

## EDITORIAL

# Does corticosteroid treatment affect the respiratory muscles?

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Atrophy and myopathy of skeletal muscles are well-known side-effects of systemically-administered corticosteroids. As recently summarized in the journal [1], animal studies and clinical observations have shown that the respiratory muscles may be involved in this process. Administration of systemic corticosteroids in animals resulted in reduction in diaphragm weight in proportion to reductions in total body and peripheral limb muscle weight [2-8]. Twitch and tetanic forces per unit cross-sectional area were the same or reduced compared to control animals. Histochemical analysis of the diaphragm showed selective type IIb fibre atrophy [3].

In the above-mentioned studies, however, short courses of supratherapeutic doses of corticosteroids were used. Therefore, it appears that in these investigations acute steroid-induced atrophy and rhabdomyolysis were studied, rather than chronic steroid myopathy. Prednisolone, in a dose of 5 mg·kg<sup>-1</sup> daily *i.m.*, administered for four weeks, appeared to produce another pattern of alterations in rat diaphragm [9, 10]. Body weight loss and fibre atrophy did not occur, but maximal tetanic tension tended to decrease. Histological examination showed myogenic changes in the diaphragm. These subtle myopathic changes are likely to occur more often in clinical practice.

Clear information on the effects of treatment with systemic steroids on respiratory muscle function in patients with asthma or chronic obstructive pulmonary disease (COPD) is not yet available. In a group of 34 asthmatic steroid-dependent patients, no correlation was found between the mean dose of steroids in the last 8 yrs and respiratory and peripheral muscle strength [11]. These, however, were out-patients on continuous treatment with low doses, and the effects of repetitive bursts of steroids, which may be more harmful, were not investigated. In a recent report, two patients with asthma and one with COPD were described with reduced respiratory and peripheral muscle strength, during prolonged treatment with high doses of methylprednisolone [12]. Tapering of the dose was followed by an increase in respiratory and peripheral muscle strength, after three to six months. In another study, eight out of 21 consecutive patients, who were admitted to hospital with acute exacerbations of COPD or asthma, suffered from generalized muscle weakness [13]. In seven of these eight patients the

average daily dose of methylprednisolone during the last six months exceeded 4 mg, while this was the case in only three of the 13 patients with normal muscle strength. This observation suggests that steroid treatment and muscle strength are interrelated.

Since myopathy is known to occur in 20-65% of patients treated with steroids [14], this high incidence of generalized muscle weakness in COPD patients under steroid treatment is not surprising. Concomitantly, the large range of incidence between different studies [14] discloses that the diagnosis of steroid myopathy may not easily be established. Classically, proximal limb muscle weakness is a prominent feature. Serum levels of muscle enzymes are within normal range, although lactate dehydrogenase (LDH) is occasionally elevated [12]. The urinary excretion of creatine is increased [15]. Electromyographic investigation of the affected muscle groups reveals polyphasic potentials of low amplitude and short duration, decreased superposition of motor units, and discrete denervation signs [15-17]. Occasional biopsies of peripheral muscles revealed type IIb fibre atrophy, without changes in type I and IIa fibres [14]. Since both treatment with systemic corticosteroids and malnutrition often occur in COPD patients, it is important to distinguish their effects on muscle fibre dimensions. In animal studies, malnutrition was shown to cause fibre atrophy of all fibre types [18], or alternatively of type IIa and IIb [19], in contrast to selective type IIb fibre atrophy, which occurs after treatment with fluorinated steroids [3, 10].

Although the magnitude of the contribution of steroids to reduced muscle strength in COPD patients remains unclear, this issue is of great clinical significance. High doses of steroids are often administered to patients in whom respiratory muscle function may already be compromised by the underlying disease. For example, in COPD, respiratory muscle strength may be reduced due to hyperinflation, malnutrition, detraining, and blood gas and electrolyte abnormalities. Any additional drug-induced reduction of respiratory muscle force may cause respiratory failure or weaning problems. Moreover, it is suggested that recovery from steroid-induced acute atrophy may take six months or even more [20, 21]. The same duration until recovery was complete has been observed in chronic steroid myopathy [12]. It may be hypothesized that repetitive high doses of steroids, given in the period that recovery is still incomplete, may have even more detrimental effects on respiratory muscle function than continuously administered low doses. This hypothesis needs further testing.

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If the respiratory muscles are severely weakened, ventilatory failure is expected to occur. In this issue of the journal, the study by NACHÁZEL and PALECEK [22] in rats demonstrated that arterial carbon dioxide tension ( $P_{aCO_2}$ ) at rest was unaltered after administration of hydrocortisone, 60 mg·kg<sup>-1</sup>, for eight days. The response to an increased ventilatory load, however, was clearly diminished in the steroid-treated animals. Although the number of animals was small, and anaesthesia may have influenced the results, this study stresses the possibly deleterious effects of corticosteroids on the ventilatory capacity. These may be even more prominent if the respiratory muscles are already weakened, as in COPD patients.

Future research should be directed towards analysis of the effects of clinically relevant doses of steroids on biochemical and histochemical characteristics, as well as towards the correlation with respiratory muscle performance in animal models. Carefully designed clinical trials may be performed to evaluate the contribution of steroid treatment to reduced respiratory muscle function. Moreover, therapeutic interventions to counteract these side-effects of steroids may be investigated. The protective effects of anabolic steroids are of potential interest [23], as well as the beneficial effects of growth hormone [24].

Clinically, attention should be paid to the possibility that exacerbation of dyspnoea in patients with COPD or interstitial lung disease treated with systemic steroids, may be caused by weakened respiratory muscles, instead of a flare up of the disease. Serial measurements of respiratory (and peripheral) muscle strength and biopsies of peripheral muscles, along with the course of creatinuria, may add to the diagnosis.

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