



STERIOD RAGE: USING AEROSOLIZED STEROIDS FOR ASTHMA TREATMENT

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In the last two issues, we discussed the different types of inhaled corticosteroids available, and hazards and effect of agents. This issue will focus on where and when corticosteroids can be used in clinical practice. The focus will be toward inhaled corticosteroids in the use of asthma and chronic obstructive pulmonary disease.

Corticosteroids are used for a wide variety of conditions with the therapeutic goal of reducing inflammation. These applications include clinical conditions such as contact dermatitis, rheumatoid arthritis and systemic lupus erythematosus (SLE), as well as asthma and COPD. They are created as topical cream applications and oral, parenteral and inhaled formulations.

Clinical use in asthma

The 200 Global Initiative for Asthma and the 2007 National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP EPR-3): Guidelines for the Diagnosis and Management of Asthma identify corticosteroids as long-term control agents rather than quick-relief agents.

Corticosteroids have traditionally been used in asthma by the oral route for maintenance therapy of severe asthma, and by the oral or intravenous route for treatment of status asthmaticus, as well as by inhalation for maintenance of asthma control. However, the increased emphasis on asthma as a disease of inflammation leading to bronchial hyperresponsiveness has shifted the use of inhaled aerosol steroids from second-line or third-line therapy to first-line, primary therapy.

The following bullets offer a summary of the pharmacological management of asthma based on the NAEPP EPR-3. The fol-

lowing summarizes the principles of corticosteroid use in asthma, based on those guidelines.

Bronchial hyperresponsiveness is characteristic of asthma and is related to the degree of airway inflammation.

- The basic pathology of asthma, previously emphasizing bronchospasm, is now understood to be a chronic inflammatory disorder of the airways resulting from a complex interaction among inflammatory cells, mediators and airway tissue. The phrase "chronic desquamating eosinophilic bronchitis" has been used to describe asthma.

- Inhaled corticosteroids are considered to be the most effective long-term therapy for mild, moderate or severe persistent asthma, and they are well tolerated and safe at recommended dosages.

- Starting inhaled steroids at a high enough dose to be effective and then reducing the dose may be needed. Alternatively, a short course of systemic corticosteroids can be used to gain control of symptoms followed by a step-down in therapy. Loss of patient confidence and compliance with prescribed use of inhaled corticosteroids may be avoided in this way, especially because steroids do not give an immediate effect as a bronchodilator does. Any reduction in pharmacological management should be monitored by symptoms, continuous need for β_2 agonists and peak flow rates.

- An increase in dose of inhaled steroids such as doubling of the current dose, if peak expiratory flow rates decline 25 percent to 30 percent, may avoid the need for oral steroids.

- If asthma is not controlled by inhaled steroids and other types of drug therapy, a short burst of oral steroids may be required to regain control of the asthma and to help clear the airways.

Early use in asthma

There is evidence that the addition of an inhaled corticosteroid to first-line β -agonist maintenance treatment of asthma reduces morbidity and airway hyperresponsiveness. It has been demonstrated in studies that subjects with mild asthma maintained on inhaled budesonide (1200 $\mu\text{g}/\text{day}$ for two years, and then 400 $\mu\text{g}/\text{day}$) had decreased bronchial response to histamine challenge compared with subjects taking inhaled terbutaline (375 μg twice daily), over a 2-year period.

Perhaps the most significant finding was that the later addition of inhaled budesonide after use of a β_2 agonist was not able

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to give as high a level of bronchoprotection as achieved by subjects who had started with and continued taking an inhaled steroid. This suggests that irreversible changes had occurred during the 2 years of β_2 -agonist therapy and supports earlier use of inhaled steroids. A meta-analysis reported that inhaled corticosteroids are best in treating asthma when kept to a therapeutic range of 400 $\mu\text{g}/\text{day}$.

Although inhaled corticosteroids are first-line anti-inflammatory agents and acceptable for primary therapy of moderate asthma in children, the antiasthmatic prophylactic agents cromolyn sodium, nedocromil sodium, and leukotriene modifiers may be used as an initial choice for long-term control therapy in mild persistent asthma (step 2 therapy) with children, because these medications have excellent safety profiles.

Acute severe asthma

Inhaled corticosteroids have not been considered useful for treatment of acute severe asthma episodes. In fact, drug labeling contraindicates this use because there is no bronchodilator effect. In addition, the dose of inhaled steroids is low compared with oral administration.

However, one study examined the addition of high, cumulative doses of inhaled flunisolide added to albuterol in emergency room treatment of acute adult asthma. Both drugs were given by MDI with a spacer. Flunisolide was given as four puffs (250 $\mu\text{g}/\text{actuation}$) every 10 minutes. Their protocol allowed three hours of this treatment with a cumulative dose of 6 mg of flunisolide each hour, and equally aggressive albuterol dosing.

The use of flunisolide resulted in better lung function at 90 minutes and afterward compared with the use of albuterol alone. Although preliminary, these results suggest that the contraindication to the use of inhaled corticosteroids for treating acute severe asthma may need to be reconsidered.

Other considerations for inhaled corticosteroid use

Other considerations in the clinical application of inhaled corticosteroids are as follows:

- High-dose inhaled steroids can be tried in cases of severe persistent asthma to replace or reduce oral corticosteroid dependence. High doses of inhaled steroids are two to four times the usual recommended dose. Oral steroid therapy can be reduced slowly while monitoring the patient's pulmonary function.
- Although more control may be achieved with high doses of inhaled steroids, side effects, including systemic effects, are also likely to increase with inhaled doses above 1 mg/day. However, if oral steroids can be replaced or even reduced, this can be an overall improvement in the risk-to-benefit ratio.
- MDI-formulated corticosteroids should be administered for oral inhalation using a reservoir device (preferably a holding chamber rather than a spacer) and all formulations should include mouth rinsing, to reduce the risk of oropharyngeal candidiasis or other fungal infections and to reduce systemic absorption from swallowed drug.
- Use of a long-acting β_2 agonist such as salmeterol in subjects with inadequate symptom control who are already receiving low to moderate doses of inhaled corticosteroids may prevent the need to increase the inhaled corticosteroid dose.
- The use of long-term β_2 agonist with corticosteroid use can improve lung function.

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• Compliance with prescribed steroid therapy by inhalation appears to be poor and can be a complicating factor in the management of asthma and COPD. The ability to reduce agents or move to once-a-day dosing may be of benefit.

COPD

The use of steroids in COPD is recognized as having potential action in relieving symptoms, and exacerbations, but has little to no effect on FEV1. The use of corticosteroids is described in the American Thoracic Society guidelines, as well as in the GOLD guidelines.

COPD is characterized by a different pattern of inflammatory cells than is seen in asthma. Whereas eosinophils predominate in asthma, neutrophils are mostly seen in COPD. Oral and inhaled corticosteroids do not influence the inflammatory changes driven by neutrophils.

Studies that are available demonstrate that corticosteroid use in COPD reduces exacerbations, symptoms, and even mortality, but has little effect on pulmonary function results. However, other studies have found that inhaled corticosteroids may slow the decline of FEV1.

In acute exacerbations of COPD, oral or parenteral steroids are often given. Short-term corticosteroid therapy has shown benefit in hospitalized patients. Patient with stable COPD should not be given systemic corticosteroids.

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