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β-AGONIST WARNINGS: WHAT DO THEY MEAN FOR ASTHMA TREATMENT?

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Asthma prevalence in Oregon is higher than the national average, affecting 7.5% of children and 9.7% of adult Oregonians.[1] The Oregon Asthma Program, which is largely based on the National Asthma Education and Prevention Program (NAEPP) (Table I), encourages step-therapy to reduce the number of attacks, symptoms, emergency visits, and hospitalizations. [2, 3] Recent warnings about long-acting beta-agonists (LABAs) post-date available guidelines.[4, 5] The goal of this article is to briefly review the guidelines and summarize the new LABA information.

Short-Acting Bronchodilators

The NAEPP recommends intermittent use of inhaled short-acting beta-agonists (SABAs) to reduce acute airway obstruction. Use more than twice a week indicates the need to consider long-term control therapy. Adverse effects include arrhythmias, hypertension, prolonged Q-T interval, hyperglycemia, and hypokalemia.

Albuterol is the class standard. Levalbuterol (*Xopenex*) is the R-isomer of albuterol. The Medical Letter and others have found no convincing evidence that levalbuterol offers significant clinical advantage over albuterol while levalbuterol is much more expensive. [6, 7]

A Cochrane review found no justification for routine add-on of anticholinergics (e.g. *Atrovent*), while acknowledging possible benefit for individual patients.[8, 9] Limited data shows patients with Arg/Arg genotypes, often unresponsive to β-agonists, may be candidates.[10]

All inhalers with chloroflurocarbons (CFC) propellant must be replaced with hydrofluroalkanes (HFA) by December 31, 2008. Recent discontinuation of albuterol CFC products led to recent shortages of both forms. The switch between albuterol inhaler types requires no dose adjustment, but HFA products may differ in taste, feel, inactive ingredients, and cost. HFA propellants can clog the actuator, and should be washed weekly and primed when not used for two weeks, more often than with CFC products.[11]

Corticosteroids

Compelling evidence showing a reduction of inflammation and lower mortality from asthma, has made inhaled corticosteroids (ICS) the drugs of choice in persistent asthma.[12] Level 1 evidence supports use of low-doses.[13] For most people the benefit occurs under 500 mcg per day of beclomethasone equivalent. With higher doses adverse effects rise steeply.

When to start ICS is not firmly established. One double-blind, random trial suggested intermittent ICS may be of benefit for mild, persistent asthma in adults.[14] Guilbert found ICS useful to control active asthma, but not to prevent asthma, in high-risk preschoolers.[15]

The Drug Effectiveness Review Project found fair evidence that ICSs in equipotent doses do not differ in ability to control asthma symptoms and reduce the need for additional rescue medication.[16] Beclomethasone (*QVAR*) and fluticasone (*Flovent*) are the most cost-effective options on Oregon's Plan Drug List.[17]

Adverse effects include adrenal suppression, oropharyngeal candidiasis, and dysphonia.[18, 19] de Vries found an association of ICS use in children with behavior changes, adrenal insufficiency, hypertrichosis, and teeth abnormalities. A limitation of these findings is reliance on self-reported adverse drug reactions. He notes that extensive studies on the effect of ICS on the growth in children has found the final adult height did not differ from expected height. [20]

Long-Acting Bronchodilators

The role of LABAs for asthma is now widely debated. Agreement exists that LABAs are not first line agents, nor should they be used alone as monotherapy.

FDA Long-Acting Beta-Agonists Recommendations [4]

- NOT initial treatment
- NOT to treat wheezing that is WORSENING or sudden
- NOT discontinued abruptly
- ONLY for patients with inadequate response to other asthma controllers, suchas low-to-medium dose ICS
- Dispensed with a patient Medication Guide

A recent meta-analysis of 19 trials concluded that LABAs increase severe and life-threatening asthma exacerbations, as well as asthma-related deaths.[5] Salpeter noted that no placebo-controlled trials of LABAs have been published. Rather trials of LABAs allowed short-acting β-agonists as needed, in both study arms. While other studies concluded LABAs improves asthma control, Salpeter observes that LABAs may have improved peak flow and symptoms, but worsened asthma control.

However, Glassroth notes that just one study that included race accounted for most of deaths in this meta-analysis; and studies failing to report disease severity, Arg/Arg genotype, and race may account for contradictions.[10] Manufacturers expressed concerns about the number of asthma deaths that could occur without using LABAs, the lack of inclusion of the Bateman study on fluticasone/salmeterol, and lack of citation for the observation that no additional protection occurred when LABA were added to ICS.[21, 22]

This controversial meta-analysis follows halting of the Salmeterol Multicenter Asthma Research Trial (SMART*). An interim analysis showed five times as many deaths or near deaths with salmeterol than with placebo and more deaths and near-deaths when no ICS were used concurrently. Post-marketing studies reviewed by the FDA Pulmonary-Allergy Advisory Committee in mid-2005 noted several short-comings. [23]

Likewise, a formoterol Phase 4 study, comparing the dose safety concluded the 24 mcg dose was not associated with an increase in serious asthma exacerbations compared to approved 12 mcg dose or placebo.[24] But, an FDA Medical Officer found the study too small to be definitive, and noted several serious problems with its design.[23]

The FDA issued a Public Health Advisory on salmeterol and formoterol last fall, affecting *Advair*, *Serevent*, and *Foradil*.[4] In March 2006, the agency strengthened black box warnings on salmeterol (Advair and Serevent) and formoterol (*Foradil*). The FDA noted that while LABAs decrease the frequency of asthma episodes, these agents are associated with risk of worsening bronchospasm. Death and life-threatening episodes have occurred.

Until further data becomes available, some advocate following existing guidelines, which call for routine use of LABAs added to ICS. Advice includes maximizing the dose of ICS before starting LABAs, obviating the supposed advantage of LABA to allow for lower doses of steroids. [10]

Fluticasone with salmeterol (*Advair*) is a fixed LABA/ICS combination. When asthma is stable in Step 3, fixed combinations provide convenience, and similar costs to the separate ingredients. There is very limited data supporting the claim of synergistic effect of the fixed combination. Particularly in light of the current debate, this drug should not be used initially.

Miscellaneous Agents

When patients remain unresponsive or intolerant to first-line agents, have severe exacerbations, or cannot use an inhaler additional options include:

- Adding an oral β-agonist, leukotriene modifier (montelukast or zafirlukast), oral steroid, or sustained release theophylline. Cochrane reviews found the weight of evidence favors ICS, then LABA add-on over leukotriene modifiers.[25, 26] Few comparative studies on leukotriene modifiers have been published.[27]
- Adding injectable Anti-IgE (omalizumab (*Xolair*). A recent Cochrane review noted that longer term assessment is required for a safety profile of omalizumab.[28] The main role is steroid sparing, but very high costs and the need for monitored injections are limiting factors.
- A recent pooled analysis failed to show statistically significant differences between cromolyn and placebo, concluding that bias likely overestimated beneficial effects of cromolyn as maintenance in children with asthma.[29]

Monitoring

If asthma worsens, first check compliance and inhaler technique. After compliance and technique are verified, consider increasing ICS dose or add-on therapy. Check for and avoid therapies such as: mucolytics that may worsen cough, large volume hydration in adults and older children or antibiotics for acute episodes unless patient has pneumonia or bacterial infection.[30] Quitting smoking and reducing exposure to second-hand smoke is high priority. Asthma may improve when gastroesophageal reflux disease is treated with a proton pump inhibitor.[31]

The Oregon Asthma Program recommends referral to an asthma specialist when a patient uses three or more asthma medications daily, takes oral steroids more than two weeks, uses frequent bursts of oral steroids or has significant unresolved side effects.

Conclusion

Recent warnings regarding LABAs underscore recommendations to evaluate patients with asthma, their therapy, and dose every three months, once asthma is controlled. ICSs, at the lowest effective dose, remain the drugs of choice for control of asthma symptoms and prevention of exacerbations.

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Table 1: ASTHMA GUIDELINES[2] For Adults & Children Over Age 5 Years

Asthma Status	Recommendation	Oregon PDL Options	Average 30-day retail cost to OHP Q2-06
Intermittent, Mild	Initiate inhaled SABA as needed For severe exacerbations: consider corticosteroids as needed	albuterol (available generically) levoalbuterol (*Xopenex*)	$45 $65
Persistent, Mild	Add routine Low-Dose ICS Consider alternatives leukotriene modifers OR sustained release theophylline for those unable to take ICS	beclomethasone (*QVAR*) low-med potency flunisolide (*Aerobid*) low-med potency fluticasone (*Flovent*) high potency triamcinolone (*Azthmacort*) low potency mometasone (*Asmanex*) high potency	$65 $100 $105 $110 $125
Persistent, Moderate	Use routine ICS in low to medium dose AND add routine inhaled LABA Consider alternatives: increase ICS within medium dose range, OR Use low to medium dose ICS AND leukotriene modifier, OR theophylline	fluticasone / salmeterol (*Advair*) formoterol (*Foradil*) salmeterol (*Serevent*) zafirlukast (*Accolate*) montelukast (*Singulair*) theophylline ER (available generically)	$160 $90 $105 $80 $90 $20
Persistent, Severe	Increase to routine high dose ICS AND LABA Add oral corticosteroids 2 mg/Kg/day, nmt 60 mg per day as needed	prednisone	$2

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