



STEROID RAGE: HAZARDS AND EFFECTS

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In the last issue we discussed the different types of inhaled corticosteroids available on the market. This issue will focus on how corticosteroids work, how they help, and side effects by their use. The focus will be towards inhaled corticosteroids, however, systemic corticosteroids will be discussed pointing out major differences.

Pharmacology of Corticosteroids

The inflammatory process can be reduced or blocked by the antiinflammatory effects of glucocorticoids. The beneficial effect of glucocorticoids in asthma and other diseases of inflammation is due to their ability to inhibit the activity of inflammatory cells and mediators of inflammation.

Mode of Action

Glucocorticoids are highly lipophilic and enter airway cells to bind to intracellular receptors. Steroids suppress a local or systemic inflammatory response by at least three general actions. In general, steroids diffuse into the cell and bind to a glucocorticoid receptor. Before binding by a steroid, the glucocorticoid receptor is in an inactive state and is bound to a protein complex termed heat shock protein 90 (hsp90), which prevents the unoccupied receptor from translocating to the nucleus of the cell. When the steroid binds to the receptor, the hsp90 dissociates, and the steroid-receptor complex then translocates to the cell nucleus. The general result of these actions is to induce gene expression for antiinflammatory proteins and receptors and to suppress gene expression for proinflammatory proteins. Overall, glucocorticoids inhibit the cytokine production responsible for recruitment and migration of inflammatory cells such as eosinophils and lymphocytes into the airway.

Glucocorticoids inhibit many of the cells involved in airway inflammation, including macrophages, T lymphocytes, eosinophils, and mast cells in the bronchial airway epithelium and submucosa, and reverse the shedding of epithelial cells and goblet cell hyperplasia seen in asthma. By decreasing cytokine-mediated survival of eosinophils, apoptosis of eosinophils occurs, reducing the number of eosinophils in the circulation and in the airway of subjects with asthma. Glucocorticoids also reduce the number of mast cells within the airways; mast cells are sources of histamine and other mediators of inflammation, and inhibit plasma exudation as well as mucus secretion in inflamed airways.

Effect on White Blood Cell Count

Leukocytes, such as monocytes, macrophages, neutrophils, and basophils, are also essential to the inflammatory response and are attracted to an area of injury by the chemotactic factors identified among the mediators of inflammation. Neutrophils usually adhere to the capillary endothelium of storage sites in the lung. Glucocorticoids cause depletion of these stores and reduce their accumulation at inflammatory sites and in exudates. This is termed demargination, and can increase the number of neutrophils in circulation as the cells leave their storage sites. An overall increase in the white cell count can then be seen in patients receiving glucocorticoids.

Effect on Beta Receptors

Beta-Adrenergic agents are among the most potent inhibitors of mast cell release, yet the asthmatic in an acute episode may be unresponsive to these drugs. A very beneficial effect of glucocorticoids is their ability to restore responsiveness to beta-adrenergic stimulation. This effect can be seen within 1 to 4 hours after intravenous administration of glucocorticoids and is the rationale for administering a bolus of steroid in status asthmaticus as part of acute treatment. Even though steroid action is slow, the sooner they are given, the sooner the asthmatic will begin to respond to beta-adrenergic drugs, and supported ventilation may be avoided. Glucocorticoids enhance beta-receptor stimulation by increasing the number and availability of beta receptors on the cell surfaces and by increasing affinity of the receptor for beta agonists.

Systemic Administration of Steroids

The complicating side effects of systemic steroid treatment are well known and provide the motivation to switch to aerosolized, inhaled steroids when possible. These complications arise from the physiological effects of steroids on the body. These physiological effects are often exaggerated with systemic drug therapy, because potency and plasma levels are higher than with the body's own steroids. A list of side effects are below:

- Suppression of the HPA axis by exogenous steroids may occur, causing inhibition of ACTH release and cortisol secretion from the adrenal gland. The length of time to recover from this suppression varies with patient, dose, and duration of treatment.
- With sufficient dose and duration, immunosuppression can be caused by systemic use of steroids. This can lead to increased susceptibility to infection by bacterial, viral, or fungal agents.
- Psychiatric reactions can occur, including insomnia, mood changes, and bipolar or schizophrenic psychoses.

Glucocorticoids restore responsiveness to beta-adrenergic stimulation - the rationale for administering a bolus of steroid in acute status asthmaticus



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- Cataract formation has been noted, and, rarely, intraocular pressure may increase with systemic steroid therapy.
- Myopathy of striated skeletal muscle can occur.
- Steroid-induced osteoporosis is debated, but is thought to be a limitation of extended steroid therapy. Aseptic necrosis of the bone is also caused by steroid therapy.
- Peptic ulcer is thought to be a complication of steroid therapy, but evidence for this is debated. Patients may often be receiving other ulcerogenic medications such as aspirin or nonsteroidal antiinflammatory drugs (NSAIDs).
- Fluid retention can occur as a result of the sodium-sparing effects of glucocorticoids, giving a puffy appearance.
- Hypertension may accompany the fluid retention or be aggravated by it.
- Corticosteroids given systemically can increase the white blood cell count, with an increase in neutrophils and a decrease in lymphocytes and eosinophils.
- Dermatological changes can occur with steroid therapy, including a redistribution of subcutaneous fat causing the cushingoid appearance of central obesity, hump back, and moon face.
- Growth of children can be slowed by prolonged systemic therapy, because corticosteroids retard bone growth and epiphyseal maturation.
- Corticosteroids lead to gluconeogenesis and antagonize glucose uptake, causing hyperglycemia. This can lead to reversible steroid-induced diabetes.

Systemic Side Effects With Aerosol Administration

The rationale for the introduction of inhaled aerosol steroids was to eliminate or reduce the side effects seen with systemic therapy. Although the aerosol steroids are administered in low doses because of their high topical activity, local side effects may occur and certain systemic side effects are also a concern. Some side effects may occur with transfer from oral therapy to the inhaled route. Three systemic effects of concern with inhaled steroids have been HPA suppression, loss of bone density, and growth restriction in children. A review and brief comment on possible systemic side effects with inhaled steroids is below:

- Adrenal insufficiency may occur after transfer from systemic to inhaled aerosol steroids. Weaning from systemic steroids to allow recovery of adrenal cortex and HPA function and careful monitoring of pulmonary function can help control this problem.
- There may be a recurrence of allergic inflammation in other organs, such as nasal polyps or atopic dermatitis, after cessation of systemic steroids.
- Acute severe episodes of asthma may occur after withdrawal from oral steroids and transfer to inhaled forms. Aerosolized steroids may not be adequate to control asthma, especially during periods of stress, and short courses of oral drug may be necessary.
- Suppression of HPA function is nonexistent or low at small doses of inhaled aerosol steroids and increases with higher doses.
- Questions have been raised about the effect of inhaled steroids on growth when used in prepubertal children. Several studies have shown that corticosteroids have an effect on growth, while others have found no connection. The benefits of inhaled corticosteroids in the treatment of asthma outweigh the possible consequence of growth reduction.
- No data have demonstrated clearly the effect of inhaled glucocorticoids on bone density and osteoporosis in asthma. However, Israel and others discovered that the higher the dose of inhaled corticosteroid, the greater the effect on bone density seen in premenopausal, asthmatic women.
- In summary, it is logical that the risks of steroid-induced adverse effects are lower with the relatively low doses of inhaled steroids compared with systemic administration.

Topical (Local) Side Effects With Aerosol Administration

Two of the most common side effects caused by topical application of inhaled steroids in the respiratory tract are oropharyngeal candidiasis (oral thrush) and dysphonia. Oropharyngeal fungal infections: Infections with *Candida albicans* or *Aspergillus niger* may occur in the mouth, pharynx, or larynx with aerosolized steroid treatment. Some form of this may be seen in up to one-third of patients taking the aerosol formulations, but such an infection responds to topical antifungal agents and seems to diminish with continued aerosol steroid use. Occurrence and severity are dose related and are more likely in patients who are also taking oral steroids. The use of a spacer device and gargling after treatment can reduce oropharyngeal deposition of the steroid and the incidence or severity of such infections. The use of Alvesco (ciclesonide), a pro-drug can reduce oral side-effects due to the pharmacological properties of the agents.

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