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Ward of Pulmonary Diseases and Phthisiology
Independent Public Hospital named after John of God in Lublin
Department and Clinic of Internal Diseases, Skubiszewski Medical University of Lublin

ADAM PODSTAWKA, JERZY MOSIEWICZ, WOJCIECH MYŚLIŃSKI

Contemporary opinions on administration of inhaled glucocorticosteroids in the treatment of chronic obstructive pulmonary disease

According to the contemporary definition, the characteristic feature of chronic obstructive pulmonary disease (COPD) is irreversible or not fully reversible limitation of bronchial airflow. This limitation is usually progressive and results from incorrect, inflammatory response of the lungs to noxious particles or gases. COPD is becoming one of the main causes of morbidity and mortality in the whole world. The crucial etiopathological factor of COPD is tobacco smoking. However, this addiction is not the only cause, as not all smokers develop the clinical manifestation of the disease. Other factors, environmental and genetic (e.g. α_1-antitrypsin deficiency) may play an important role in it (8).

Chronic inflammatory process, proteinase-antiproteinase imbalance and oxidative stress, are the reasons for destruction of pulmonary parenchyma, leading to emphysema and irreversible changes within small airways.

The pathogenesis of inflammation in COPD has not been fully understood. It is known that the crucial role in initiating and sustaining the inflammatory process within the airway walls, as well as in the pulmonary parenchyma and pulmonary vessels is played by macrophages, CD8 lymphocytes and neutrophils. Macrophages are cells coordinating the inflammatory response, because they secrete the mediators which intensify neutrophilic inflammation, such as tumor necrosis factor (TNF-α), interleukin 8 (IL-8), and leucotriene B_4 (LTB_4). The patients with COPD revealed an increased number of macrophages in large and small airways, as well as in the lung parenchyma, whereas CD8 lymphocytes, found in the largest number in the bioptates of bronchial mucosa and the lung parenchyma, are responsible for the persistence of inflammation. They release perforins, granzyme-B and TNF-α, which cause cytolysis and apoptosis of alveolar epithelial cells. Active neutrophils, secreting numerous proteinases, including neutrophil elastase (NE), cathepsin G and proteinase 3 contribute to the parenchymal destruction and mucus hypersecretion. The presence of neutrophils is mainly found in sputum and broncho-alveolar lavage (BAL), and also in tobacco smokers who do not suffer from COPD. It is also a well-known fact that tobacco smoke stimulates macrophages and epithelial cells to produce TNF-α, which, through the activation of the nuclear transcription factor κB (NF-κB), intensifies the gene expression for IL-8, responsible for neutrophil recruitment and activation. In COPD patients IL-8 is present at high concentrations in induced sputum and broncho-alveolar lavage, and thus it can serve as a marker of the inflammatory response intensification. The increased oxidative stress, observed in COPD, intensifies the inflammatory reaction (NF-κB activation) and disturbs proteinase-

antiproteinase balance, activates matrix metaloproteinases (MMP), inactivates α_1-antitrypsin and the secretory leucoproteinase inhibitor (SLPI). The role of eosinophils in COPD is uncertain, however, their number increases in airways during disease exacerbation periods. The respiratory epithelial cells release numerous inflammatory mediators, and in patients with COPD they reveal increased E-selectin expression, involved in neutrophil recruitment and adhesion (8).

So far, despite intense studies, no methods of COPD treatment have been worked out, which could reverse or inhibit the progression of this disease. However, there exist a wide range of medicines decreasing its symptoms and improving patients' life comfort. Valuable drugs, used in obstructive pulmonary disease, though not deprived of many side-effects, include glucocorticoids, administered orally, parenterally, and recently also inhaled. The results of randomized studies that have been conducted in the recent years, have strengthened the position of inhaled glucocorticosteroid in COPD treatment. Although these drugs do not decrease the rate of the decline of pulmonary function, in severe forms of the disease they markedly limit the number of exacerbations, improve the quality of life and reduce mortality.

Glucocoricosteroids belong to the most effective anti-inflammatory medicines with multidirectional influence on human immune system. The biological effect of their action depends on the connection with the cytoplasmatic glucocorticoid receptor (GR). The GR-glucocorticoid complex inhibits the activation of transcription factors, or passes directly to the cellular nucleus, activating the transcription of appropriate genes (GRE – glucosteroid response elements). Glucocorticosteroids inhibit the inflammatory process by increasing the production of anti-inflammatory proteins: lipocortin-1 (A_2 phospholipase inhibitor), antagonist of the receptor for IL-1, secretory leucoproteinase inhibitor (SLPI), neutral endopeptidase, immunomodulatory protein CC-10, inhibitor NF-κB, anti-inflammatory IL-10. They inhibit the activation of NF-κB and of the activating protein (AP-1), transcription of many cytokines (IL-1, -3, -4, -5, -6, -9, -11, -13, -16, -18, TNF-α, granulocyte-macrophage colony stimulating factor – GM-CSF, stem cell factor – SCF) and chemokines (IL-8, Regulated on Activation, Normal T cell Expressed and Secreted – RANTES, macrophage inflammatory protein-1α – MIP-1α, macrophage chemotactic protein-1 – MCP-1, MCP-3, MCP-4, eotaxin). They also inhibit the transcription of enzymes (cyclooxygenase 2 – COX-2, cytoplasmic phospholipase A_2 – $cPLA_2$, inducible nitric oxide synthase – iNOS) and the expression of adhesion molecules ICAM-1, E-selectin, as well as the inflammatory receptors NK_1 and NK_2. Besides, they induce eosinophil and T-lymphocyte apoptosis. Glucocorticosteroids increase the expression of receptors for β_2-agonists and prevent their down-regulation (1).

The effect of glucocorticosteroids on the survival time of the patients with COPD, their vital activity and intensification degree of inflammatory changes is still controversial. However, we know that they do not inhibit neutrophil inflammation. Some studies suggest that large doses of inhaled corticosteroid may reduce the number and activity of neutrophils, cytokine production and the concentration of proteases in induced sputum. Others do not confirm this fact. However, differences in the results of these studies may be the effect of the manner of patient selection, length of treatment and of the administered dose (2). Nevertheless, there seems to exist an unknown molecular mechanism of resistance to glucocorticosteroids in the airways in COPD patients. It is suspected that such a resistance effect is revealed by tobacco smoke, inhibiting histone deacetylase in alveolar macrophages, which increases cytokine expression and inhibits the anti-inflammatory effect of glucocorticosteroids (9).

It is worth stressing that inflammation in bronchial asthma significantly differs from inflammation in COPD. The most frequent causative factor of asthma is an allergen, mastocytes are activated, inflammation occurs as a result of eosinophil and Th_2 CD4 lymphocyte activation and glucocortico--steroids inhibit the inflammatory process very effectively. However, in as many as 10% of patients COPD coexists with bronchial asthma. Obviously, in this group of patients glucocorticosteroids are much more effective than in the "pure" population of patients with COPD.

The breakthrough in COPD treatment with inhaled glucocrticosteroid occurred in the year 2000, when the results of a long-term study ISOLDE (The Inhaled Steroids in Obstructive Lung Diseases in Europe) were published. The study revealed that fluticasone treatment in the dose of 2 x 500 μg/day of the COPD patients with forced expiratory volume in one second (FEV_1) of 50% of the predicted value reduced the annual frequency of exacerbations by 25%, as compared to placebo. The deterioration of the quality of life was also slower. Like in previous studies, it was found that inhaled glucocorticosteroids do not inhibit the progression of disease, because, in comparison to placebo, they do not influence the rate of annual FEV_1 decline (3). However COPD exacerbations may accelerate the decrease of lung function, which is suggested by one of the British studies (6). It revealed larger FEV_1 decline in patients with more frequent exacerbations (more than 3 per year), as compared to patients with less frequent exacerbations. Thus, the administration of inhaled glucocorticoid, reducing the number of exacerbations may indirectly decrease the rate of FEV_1 decline.

In the TRISTAN study (TRial of Inhaled STeroids ANd long-acting β_2-agonist), by means of double blind test controlled by placebo, the researchers evaluated the effects of simultaneous administration of the long-acting β_2-agonist – salmeterol, and a glucocorticoid – fluticasone through inhalation in the group of 1,465 patients suffering from COPD. Their FEV_1 level before the administration of a bronchodilatator was 25–70% of the predicted value, FEV_1 increased by less than 10% 30 minutes after inhalation of 400 μg of salbutamol. Their FEV_1/FVC rate before the bronchodilatator administration was less or equal to 70%. The history indicated the presence of the chronic bronchitis symptoms for at least 10 years, tobacco smoking intensity – 10 pack-years (equivalent of 20 cigarettes smoked daily for 10 years), at least one episode of acute COPD exacerbation a year in the previous 3 years, as well as at least one exacerbation requiring treatment with oral glucocor--ticosteroids and/or antibiotics in the year that preceded the commencement of the study. Patients with diseases other than COPD were not included in the study, as well as those requiring regular oxygen therapy, those being given systemic glucosteroids, or large doses of inhaled glucocorticosteroid (more than 1000 μg of beclometasone, budesonide, flunisolide, or more than 500 μg fluticasone a day), or antibiotics during 4 weeks preceding the 2-week introductory period (4).

This study revealed that the administration of salmeterol (2 x 50 μg/day) together with fluticasone (2 x 500 μg/day) for the period of 12 months causes decrease in frequency of all COPD exacerbations by 25%, and as far as the exacerbations requiring the administration of oral glucocorticosteroids are concerned – by as much as 39%, as compared to placebo. In patients with FEV_1 below 50% of the predicted value, the number of exacerbations decreased by 30%, whereas in patients with FEV_1 above 50% this reduction was only 10%, as compared to placebo. Such a combined treatment significantly improved the FEV_1 value, measured before the administration of subsequent dose of the drug, as well as after bronchodilatator administration. Reduction of dyspnea, decrease of the use relief medication and a smaller number of night-time awakenings were also observed. The quality of life, evaluated according to SGRQ (St. George's Respiratory Questionnaire) significantly improved, which manifested itself through the decrease of the intensification of symptoms reported by the patients (before and after-effort dyspnea, larger effort intolerance) by 4 points (4).

Also associated treatment with formeterol and budesonide in COPD patients with FEV_1 below 50% of the predicted value reduced the frequency of severe exacerbations by 24%, as compared to placebo and by 23%, as compared to formeterol. Such a treatment resulted in the increase of FEV_1 by 15%, as compared to placebo and by 9% as compared to the treatment with budesonide. The decrease of disease symptoms intensity, evaluated in a point scale, limitation of the necessity of immediate administration of short-action β_2-agonits, as well as favorable influence on the quality of life were also observed (20).

Soriano et al. demonstrated that the administration of inhaled glucocorticosteroid in the post-hospital period in patients with severe COPD reduces the risk of death or rehospitalization by 16%, and in connection with a long-acting β_2-agonists by as much as 41% (18).

The ultimate explanation of the significance of associated treatment of COPD patients is to be accomplished by the present TORCH study (Towards a Revolution in COPD Health), evaluating the long-term effects of fluticasone and salmeterol on survival time. The study is to be finished in the year 2006.

According to the instructions of GOLD of the year 2003 (Global Initiative for Chronic Obstructive Lung Disease), the chronic treatment with inhaled glucocorticosteroid is indicated in patients with subjective symptoms, where FEV_1 is less than 50% of the predicted value (severe and very severe COPD) and recurrent exacerbations (3 and more within the last 3 years). It was also demonstrated that associated treatment with an inhaled glucocorticosteroid and long-acting β_2-agonists is more effective than using only one of these medicines. At the same time, the latest GOLD report states that long--lasting treatment with inhaled glucocorticosteroids in COPD may be justified only in patients with constant, significant response of FEV_1 to the treatment with these medicines. To achieve this, in a stable period of the disease, glucocorticosteroid reversibility testing should be performed after administration of an inhaled glucosteroid. The FEV_1 value, obtained after administration of a bronchodilatator (e.g. salbutamol 400 μg) is the initial value in respect to which the increase of this variable is calculated after a 6 – 12 week treatment with inhaled steroid (e.g. fluticasone 2 x 500 μg, or budesonide 2 x 600 μg/day, or beclometasone 3 x 500 μg/day). The test is regarded as positive when FEV_1 increases by at least 200 ml and by 15% in respect to the initial value (8).

In the treatment of COPD exacerbations it is recommended to administer oral or intravenous glucocorticosteroids, because they shorten the duration of an exacerbation and cause faster improvement of pulmonary function. Implementation of such a treatment should be considered as a supplement of bronchodilating treatment, if the initial FEV_1 is less than 50% of the predicted value (8). Nevertheless, Maltais et al. demonstrated that the alternative for systemic glucocorticosteroids in the treatment of exacerbations taking their course without respiratory acidosis might be budesonide, administered in nebulization (13).

Inhaled glucocorticosteroids cause much less side-effects than those, which are administered systemically. However, they may cause hoarseness and dysphonia (9.4% in the group taking fluticasone versus 4.3% placebo, according to the ISOLDE study), irritations (11.6% vs 7.3%), as well as candidiasis of throat and oral cavity (11% vs 6.5%) (3). Slight disturbances in cortisol secretion were also observed, however, without clinical features of hypoadrenalism (in no more than 5% of patients in the ISOLDE study) (3). In the EUROSCOP study (15) the increased frequency of skin bruises was described during inhaled steroid therapy (10% in the group taking budesonide, 4% in the group taking placebo).

It was proved that the administration of inhaled glucocorticosteroid is connected with the increased risk of posterior subcapsular and nuclear cataracts. The increase of subcapsular cataracts risk by 27% occurred in inhalatory administration of beclometasone, when the cumulative dose of this medicine was more than 2000 mg (5). However, to explain whether newer inhaled glucocorticosteroid cause the increase of cataracts risk, further prospective studies are required. A relationship was found between the administration of inhaled glucocorticosteroid and the occurrence of increased intraocular pressure and glaucoma in patients with a glaucoma family history. Therefore, in this group of patients carrying out ophthalmologic consultation is recommended (14).

Osteoporosis is one of the most severe undesirable effects of the administration of systemic glucocorticosteroids, because, as a result of this disease more than 25% patients subject to long-term treatment with these medicines suffer from bone fractures (16). It was proved that a cumulative dose exceeding 1000 mg of prednisolon administered many times during the treatment of COPD exacerbations is related to increased frequency of lumbar spine osteoporosis (7). It was also determined that inhaled glucocorticotherapy accelerates the pace of bone mass depletion when large doses of these medicines are administered, as well as when they are used alternately (every other day) (16).

Suissa et al. (19) described the increase of upper limb bone fracture frequency in older patients by 12% at the increase of daily dose by every additional 1000 μg of inhaled glucocorticosteroid in beclometasone equivalent units during 4-year administration of the recommended doses, whereas 8 years of analyses revealed the increase of femoral neck fracture risk as late as during the administration of inhaled glucocorticoid in a daily dose exceeding 2000 μg.

Additional factors increasing the risk of pathological fractures resulting from osteoporosis, connected with COPD patients' population character are: advanced age, low physical activity, tobacco smoking in the past and associated diseases. Therefore, during long-term administration of inhaled glucocorticosteroid to patients with COPD, calcium compounds, vitamin D and bisphosphonates should be administered preventively. To measure the bone mineral density (BMD) and forecast the imminence of fractures, densitometric techniques are applied, whereas to evaluate the bone metabolism activity and bone-formation processes biochemical markers discovered in the recent years can be used. These are: carboxy-terminal propeptide of type 1 procollagen (P1CP), carboxy-terminal cross-linked telopeptide of type 1 collagen (1CTP) and osteocalcin (10).

After long-lasting systemic steroid therapy we can expect post-steroid diabetes syndrome, which results in β-cells depletion, and thus to relative or absolute insulin deficiency, while inhaled glucosteroid administered in large doses may impair glucose and lipid metabolism in healthy patients, as it was demonstrated in one of the studies (12). It revealed that using beclometasone in the daily dose of 2 x 500 μg for 4 weeks causes the increase of glycemia 30 minutes after loading with 75 g glucose to the level of 128 mg% versus 121 mg% placebo, as well as the increase of serum insulin concentration with empty stomach by 36% after the end of treatment. The increase of total cholesterol, HDL cholesterol and lactate concentrations with empty stomach were also observed: (total cholesterol: 178 mg% vs 161 mg%, HDL cholesterol: 45 mg% vs 37 mg%). In another study, in patients with uncontrolled bronchial asthma, large doses of inhaled glucocorticosteroid significantly improved glucose tolerance and decreased insulin resistance in the initial period of treatment (11). In the "Medline" medical database at present there is no literature concerning the influence of inhaled glucocorticosteroid on the development of arterial hypertension, or chronic peptic ulcer disease.

Using nebulizers, turbuhalers and appropriate volume countershafts (spacers) to MDI pressure inhalers decreases systemic absorption of inhaled glucocorticosteroid and limits the occurrence of undesirable effects. However, it seems that the future of inhaled steroid therapy will belong to the agents of even better pharmacokinetics and pharmacodynamics (17).

There are many advocates and adversaries of inhaled glucocorticotherapy in COPD. Its advisability is confirmed by the directions of GOLD of the year 2003, based on the results of clinical and epidemiological studies. Prior to the onset of treatment with inhaled glucocorticosteroid, the severity criterion should be taken into consideration (III and IV degree of the disease), as well as positive results of glucocorticosteroid reversibility testing and the frequency of exacerbations. However, in each case one should think about side-effects, which can be prevented. It also seems that further studies of molecular and cellular mechanisms of COPD pathogenesis should lead to the recognition of more effective methods of treatment that could slow down or stop the progression of the disease.

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SUMMARY

The contemporary medicine is looking for new, more effective methods of treatment for patients suffering from chronic obstructive pulmonary disease (COPD), whose number is systematically increasing. It seems that main challenges involve improving treatment efficiency, preventing exacerbations and inhibiting the progression of the disease. The aim of this paper is to briefly present the contemporary knowledge of the application of inhaled glucocorticosteroid in COPD treatment, their effectiveness and side-effects. According to the present state of knowledge, inhaled glucocorticosteroid do not inhibit the neutrophil inflammation in COPD. However, they significantly restrict the inflammatory response in severe forms of the disease, which, practically, means decrease of exacerbation frequency, life quality improvement and mortality reduction in these patients. Inhaled glucocorticosteroids, just like systemic glucocorticosteroids, do have many side-effects, but they can be effectively prevented.

Współczesne poglądy na zastosowanie glikokortykosteroidów wziewnych w leczeniu przewlekłej obturacyjnej choroby płuc

Współczesna medycyna szuka nowych, skuteczniejszych metod postępowania z chorymi na przewlekłą obturacyjną chorobę płuc (POChP), których liczba systematycznie wzrasta. Wydaje się, że główne wyzwania odnoszą się do podniesienia skuteczności leczenia, zapobiegania zaostrzeniom i hamowania progresji choroby. Celem pracy jest skrótowe przedstawienie współczesnej wiedzy na temat zastosowań glikokortykosteroidów wziewnych w leczeniu POChP, ich skuteczności i działań ubocznych. Według obecnego stanu wiedzy glikokortykosteroidy wziewne nie hamują zapalenia neutrofilowego w POChP, jednak znacznie ograniczają odpowiedź zapalną płuc w ciężkich postaciach choroby, co w praktyce przekłada się na zmniejszenie częstości zaostrzeń, poprawę jakości życia i redukcję śmiertelności u chorych. Glikokortykosteroidy wziewne, podobnie jak systemowe, nie są pozbawione wielu działań niepożądanych, których wystąpieniu można skutecznie zapobiegać.