

EFFECTS OF CORTICOSTEROID TREATMENT ON RESPIRATORY MUSCLES FUNCTION IN PATIENTS WITH SEVERE OBSTRUCTIVE LUNG DISEASE

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Abstract

Glucocorticoids have remodelled the treatment of patients with obstructive lung disease (OLD) because they target inflammation, as they represent one of their pathogenic mechanisms. The current therapeutic indications are asthma and chronic obstructive bronchopulmonary disease (COPD), the severe form and the frequent exacerbation phenotypes, the eosinophilic predominant inflammation subtype. Through knowledge of the possible adverse effects of long acting inhaled corticosteroids, regarding the reduction of long-term respiratory muscle performance, could lead to the development of new therapeutic approaches, meant to increase the survival rate and the quality of life in patients with obstructive pulmonary disease.

Rezumat

Glucocorticoizii au revoluționat tratamentul pacienților cu afecțiuni pulmonare obstructive, aceștia țintind procesul inflamator, ca mecanism principal implicat în patogeneza acestor boli. În prezent, indicațiile terapeutice sunt astmul și bronhopneumopatia obstructivă cronică (BPOC), forma severă și fenotipurile frecvent exacerbate, în special subtipul predominant eozinofilic. Progresul științific privind elucidarea efectelor adverse ale corticosteroizilor inhalatori asupra performanței, pe termen lung, a mușchilor respiratori, ar putea conduce la dezvoltarea unor noi abordări terapeutice cu scopul creșterii ratei de supraviețuire și îmbunătățirii calității vieții la pacienții cu afecțiuni pulmonare obstructive.

Keywords: corticosteroids, asthma, COPD, muscle dysfunction

Introduction

Corticosteroids (CS) have dramatically improved the treatment possibilities for patients with obstructive lung disease, because they target several steps of the central pathogenic mechanism, the inflammation. However, systemic administration of CS limited the therapeutic dose, causing various adverse reactions. To some extent, these limitations have been overpassed by the introduction of inhaled CS that have a significantly lower absorption rate. The initial enthusiasm for this new route of medication delivery allowed the long term treatment (years), without severe adverse drug reactions in the vast majority of patients. Inhaled CS are currently recommended for the long term control of asthma and for the frequent exacerbated phenotype of patients with severe chronic obstructive bronchopulmonary disease (COPD). During exacerbation, the ventilation is significantly reduced and the effective CS distribution in the respiratory airways diminishes; therefore, in the

severe exacerbations of the obstructive lung diseases (asthma, COPD), systemic corticotherapy is frequently associated, increasing the burden of CS treatment in these patients. The adverse drug reactions are minimal for a daily dose of 30 mg of prednisone (or equivalent), for 2 weeks, and this dose is considered safe for the CS, no matter the origin of the underlying disease [1]. Recent research highlights the cortisone-induced myopathy (CIM) that becomes evident even after high doses of inhalatory CS, particularly fluorinated and reinforces the importance of clinical evaluation of the CIM risk [2-4]. Our article discusses the implications of the CS treatment in OLD (obstructive lung disease), in which pathophysiological myopathy modifications are already induced by the chronic respiratory disease.

Physiopathological modifications of the respiratory muscles in OLD

Although impairment of the respiratory muscle fibres is a rather early event in the evolution of COPD (stage I or II) [3, 4], the contraction force of the diaphragm is maintained at normal or even higher level until the advanced stages of the disease [5-7]. To maintain its contraction force, the myosin fibres of the diaphragm require adaptive changes to the permanent overload: the type II fibres transform in the type I fibres, increasing resistance, but reducing their contraction force generation. The calcium ATP-ase of the sarco-plasmic reticulum (SERCA) switches from the rapid functioning isoform to the slow reacting one, delaying the muscle relaxation [8]. The number of mitochondria increases, the capillary bed opens and oxidative enzymes activity is enhanced [9]. As the adaptive processes become permanent, reactive oxidative species increase and glycolysis is impaired, with negative impact on muscle contraction. Loss of muscular mass by more than 18% [10] from lack of utilization and denutrition, enhanced protein catabolism related to turnover modification induced by chronic inflammation status, hypoxia, oxidative stress and mitochondrial dysfunction [11, 12] are common findings in the severe form of COPD. Particularly in exacerbations, the muscle mass becomes a source of amino acids for hepatic gluconeogenesis maintenance [13] or inflammatory cytokines secretion. The atrogenes, a set of genes that are commonly induced during severe exacerbations, are very active and their products (atrogin-1, muscle ring-finger-1 (MuRF-1) maintain the atrophy inducing transcription factor, forkhead transcription factors 1 (FoxO-1) and 3 (FoxO-3) at elevated levels even after the clinical critical phases have been overpassed [14].

In COPD, the maximal contraction force of the respiratory muscles is reduced. The contractile system impairment is substantiated by the reduction of the velocity and number of myosin-actin cross-bridges formation [3] and the alterations in the Ca^{2+} -myosin binding [15]. The pronounced reduction of the inspiratory muscles force with severe hypercapnia is an important cause of mortality in COPD.

Corticosteroid action on respiratory muscles

CIM is characterized by a global muscle mass reduction based on a favoured protein catabolism and a functional impairment of the mitochondria together with electrolytic and membrane excitability modifications. Muscle cells regeneration rate is significantly slowed down. However, rhabdomyolysis, the acute form of CIM, is rare. More often, CS induce a chronic proximal myopathy of the lower limbs, with mild or moderate increase of serum creatine kinase or troponins. Similar to the

COPD related myopathy, type II fibres are preferentially lost and MuRF-1 is upregulated, increasing the degradation of the myosin chains [16, 17]. In most cases, the symptoms are reversible after 4-6 weeks of CS withdrawal. Even in healthy subjects, 4 mg *per os* dexamethasone administration for only 4 days lowered the testosterone level, the transcription factors related to the androgens, and insulin growth factor 1 (IGF1) in muscle tissue [18]. Decreased muscle proteins turnover was reflected in a low plasma level of myoglobin and creatin kinase (CK). These findings raised the hypothesis of a subclinical modification of the muscle cells, before clinical signs of muscular force reduction and fatigue could be objectivized.

After long term inhalatory therapy, for more than 1 year, reduction in muscle force has been reported [19]. CS have a complex influence on the metabolic equilibrium of muscle cells. On one side, CS reduce inflammatory cytokines, particularly the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and the protein activator 1 (AP-1) in a very efficient dose response relation. As these cytokines have mainly catabolic effects, CS promote anabolism. On the other side, anabolic stimuli of the muscle cell (IGF1, insulin and testosterone) are negatively influenced by CS treatment. This is supported by the impairment of the glucose test in COPD patients treated with inhalatory budesonide after only 8 weeks of treatment [20]. Another pro-atrophic mechanism of CS is the inhibition of the growth and differentiation factors of satellite cells to adult muscle cells, myostatin and myogenin, [21] and the upregulation of the atrogenes. Deconditioning muscle atrophy responds to a combination of exercises and amino acid administration by increasing IGF1 [22-24] and it could also benefit from antioxidant treatment [25]. No conclusive data is available regarding CIM prevention through similar therapeutical approach. The issue is particularly important in the advanced stages of COPD, as the reduction of muscle mass is part of the cachectic syndrome.

The intensive care unit acute weakness and the long term muscular impairment in 183 survivors of acute lung injury was associated with the mean daily dose of corticosteroid [26] and reported also in several incidental cases [27].

A 444 randomized trial of COPD patients supports the current recommendation of short term use of oral corticoid therapy [28]. The studies underlined that long term corticoid administration deteriorates the life prognosis from reduction of the strengths of the respiratory muscles. The muscle mitochondrial dysfunction was also confirmed in other clinical smaller descriptive studies in a dose relation [29].

Nevertheless, corticoid therapy remains a benefit in short term administration.

Conclusions

The CS therapy impact on respiratory muscles is still a debated subject; there is definitely a need for further evaluation and a better definition of patients at myopathy risk. In both asthma and COPD, the CS indication remains firm for patients with a predominant eosinophilic inflammation, with an increased sputum and blood eosinophils and high IgE levels. Between CIM and natural evolution of COPD there are many pathophysiological interferences: the reduction of the number of type II fibres, the atrogens activation, the predominant catabolic processes, impairment of the energy metabolism. A clarification concerning their additive or synergic action, if any, is necessary, as current reported results of the CS trails in OLD have not answered to this particular question. Identification of new molecules that have only transrepression action and lack transcription actions have been proposed [12, 29] as a solution to obtain the anti-inflammatory action, without a direct interference of metabolic pathways. Enriching the knowledge of the CS effects on respiratory muscle performance could lead to new directions of pharmacological and/or non-pharmacological therapies (pulmonary rehabilitation, nutrition support, etc.) to increase survival of patients with OLD.

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