

Louisiana Drug Utilization Review (LADUR) Education

Risks Associated With Inhaled Corticosteroid Therapy

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The Role of the Peak Flow Meter in the Management of Asthma

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Note: This is a two-part article

Issues in "Risks Associated With Inhaled Corticosteroid Therapy"

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- Generally, ICS provide a high topical potency to reduce lung inflammation with relatively low systemic toxicity.

Issues in "The Role of the Peak Flow Meter in the Management of Asthma"

- ...a peak flow meter has been shown to achieve significant improvements in health outcomes for asthmatics...

Risks Associated With Inhaled Corticosteroid Therapy

All pharmacotherapy is a composite of benefits versus risks. This review primarily evaluates risks associated with the use of inhaled corticosteroids (ICS) in the treatment of asthma. Before beginning this analysis, however, one should remember that ICS are considered a standard of care in asthma therapy and are used routinely for patients with chronic obstructive pulmonary disease (COPD). The 2002 NAEPP Expert Panel Report documents strong evidence that ICS improve long-term outcomes for asthmatic children. In the 2002 review, evidence from randomized clinical trials demonstrated that ICS are associated with fewer hospitalizations, fewer urgent care visits, better symptom scores, fewer oral steroid bursts, and better forced expiratory volume in the first second (FEV1) before and after treatment and that none of the other asthma medications reviewed were as effective in improving reviewed outcomes. Furthermore, ICS are considered first line treatment for mild persistent, moderate persistent, and severe persistent asthma. Generally, ICS provide a high topical potency to reduce lung inflammation with relatively low systemic toxicity. The benefits of pharmacotherapy, however, are always countered by associated risks.

Adverse effects associated with chronic ICS therapy generally are classified into the following areas of concern:

Systemic Effects

- Adrenal Suppression
- Bruising
- Cataracts
- Glaucoma
- Growth Suppression in Children
- Osteoporosis and Fractures
- Thinning of the Skin

Local Effects

- Candidiasis
- Dysphonia

Systemic Effects

Systemic absorption of ICS can be secondary either to oral or pulmonary mechanisms. Generally, the amount absorbed depends on the type of inhaler device, particle size, disposition site, kinetic and physiochemical properties (lipophilicity), and technique of use. Some analogs (fluticasone) are absorbed to a greater extent in patients with severe asthma and reduced lung function compared to budesonide, which is not affected by patient medical status. Most currently available ICS, however, have limited systemic bioavailability due to high rates of first pass metabolism. As a comparison, fluticasone has a first-pass rate of 99% versus oral prednisolone with a rate of 20%. Systemic effects secondary to ICS are influenced by several factors including dosage, type of device employed, patient technique, and characteristics of the individual drug.

Adrenal Suppression

Early dose-response investigations suggested that ICS causes the potential for adrenal suppression. A later observational study of 33 patients linked adrenal crises to patients receiving ICS therapy. This later study indicated that patients seemed to recover after the drug either was reduced or discontinued. Thirty of the 33 patients in this study were taking fluticasone (Flixotide, Flovent), typically for a one to two year duration. More recently, case reports of 17 patients implicate ICS with adrenal crisis. Of this group, 14 patients were receiving fluticasone.

An early systematic review with meta-analysis identified suppression of the hypothalamic axis with ICS. The clinical significance of this effect, however, was questioned.

Growth Suppression in Children

In assessing the clinical effects of ICS, it is helpful to remember that metered-dose inhalers (MDIs) and dry powdered inhalers originally were developed for use in adults. Changing pharmacokinetic-as well as pharmacodynamic-effect as children mature and varying adherence to inhaler device therapy can cloud both

benefits and risks associated with ICS.

Several mechanisms related to glucocorticoid growth suppression in children are postulated. These include inhibition of pituitary growth hormone (GH) secretion, GH receptor expression, insulin-like growth factor-1 (IGF-1) bioactivity, collagen synthesis, and adrenal and androgen production.

A recent retrospective review of 21 asthma patients less than 5 years old analyzed the impact of ICS on growth. Results demonstrated a 3.4% reduction in height percentile in treated children, but this difference did not reach statistical significance.

In a review of randomized, blinded clinical trials, Leone, et al., found that ICS are associated with a slower short-term vertical growth rate in children, but that this effect is small and that adult height attained by asthmatic children treated with ICS is not different from non-asthmatics. Further conclusions indicate that ICS use did not correlate with lower bone density in children. Among adult patients, however, those who take high doses of corticosteroids for many years may experience adverse effects on bone density.

An earlier clinical trial of 241 children comparing beclomethasone and salmeterol found that linear growth in subjects receiving beclomethasone (Beclovent, Ovar, Vanceril) in one arm was significantly reduced when compared to the salmeterol (Serevent) arm. A reduction of ~1.5 cm/year in growth of prepubertal children treated with 400 mcg/day of beclomethasone has been demonstrated in additional studies.

A randomized, parallel group trial of 100 prepubertal children with perennial allergic rhinitis treated with intranasal beclomethasone noted a significant difference in mean standing height between the test subjects (5.0 cm) and the placebo group (5.9 cm). Differences in growth were evident as early as one month after beginning therapy.

Another recent placebo-controlled trial examined the effect of ICS on 654 infants born to women with asthma. Measured endpoints were mean birth size and size for gestational age, and no adverse significant difference was demonstrated in the ICS group versus the placebo group.

Osteoporosis and Fractures

A recent case-controlled analysis of 273,456 asthmatic children aged 5 to 17 years led to the conclusion that ICS use does not materially increase the risk of fracture compared with non-exposed subjects. Evidence suggested, however, that longer term use of ICS in patients with comitant or past oral steroid exposure may slightly increase fracture risk.

A recent one year review of 124,655 Danish patients with documented fractures (hip, spine, forearm) failed to show an association between ICS (except prednisolone) and type of fracture.

A case-controlled review of 16,341 hip fracture patients found a risk of hip fracture associated with ICS use, with an odds ratio of 1.19 to 1.87 compared to controls. Additional case-control investigations found a general dose-response relationship between ICS use and hip fracture and an increase in hip fracture among subjects receiving doses of 700 mcg/day or greater.

Another case-controlled study of nearly 90,000 subjects with asthma or COPD evaluated the risk of nonvertebral fracture associated with ICS exposure. For ICS exposure as a class, or with fluticasone alone, no increased fracture risk was observed and no dose-response effect was noted.

A meta-analysis of 11 trials evaluated the effects of ICS on bone in patients with asthma and COPD. A significant deleterious effect was caused by ICS on bone mineral density of the lumbar spine, and at the hip or femoral neck. The impact of ICS on hip fracture demonstrated an odds-ratio of 1.6 compared to controls. No significance was shown relative to lumbar fracture rates.

The least deleterious bone effect was seen with budesonide (Pulmicort), followed by beclomethasone dipropionate, then triamcinolone (Azmacort, Nasocort).

Skin Thinning/Easy Bruising

The Lung Health Study II--a randomized, multicenter, placebo-controlled trial--evaluated the occurrence of bruising, rashes, slow healing, or other skins lesions in 1,086 COPD patients receiving ICS. An increased risk of bruising and slow healing was demonstrated in those receiving ICS. Rash incidence was less in the ICS cohort versus those receiving placebo. Cutaneous effects were more prominent in older patients in general, with greater risk specifically in elderly females.

Cataracts

A recent case-controlled observational study of 15,479 patients with cataract evaluated whether low doses of ICS are associated with an enhanced risk for cataract formation. Results suggested a significant causal association between cataracts and higher ICS dose, as well as longer duration.

Most data relative to ICS and cataract formation comes from earlier studies. A multicenter, randomized trial of 384 subjects receiving beclomethasone for one year found no increased risk of cataracts. Two similar observational studies of 333 and 485 subjects, respectively, came to similar conclusions.

Garbe's case-controlled analysis of 3,677 subjects found an increased risk of cataract extraction in patients 65 years of age and older. The CAMP Research Group monitored the development of posterior subcapsular cataracts in 311 children receiving BUD over a period of six years and found only one child who developed cataracts. A more recent evaluation of 95 children receiving ICS over 2 +/-1 years found that none of the subjects developed cataracts.

Glaucoma

An earlier case series demonstrated a small risk of glaucoma associated with ICS therapy. A later case control study of approximately 50,000 patients found that prolonged, continuous use of ICS was the only significant risk factor for glaucoma. A recent, small (n=95) cohort study of children demonstrated no glaucoma (or ocular hypertension) associated with ICS over a two year period.

Special Populations--Pregnancy

In a case-controlled investigation, 467 cases were reviewed to determine if an association exists between ICS and risk of pregnancy-induced hypertension or pre-eclampsia. No significant risk increase was determined among those who used ICS during pregnancy.

A significant increase in both end points was noted in those subjects with markers for uncontrolled and severe asthma.

Local Effects

An earlier cohort study evaluated local side-effects of ICS in 639 asthmatic children receiving beclomethasone dipropionate or budesonide. Overall, 63.3% of children less than six years of age and 59.5% of those older than six reported one local adverse effect. Cough (39.7%) was dependent on young age, use of BDP, and primarily use of a spacer device. Dysphonia (11.1%) was favored by high doses of both drugs and by spacer use. Thirst (21.9%) and hoarseness (14.1%) were reported with both BDP and BUD. The occurrence of oral candidiasis (10.7%) could not be associated with any given predisposing factor. ICS appear to cause dysphonia by inducing myopathy of the vocal cords.

Oropharyngeal effects of ICS can be reduced by rinsing the mouth and spitting after use and by using spacer devices. If ICS are delivered through a face mask (as with infants), then the nasal-perioral area should be cleaned with a damp cloth after each treatment.

Risk Reduction - Reduction of Dosing Frequency and Amount

Once-daily dosing frequently maintains control for patients with milder asthma and may reduce average effects. Most cases of moderate asthma can be

controlled with twice daily dosing of most of the inhaled corticosteroids. NAEPP guidelines recommend initial higher and more frequent dosing, followed by dose tapering once control has been reached.

Dosing Schedule

The NAEPP Guidelines address chronobiological ICS dosing to reduce adverse effects and enhance efficacy. For once-daily dosing, administration between 1,500 and 1,700 appears to improve both outcomes.

New Drugs

A new generation ICS, ciclesonide, with unique pharmacokinetic properties, has been developed with the intent of reducing both systemic and local adverse effects. Added advantages include once-daily dosing and increased patient adherence. Ciclesonide is inactive until it reaches the lung and demonstrates high protein binding, low oral bioavailability, and rapid clearance. Additionally, short duration placebo-controlled studies have demonstrated minimal local and systemic effects with this ICS.

Conclusion

The weight of clinical evidence currently favors a conclusion that the benefits derived from careful and evidential use of ICS in asthma therapy significantly exceed potential risks. Routine inhaled corticosteroid use is recommended in the most recent national asthma guidelines. As those guidelines are applied to increasingly larger numbers of asthma patients, evidence-based clinical data also will increase to better assess inherent risks and benefits of ICS therapy.

The Role of the Peak Flow Meter in the Management of Asthma Present State of Asthma

Currently, the control of asthma is an obtainable goal. Treatment has changed with the growing understanding of the pathophysiology of asthma, and control is possible with the use of inhaled steroids and established guidelines. Maintaining control is done through:

- A stepwise approach to pharmacotherapy,
- Patient education about their medications,
- Patient education on environment control,
- A partnership with the patient to control their disease through self-management.

The clinician should employ any tool or device that aids in this control. In

randomized controlled trials, a peak flow meter has been shown to achieve significant improvements in health outcomes for asthmatics when incorporated into a written action plan.

Current Recommendations

Long-term daily peak flow monitoring is recommended for managing moderate-to-severe persistent asthmatics or those with a history of severe exacerbations. It is suggested that asthmatics with poor symptom perception can benefit from a peak flow meter. Mild intermittent or mild persistent asthmatics may use a peak flow meter if the family/patient and/or clinician feel it will have benefit, but this is not a strong recommendation. All recommendations assume that peak flow monitoring is part of a written action plan.

Differing opinions exist about which method is more efficacious- the use of a peak flow meter or a symptom monitoring approach. Regardless of the method used, it is strongly recommended that either approach should be part of a written patient action plan. For those clinicians who want to incorporate the use of a peak flow meter in an action plan, the following information will be helpful.

What is a peak flow meter and how is it used?

A peak flow meter is an inexpensive, simple device that measures how well air moves out of the large airways of the lungs. The least complicated device should be used. It is used to establish the patient's best Peak Expiratory Flow (PEF).

Instructing the Patient to Use a Peak Flow Meter

The peak flow meter is simple to use. Instruct the patient to do the following:

1. Stand up straight*, and place the pointer on the peak flow meter to zero.
2. Hold the peak flow meter so that the vent is not obstructed, and take in a deep breath.
3. Place the mouthpiece in the mouth, and seal with the lips (keeping the tongue away from the vent).
4. Blow air as hard and as fast as possible thru the mouthpiece, and write down the number obtained.
5. Wait 15 to 30 seconds, repeat the above steps, and take the highest number as the personal best.

* Note: For those patients who are disabled and cannot stand, it is acceptable to be seated in an upright position for a peak flow meter reading.

Establishing a Personal Best with the Peak Flow Meter

The personal best is a number that can be used by both the physician and patient to assess their current disease and adjust therapy. Ideally, your patient's

personal best PEF should be estimated after a 2 to 3 week period in which the patient records PEF two to four times a day. This is usually achieved in the early afternoon after maximal bronchodilator therapy. This 'best' should be marked on the peak flow meter. A short course of oral steroids may be needed to establish this.

The personal best should be reevaluated and checked periodically. A personal best should be done every 6 months for moderate-to-severe persistent asthmatics and children. Progression of the disease and patient growth will affect the personal best value.

Tips for Instructing the Patient

Inform the patient that this device will help them understand and control their asthma. Keep all explanations simple, and check frequently to find out if they understand what you have explained. Use the following outline:

1. Explain peak flow meter use in words.
2. Demonstrate how to use it.
3. Allow the patient to explain how to use it to you.
4. Allow the patient to demonstrate the technique to you.

If you choose to use a peak flow meter in the action plan, encourage the patient to use it on a regular basis and record the results in a daily diary. Current recommendations call for a peak flow reading in the morning when the patient awakens and *before* using their medication. Action plans should be based on percentages of their personal best PEF.

The usual break points for action are: 80% of their personal best and above signals good control; 50% to 80% indicates caution and a need for medication; 50% and less indicates medical alert and patient needs to seek immediate medical help.

Review and repetition of peak flow meter instructions for use are important. Patients should not interchange brands of peak flow meters, and when buying a new one, a new 'best' should be established.

Recent Study Results regarding Peak Flow Meters

A review of the literature indicates that education in asthma self-management, which involves self-monitoring by either peak expiratory flow or symptoms coupled with *regular medical review* and a *written action plan*, improves health outcomes for asthmatic adults. Individualized written action plans based on PEF are equivalent to action plans based on symptoms. Reducing the intensity of self-management education or level of medical review may reduce the effectiveness.

Conclusion and Summary

A peak flow meter when coupled with medical review and an action plan can have positive health benefits in asthmatics diagnosed as moderate persistent to severe persistent and in those who have severe exacerbations.