Do steroids interfere in dyspnoea sensation?

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Abstract  Dyspnoea remains a remarkable clinical problem and a therapeutic challenge, mainly in chronic respiratory conditions. This study investigated the potential effects of steroids on dyspnoea sensation regardless of their pulmonary anti-inflammatory actions. Sixteen healthy men (mean age ± SD = 22.5 ± 1.6 years) developed uncomfortable breathing by the use of inspiratory resistors (loads of 0, 7, 14 and 21 cm H₂O/l/s) and breathholding 6 h after taking 40 mg of prednisone (Pred) or placebo (Plac). Respiratory discomfort during breathing with loads was evaluated with a 100 mm visual analog scale. The maximum voluntary apnoea time did not differ between the prednisone and placebo days (Plac= 96 ± 11.8 s x Pred= 105 ± 12.2 s) and prednisone did not influence the dyspnoea sensation induced by different inspiratory loads (0 cm H₂O/l/s: Pred= 2.8 mm x Plac= 1.9 mm; 7 cm H₂O/l/s: Pred= 18.3 mm x Plac= 18.6 mm; 14 cm H₂O/l/s: Pred= 33.0 mm x Plac= 34.1 mm; 21 cm H₂O/l/s: Pred= 48.1 mm x Plac= 49.6 mm). Prednisone intake was associated with a significant increase in minute ventilation during breathing with no inspiratory loads (Pred= 11.9 l/min ± 1.28 l/min x Plac= 9.95 ± 0.86 l/min). Although steroids certainly may improve respiratory conditions due to anti-inflammatory actions, available evidence does not support any specific beneficial effect of these drugs on the perception of dyspnoea itself.

Keywords  dyspnoea; steroids; pulmonary function; analog scale.

Dyspnoea is one of the most common complaints among patients with cardiorespiratory diseases and is often the reason why a person seeks medical care. The presence of unpleasant respiratory sensations is the most important symptom affecting the quality of life in patients with chronic respiratory failure (1,2). Although our knowledge about the physiological mechanisms that generate the respiratory sensations has increased in the past two years, dyspnoea still remains a tremendous clinical problem and a therapeutic challenge (3). An agent able to reduce dyspnoea without significant side-effects would never be a substitute for specific therapy directed at the underlying respiratory disorder, but could be useful, mainly when the condition is irreversible (4).

Steroids are chemical agents with multiple physiological and therapeutic actions (5). Cortisol release is an important metabolic component of the fight or run response to stress conditions. In addition, we have observed in our clinical practice that some patients with chronic obstructive pulmonary disease (COPD) report improvement of their symptoms on oral prednisone, although pulmonary function parameters do not change. Therefore, we raised the hypothesis that steroids could have a beneficial effect on dyspnoea sensation independent of their well-known pulmonary anti-inflammatory actions.

The present study was designed to investigate the effects of oral prednisone vs placebo on respiratory sensations in a group of healthy volunteers who developed uncomfortable breathing by the use of inspiratory resistors and keeping voluntary apnoea.

MATERIAL AND METHODS

Subject

Sixteen non-smoking, healthy male volunteers participated in the study after giving informed consent. None of the subjects had respiratory symptoms, past pulmonary illnesses and all had a normal physical examination. Special care was taken to exclude subjects with a history of asthma or wheezing during childhood. Age ranged from 19 to 25 years, with a mean ± SD of 22.5 ± 1.6 years. The study was approved by the Ethics Committee of Hospital das Clínicas de Ribeirão Preto.
Methods

Study design: Dyspnoeic sensations were induced by breathholding and breathing with different inspiratory resistive loadings. The volunteers came to the pulmonary function laboratory three times. On the first day (D-I), they performed spirometry and dyspnoea tests in order to familiarize themselves with the maneuvers. On the second (D-2) and third days (D-3), they were medicated with placebo or with 40 mg of PO prednisone 6 h before the tests. Drug or placebo was administered at random and in a double-blind manner. All tests were performed around midday at least 2 days apart, and with the subjects breathing room air.

Spirometry: Basal pulmonary function data were obtained using a Pulmonet Godard spirometer. Procedures were performed according to American Thoracic Society recommendations (6). Forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁) and the middle curve forced expiratory flow (FEF₂₅₋₇₅%) were analyzed as predicted of normal values. The FEV₁/FVC ratios were expressed as percentage values. The predicted normal values were based on Crapo et al. (7).

Breathholding: When the volunteers arrived at the pulmonary function laboratory they received an explanation of the proceedings and, after a brief resting period, were asked to hold their breath at the total lung capacity level, the most they could. An observer employed a chronometer to measure the apnoea length, while the volunteers used hand signaling to indicate the beginning and the end of the breathholding period. The maximum voluntary apnea time was measured twice, at least 15 minutes apart, and the duration was expressed as seconds. The best value obtained between the two maneuvers was chosen for analysis.

Breathing with inspiratory loads: Each subject breathed through an oral one-way valve system during the experiment. A nose clip was placed to assure no air leaks. The valve expiratory port was connected to a Collins Multimodal Lung Analyzer (model 02303) in order to register the respiratory pattern and tidal volume with a graphic ink system. End-tidal carbon dioxide tension (PetCO₂) was measured with a CO₂ analyzer through a port in the expiratory limb. The same equipment is fitted with a pulse oximeter that was connected to one finger to continuously monitor the arterial oxygen saturation (DX 7100 ETCO₂/SPO₂ reader, Dixtal, SP). An adjustable resistor device employed in respiratory muscle training (Threshold IMT®, Healthscan, NJ) was connected to the valve inspiratory limb in order to introduce variable respiratory loads. The volunteers were asked to breath in the system without the resistor device (0 load) and with loads 7, 14 and 21 cm H₂O/l/s. The different loads were applied at random and in a blinded manner for the volunteers. The subjects breathed over a period of 2 min at each load and, at the end of the second minute, their respiratory parameters were recorded and they were asked to rate the degree of respiratory discomfort using a visual analog scale (VAS) (8). The analogue scale consisted of a vertical 100 mm line with the number zero at the bottom and the number 100 at the top. The volunteers were instructed to consider zero as the indication of no respiratory sensation at all and 100 a sensation that was intolerable.

Statistical analysis: Data are reported as means and standard error of the means (±SEM). Comparisons of the measurements obtained with prednisone and placebo were made using the paired t-test or Wilcoxon non-parametric test. A P value <0.05, corrected for multiple comparisons, was considered to be significant.

RESULTS

All the volunteers showed normal spirometric parameters. Pulmonary function data were expressed as percentage of the predicted normal values; FVC = 94±1.7%, FEV₁ = 93±1.5%, FVC/FEV₁ = 97±0.8%, and FEF₂₅₋₇₅% = 91±1.3%. Eight volunteers received placebo on D-2 and prednisone on D-3, and the remaining eight subjects took the drugs in an inverse order. The mean time interval between D-2 and D-3 was 4.4±0.7 days (range: 2–10 days).

The mean maximum voluntary apnoea time did not differ between the prednisone and placebo days (Placebo = 96±11.8 s × Prednisone = 105±12.2 s; Fig. 1).

Overall, prednisone did not lead to changes in tidal volume, exhaled carbon dioxide levels or arterial oxygen saturation at any load, compared to placebo. Prednisone intake led to increases in respiratory rate and minute ventilation, but the only change that reached statistical significance was an increase in respiratory rate at the 7 cm H₂O/l/s load.

![Fig. 1. Maximum voluntary apnoea times for 16 volunteers after taking placebo or 40 mg of prednisone.](image-url)
The use of prednisone did not influence the mean dyspnoea sensation induced by different inspiratory loads either (Fig. 2).
exercises, breathing hypercapnic gas mixtures, or the application of ventilatory restraints (16). Previous papers have employed normal volunteers breathing in respiratory circuits with loads, and measurement of breathholding times as methods to investigate physiological aspects and potential drug treatments for dyspnoea (9,12,16). Using the latter instruments Nishino et al. were able to demonstrate remarkable prolongations of the breathholding time and the period of no respiratory sensation after inhalation of furosemide (9). These authors also showed a decrease in the degree of respiratory discomfort associated with breathing with inspiratory loads after furosemide inhalation in comparison to placebo. We employed similar methods for practical reasons. Furthermore, we could also investigate the steroid effects on dyspnoea generated by distinct mechanisms.

In the present investigation, the oral administration of 40 mg of prednisone 6 h before the studies did not significantly improve the breathholding time or the degree of respiratory discomfort induced by different inspiratory loads in a group of 16 healthy young volunteers, nor did it lead to important changes in respiratory physiological parameters. Prednisone intake was only associated with a statistically significant increase in minute ventilation during breathing in the circuit with no inspiratory loads. Considering that increases in ventilation are generally related to worsening in dyspnoea, this finding may be interpreted as further evidence against a beneficial effect of steroids on respiratory sensations.

In daily clinical practice, we have observed some patients with stable advanced COPD who are not able to taper off oral steroids due to worsening respiratory symptoms. Sometimes subjects with end-stage pulmonary fibrotic disorders also report less dyspnoea and improvement in well-being after a short trial of prednisone or methylprednisolone. In both situations, the subjective amelioration of symptoms is not correlated with pulmonary function or arterial blood gas improvements. Based on the present results, we believe that these reports may probably be the expression of a non-specific action of steroids on the CNS leading to mood elevation and euphoria despite unchanged dyspnoea perception and pulmonary status (5). However, it is worth to emphasize that this study did not evaluate the chronic or the multidose effects of steroids on dyspnoea sensation. The administration of prednisone on higher doses or for longer periods of time might have yielded different results.

In conclusion, although steroids may certainly improve respiratory conditions due to their anti-inflammatory actions, doctors should be aware that the available evidence does not support any specific beneficial effect of these drugs on the perception of dyspnoea itself.

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REFERENCES