[16]

Respiratory muscle strength

Respiratory muscle strength was assessed by measuring the maximal inspiratory and maximal expiratory pressures (PI_{max} and PE_{max}, respectively) generated against an occluded airway at the functional residual capacity with the individual in a sitting position and using a nasal clip. We used an aneroid manovacuometer calibrated in cm H_2O (IMEBRAS®, Brazilian Industry). For both the PI_{max} and the PE_{max}, the subject maintained the contraction for 1 s and the highest value obtained (among 10 tries) was considered as the maximum. For the inspiratory measurement, the apparatus contained a 1 mm-hole to avoid closure of the glottis. Cheek compression was performed during the expiratory maneuver. To train the subject in the maneuver and to evaluate the reproducibility of the measurement, the PI_{max} and the PE_{max} were measured 10 times with an 1 min rest interval among them on 3 consecutive days. During the 4 weeks of the study with each aerosol this measurement was performed weekly with 5 measurements.

Respiratory muscle endurance

Respiratory muscle endurance was measured with a T piece adapted to the aneroid manovacuometer, with the subject inspiring through an orifice and generating a pressure corresponding to 80% of his PI_{max} in each respiratory cycle. The maximum time, in seconds, that the individual could tolerate performing 20 inspirations per minute was considered as the endurance measurement. This measurement was taken before the use of the flunisolide or placebo aerosol and in the second and fourth weeks of their use.

Handgrip strength

A dynamometer, calibrated in Kgforce (KgF) was utilized for the measurement of handgrip strength. This measurement was performed for 3 consecutive days with 5 reproductive forces to find the best value. The subject remained seated, with the forearm rested on the arm of a chair and the fist supported by the opposite hand; the maximum voluntary handgrip strength maneuver had to be maintained for 1 s. This measurement was carried out again on the same days as the respiratory muscular strength measurements.

Handgrip endurance

This maneuver was performed in the same position as described above. The maximum time, in seconds, that the individual could tolerate performing 20 handgrip movements per minute, reaching 50% of the maximum voluntary strength was considered to be the endurance time. This maneuver was repeated on the same days as the respiratory muscle endurance measurements.

Nutritional evaluation

The body mass index (BMI) was obtained by dividing the subject's weight by the height squared (kg/m^2); arm circumference (AC): the circumference of the non-dominant arm was measured, in centimeters, at the mid point of the arm parallel to the body. The middle point of the arm was determined as the half-way point between the acromion and the olecranon; arm muscular circumference (AMC): the AMC was calculated using the following equation, in centimeters: AMC = AC−(3.1416 × triceps cutaneous skinfold thickness);

Triceps cutaneous skinfold thickness (TCST)
The adipose tissue was pinched between the thumb and the index finger at the mid point of the arm and the measurement was taken, in mm, with a CESCORF® Skinfold Instrument (Japanese Industry). The measurement was repeated at least three times and variations greater than 4 mm were not accepted. The median value was considered as the TCST.

The nutritional evaluation measurements were performed before the study and after 1 month of aerosol therapy both for the placebo and flunisolide treatments.

Statistical analysis

Data were reported as mean ± SD. For data analyses, the following non-parametric tests were applied: Analysis of variance by the Friedman test to compare the PI_{max}, PE_{max} and handgrip strength variables on the 3 consecutive days of pre-randomized measurements and to compare the respiratory muscle and handgrip strength and endurance variables at the different times of the study (0–4 weeks and 0, 2 and 4 weeks, respectively); the Wilcoxon test for two non-independent samples was used to compare, for each subject, the pre-placebo and pre-medication parameters. In all the tests $P \leqslant 0.05$ was considered significant.

Results

Thirteen volunteers completed the respiratory muscle strength and endurance measurements; one volunteer could not perform the measurements of the handgrip strength and endurance and arm muscular circumference due to the immobilization of his arm following a wrist fracture during a car accident. So those measurements were performed in 12 volunteers.

The mean ± SD of subjects age (years), weight (kg) and height (cm) were, respectively, 30.1 ± 7.7, 75.2 ± 11.4 and 173 ± 4.3. The mean ± SD (% predicted) of forced vital capacity (FVC) (L), forced expiratory volume in the 1 s (FEV_1) (L) and FEV_1/FVC 5.3+0.7(100.4%), 4.3+0.6 (98.4%) and 84.3+5.4%, respectively.

The respiratory muscle strength measurements taken on 3 consecutive days before the start of the study were reproducible with no significant differences (PI_{max} = 182.1 ± 8.0 cm H_2O × 182.9 ± 9.2 cm H_2O × 180.4 ± 9.7 cm H_2O, respectively; PE_{max} = 140.0 ± 22.5 cm H_2O × 140.8 ± 24.9 cm H_2O × 142.3 ± 26.2 cm H_2O, respectively) (Fig. 1). The same was observed for the handgrip strength (4.6 ± 0.7 KgF × 4.7 ± 0.8 KgF × 4.8 ± 0.9 KgF, on the 1st, 2nd and 3rd days, respectively; Fig. 2).

The statistical analysis showed that the individuals presented no difference on the values pre-placebo and pre-flunisolide periods for all variables studied (BMI = 24.8 ± 0.9 kg/m^2 × 24.8 ± 0.9 kg/m^2; PI_{max} = 178.5 ± 19.6 cm

$H_2O \times 182.3 \pm 20.3$ cm H_2O; $PE_{max} = 148.9 \pm 22.6$ cm $H_2O \times 146.5 \pm 27.6$ cm H_2O; handgrip force $= 5.0 \pm 0.3$ KgF $\times 4.9 \pm 0.3$ KgF; AMC $= 27.4 \pm 1.3$ mm $\times 27.4 \pm 1.8$ mm; respiratory muscle endurance $= 1205.5 \pm 957.2$ s $\times 1161.2 \pm 1034.7$ s and handgrip endurance $= 666.7 \pm 274.7$ s $\times 674.1 \pm 330.9$ s, respectively). This allowed us to join all patients into two groups, placebo and flunisolide.

There was no decrease in the PI_{max} and PE_{max} during weeks 1–4 when the subjects used flunisolide and when they used placebo aerosol (Table 1).

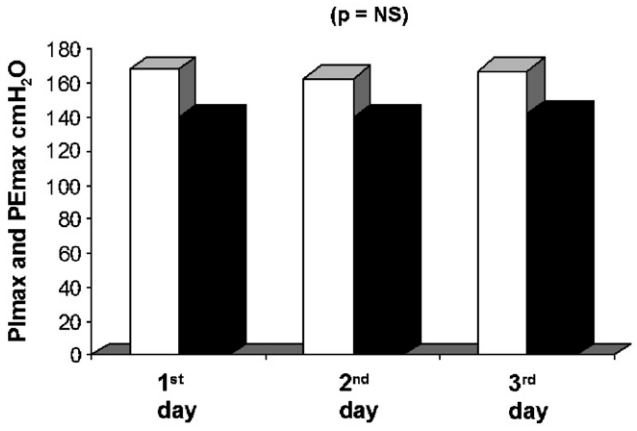

Figure 1 Mean of PI_{max} (white) and PE_{max} (black) taken in three consecutive days, as basal values, in 13 normal subjects.

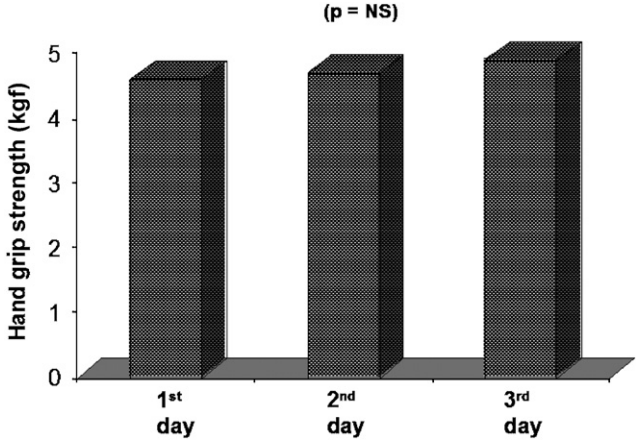

Figure 2 Mean of handgrip strength in three consecutive days, as basal values, in 13 normal subjects.

The handgrip strength was used to evaluate the peripheral skeletal muscles and to act as a control for the respiratory muscles. No statistically significant changes were seen in the handgrip force during the utilization of flunisolide (4.9 ± 0.8 KgF $\times 4.9 \pm 0.8$ KgF $\times 5.1 \pm 0.8$ KgF $\times 5.1 \pm 1$ KgF) or placebo (5.1 ± 1 KgF $\times 4.9 \pm 1$ KgF $\times 5.2 \pm 0.9$ KgF $\times 5.3 \pm 1.2$ KgF) during weeks 1, 2, 3 and 4, respectively (Fig. 3).

The respiratory muscle endurance recorded during the use of placebo and flunisolide are demonstrated in Fig. 4. There was a progressive increase in the endurance time during the use of both flunisolide (1161.2 ± 886.9 s $\times 1191.6 \pm 959.1$ s $\times 1451.4 \pm 924.1$ s) and placebo (1210.2 ± 886.9 s $\times 1228.8 \pm 813.7$ s $\times 1488.5 \pm 1052.3$ s) in weeks 0, 2 and 4, respectively, but this increase was just statistically significant on the 4th week of the flunisolide group. A similar effect was seen with the handgrip muscle endurance. Although there was an increase in the time from week 0 to weeks 2 and 4, both in the flunisolide group (674 ± 305.1 s $\times 715.9 \pm 283.2$ s $\times 880.8 \pm 357.7$ s) and in the placebo group (666.7 ± 252.7 s $\times 718.4 \pm 362$ s $\times 821.5 \pm 393$ s), respectively, this increase was just statistically significant in the flunisolide group (Fig. 4).

No alterations in the BMI or the AMC were seen following the administrations of the placebo (BMI $= 24.8 \pm 3.4$ kg/m^2 $\times 24.9 \pm 3.0$ kg/m^2; AMC $= 27.4 \pm 1.3$ mm $\times 26.9 \pm 1.3$ mm) or flunisolide (BMI $= 24.8 \pm 2.9$ kg/m^2 $\times 24.3 \pm 3$ kg/m^2; AMC $= 27.3 \pm 1.9$ mm $\times 26.9 \pm 1.9$ mm), respectively (P = NS).

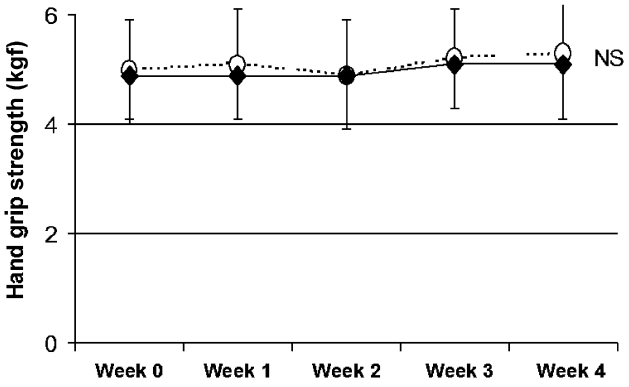

Figure 3 Mean (+ SD in bars) of handgrip strength during the use of 1000 mcg inhaled flunisolide (♦), and placebo (○), for 1 month, in 12 normal subjects.

Table 1 The inspiratory and expiratory pressures during the whole study.

	Week									
	0		1		2		3		4	
	Placebo	Flunisolide	Placebo	Flunisolide	Placebo	Flunisolide	Placebo	Flunisolide	Placebo	Flunisolide
PI_{max} (cm H_2O)	178.5±19.6	182.3±20.0	185.8±11.0	185.8±12.2	183.5±14.6	181.9±19.3	187.7±7.7	183.9±16.1	186.2±10.2	185.4±13.7
PE_{max} (cm H_2O)	148.9±22.6	146.5±27.6	149.2±23.2	142.7±27.5	147.7±20.3	144.6±28.6	143.1±23.7	144.2±25.9	145.0±22.5	139.6±23.1

The values are expressed as mean±SD.

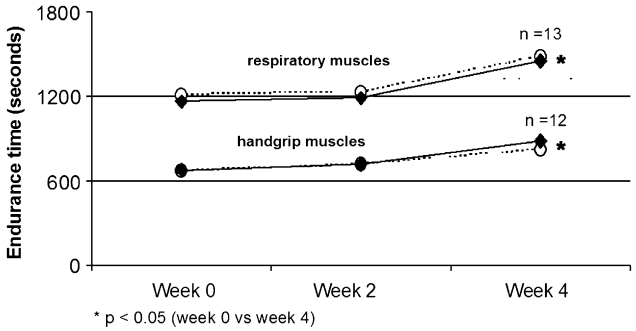

Figure 4 Respiratory and handgrip muscles endurance time (seconds) during the use of 1000 mcg inhaled flunisolide (♦), and placebo (○), at weeks 0, 2 and 4.

Discussion

The aim of this study was to determine if the use of inhaled flunisolide for 1 month would bring any alteration in the strength and/or endurance properties of the respiratory muscles and the peripheral muscles (represented, in this study, by the handgrip muscles). Although corticosteroid inhalation has been used for many years, we do not know of any study about the adverse effects of this form of administration upon the respiratory and peripheral muscles. Due to the adverse effects the use of systemic glucocorticoids may bring, the inhalatory via has been often used for their administration and is considered to be an alternative method for supplying this medication for patients with airflow obstruction. Inhaled corticosteroids produce the desired anti-inflammatory effect in the airways, with minimal systemic absorption.[17] However patients with severe obstruction, may require the use of high doses of corticosteroids, which may increase the potential for adverse effects systemic occurrence.

One of the undesirable effects of systemic glucocorticoids is that they can cause motor dysfunction as a consequence of the direct effects of the steroids upon the skeletal muscles which include the reduction of muscular mass,[5] loss of myofibril protein and susceptibility to fatigue.[18–20] The extent a muscle is affected, varies according to the composition of its fibers[21] which may be variable in animal and human muscles, depending on the predominance of Type I or Type II fibers.[22] In steroid myopathy, the Type II fibers are the most affected.[23]

The locomotor muscles with predominantly postural function seem to be less susceptible to corticosteroid-induced myopathy.[24] Based on these considerations, it would be expected that the red skeletal muscle fibers with continuous activity should be more resistant to steroid-induced myopathy. However a study on the costal diaphragm of rats demonstrated that the sarcoplasmic reticulum and myofibril proteins were reduced by the use of high doses of prednisolone without any significant alteration in the fibers of the vertebral portion.[25] This more intense lesion in the costal section may decrease the respiratory muscle endurance, as this muscle has a predominance of slow contraction fibers.[26] We have evaluated both the strength and endurance of the respiratory and handgrip muscles, based upon the fact that the respiratory muscles predominantly present characteristics of endurance and the handgrip muscles have a greater predominance of force fibers.

A dose of 1000 mcg of flunisolide was chosen in the study as this is considered to be a moderate-to-high dose and it is usually prescribed in daily practice; in addition, previous studies indicate that low or moderate doses of oral corticoidsteroid have little or no effect upon the ventilatory muscular performance.[27] Thus, the possibility that the respiratory muscular strength may be compromised by small doses using the inhalatory via could be discarded.

The primary finding of our study was the fact that there was no decrease in the respiratory muscle force (PI_{max} and PE_{max}) after the use of flunisolide for 1 month. This study had an 80% power to detect a difference of 25 cm H_2O or more in the PI_{max} between the treatments. Such difference can be assumed to be clinically important, because an increase of such amount can be related to structural respiratory fiber muscles changes in COPD patients,[14] as well as patient-oriented outcomes, such as a decrease in dyspnea sensation and increase in exercise tolerance and quality of life.[13] It has to be considered, however, that on the basis of this study design a steroid-induced myopathy by inhaled corticosteroids can not be fully excluded and further studies are required , specially addressing a longer treatment time.

Study limitations

Respiratory and handgrip muscles endurance measurements variation: the experimental design included multiple measurements of the endurance muscle properties in the period following randomization and treatment arms. This could probably induce a training effect[28] and neutralize any weakening property of the inhaled fluticasone. However, for the respiratory muscle endurance test, previous studies have defended the idea that a learning period, consisting of 1–3 tests, should be used to obtain reproducible results.[29–31] Indeed, the finding of greater respiratory muscle endurance at the end of the treatment period may reflect a training effect due to the multiple measurements carried out during the study period. The analysis of the response to nerve stimulation would be indicated to exclude the possibility of a learning effect, or a submaximal effort at the beginning of the study. However, this outcome measurement was not considered before the beginning of the study, and was not performed. In addition, there was an inadequate sample size to detect differences for the peripheral and respiratory endurance muscle parameters, because of the wide spread of these data (SD values of 90%, on average).

Subject's adherence and study design

Some criticisms can be made regarding the cross—over design of this study, because of the risk of carry-over effects of the first treatment in the second treatment. However, an accepted wash out period of 2 weeks (to minimize the effects of inhaled corticosteroids) was adopted to avoid the carry-over risk. In addition, the measurements before the two periods of placebo or flunisolide showed no difference at all, proving that no carry over effect has happened. Despite all subjects were graduate students and

very familiar with clinical research and the importance of adherence to the protocol, there were no objective measurements to assess adequate adherence.

Maximal inspiratory and expiratory values: in some subjects, the baseline $P_{E_{max}}$ was inferior to the PI_{max} values. This fact is not usual, and this finding could be possibly explained by an uncomfortable sensation when performing the $P_{E_{max}}$ measurement due to the Valsalva phenomenon. However, this pattern was maintained during the study (which showed an increase in $P_{E_{max}}$ and PI_{max} values), and the experience in performing the static pressures, as well as motivation or other confounding factors could then be excluded.

Our results indicate that a high dose of inhaled corticosteroid during a short period (1 month) has no effect upon the strength and endurance of the respiratory and handgrip muscles. These results may not be extrapolated to other doses and longer treatment duration. New studies are necessary to determine whether subjects with chronic respiratory disease reproduce this finding.

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