

Respirations

Winter 2007

Must read! Must read! Must read! I realize that everyone is extremely busy this time of year but in this edition of “*Respirations*” we will give you the bottom line on some very important challenges that you have or will come across in your practice. First up will be a “not your typical” review of the asthma controller medications...these are all the things your drug reps prefer not to discuss with you but parents may yet ask.. Then we will review newborn cystic fibrosis (CF) screening and the challenges you and your patients’ parents might face.

Now that I have got your attention, I also would like to thank you for the opportunities to work with so many of your families. It has really been our pleasure! LCK (Lee.Choo-Kang@Mercy.net)

Asthma Medications

The latest revision of the National Asthma Education and Prevention Program (NAEPP) guidelines¹ released this summer is based upon careful review of thousands of peer-reviewed articles. In it, recommendations are assigned a grade of A (rich body of evidence from randomized controlled trials) through D (panel consensus judgment) depending upon the strength of the supporting scientific evidence. It should be alarmingly obvious to anyone caring for young children that little of what we do beyond prescribe low-dose inhaled corticosteroids (ICS) for persistent asthma has been adequately studied.

Most providers know about the black box warning that was added by the FDA to long-acting beta agonists (LABA). Data for this advisory came from the Salmeterol Multi-Center Asthma Research Trial (SMART), a large 28-week placebo-controlled U.S. study that examined the safety of salmeterol added to usual asthma therapy. Subjects on salmeterol showed a statistically significant increase in asthma-related deaths (13 deaths out of 13,176 patients) compared to those subjects receiving placebo (3 deaths out of 13,179).

The SMART data is by no means unique. Salpeter et al.² in a meta-analysis of 19 different trials with 33,826 participants found that LABA usage increased exacerbations requiring hospitalization (OR, 2.6 [95% CI, 1.6 to 4.3]), life-threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]) and asthma-related deaths (OR, 3.5 [CI, 1.3 to 9.3]) compared with placebo. Children on LABA (OR, 3.9 [CI, 1.7 to 8.8]) were even more likely to be hospitalized than adults (OR, 2.0 [CI, 1.1 to 3.9]).

The potential mechanism(s) by which LABA use may result in increased asthma morbidity and mortality is speculative. Possible explanations include an idiosyncratic response to LABA due to genetic variations found in a small number of patients. Another theory is the development of bronchodilator tolerance. This mechanism is supported

by earlier studies which showed decreased protection from exercise-induced bronchospasm with repetitive LABA use. Long term use of LABA may also be associated with a decreased responsiveness to rescue short-acting bronchodilators like albuterol. Furthermore, it appears that the worse the bronchospasm the greater the lack of responsiveness.

Although most of the current use of LABA in children is done in conjunction with ICS, there is little evidence that this practice will prevent potential adverse outcomes. In addition even if ICS could prevent tolerance from LABA use, the optimal or lowest required dosage of ICS has not been clearly established.

The FDA is now recommending to the Pediatric Advisory Committee that a thorough risk-benefit analysis for salmeterol (Serevent) asthma treatment is warranted as the product may have an unfavorable risk-benefit profile for use in children. The committee was supposed to convene of November 28th.

There are several options for ICS now available for the treatment of persistent asthma in children. Notables on the list include budesonide (Pulmicort), fluticasone (Flovent), beclometasone (QVAR) and mometasone (Asmanex). Budesonide (plus formoterol) and fluticasone (plus salmeterol) are also available as Symbicort and Advair, respectively. ICS all appear to be better than placebo in the control of persistent asthma. However all ICS should not be considered equal in terms of efficacy and effectiveness. Further complicating matters are the different delivery devices used. Even in studies comparing the same drug in different delivery devices such as metered dose inhaler versus dry powder inhaler (e.g. Flovent), there are differences in the amount of lower airway deposition of the drug and subsequently in its clinical benefit as well as potential for side effects. The new Pulmicort Flexhaler interestingly produced slightly lower responses compared to an equivalent dose of budesonide administered by the now unavailable Turbuhaler device. However the richest safety data especially regarding growth suppression probably exists for budesonide. Compared to non-asthmatic children and children with asthma not treated with ICS, patients treated with budesonide for a mean of 9.2 years (range 3-13 years) of budesonide treatment at a mean daily dose of 412 micrograms (range 110-877 micrograms) still attained final adult predicted heights.

It would only be fair to close with a few words about leukotriene modifiers. Montelukast (Singulair) is a popular medication for the chronic management of asthma and allergic rhinitis. It recently gained FDA approval for treatment of exercise-induced asthma. Montelukast is

a leukotriene antagonist receptor antagonist and is generally considered a safe medication. Its most significant potential adverse effect is Churg-Strauss syndrome (CSS) which was initially considered a consequence of a pre-existing condition that was unmasked by withdrawal of systemic steroids. Interestingly, there have been reports of CSS in adult asthma patients treated with montelukast in the absence of prior systemic steroids. From a pediatric perspective CSS has been reported in a child as young as 6 years of age. CSS is perhaps still a rare enough entity for us to not worry about. However more parents seem to be raising issues of aggressive behavior, hyperactivity, cognitive and sleep changes. The package insert for Singulair in fact lists these symptoms under post-marketing experience but do not discuss their incidence. Although such side effects are more commonly attributed to other medications like corticosteroids, adrenergic bronchodilators and antihistamines that the child may be taking, it would still be prudent not to ignore any possibility.

After reading this you should have some concerns about the safety and even effectiveness of the asthma medications currently prescribed. I can attest that we do! Monitoring of lung function by spirometry as well as exhaled nitric oxide, a marker of lower airway inflammation helps us to adjust medications appropriately. We also do a lot of careful objective assessment and reassessment (identification and reduction of triggers, treatment of co-morbidities, optimization of inhaler technique and improvement in adherence) of our patients to determine the minimal amount of medication required to control their asthma. LCK

References:

1. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>
2. [Ann Intern Med.](#) 2006 Jun 20;144(12):904-12.

Cystic Fibrosis Newborn Screening

Starting January 2007 the state of Missouri initiated a pilot program to add Cystic Fibrosis testing to our expanded newborn screening program. Newborn screening for CF is recommended by the CDC and our program follows other successful state newborn screening programs such as those in Colorado and Washington¹. Missouri measures newborn Immunoreactive Trypsinogen (IRT) which is a marker of pancreatic inflammation elevated in newborns with both pancreatic sufficient and insufficient CF. False positives are common and an elevated IRT can be noted in some healthy infants, preterm infants, and in patients with some component of pancreatic dysfunction. IRT testing is conducted on newborn blood spots and easy to obtain. Gregg et al in *Pediatrics* reported their data from nearly 10 years ago showing 0/1401 infant had CF with an IRT 100-140ng whereas 20/83 patients with CF had a level above 300ng². The state of Missouri has implemented a two tier system with first newborn screen collected at days 1-3 (typically after 24 hours) of life and a second screen collected

after 1 week of age. IRT levels of < 100ng on the first screen and an IRT < 70ng on the second screen are considered normal. If levels are elevated a POSITIVE screen is noted and further testing (sweat test) and evaluation by a pediatric pulmonologist is warranted. Since implementing the screening program nearly 60,000 infants in Missouri have been tested and 16 infants have been diagnosed with CF (incidence rate of 1:3718).

In order to avoid missing an infant with CF, the current cut-off values for IRT in the MO screening program are relatively low. As a consequence, false positive are common. A busy pediatric practice may see anywhere from 3-6 false positive results per year. In fact three out of four infants with two elevated IRT values do not have CF after further evaluation. However from both a medical and psychological perspective, it is necessary to evaluate any child with a positive CF screen immediately. Parents report a positive screen as a frightening experience and seek prompt and reliable medical expertise to either correctly diagnose the disease or show the screen was falsely positive. Along with a thorough history and physical exam, the work-up for a positive CF newborn screen includes a quantitative Pilocarpine Iontophoresis sweat chloride (qPIT) test. It is important that the facility has ample experience with the testing procedure to ensure reliable results (>400 studies done in 2007 at SJMMC). Specific genetic tests may sometimes be indicated depending upon clinical circumstances.

Take home points for Missouri newborn CF screening includes (1) the IRT/IRT test is only a screening tool and if positive further evaluation is needed (2) As with any patient where there is a clinical suspicion for CF, pediatric pulmonary consultation is recommended. At St. John's Mercy Children's Hospital both physicians not only have extensive training and experience in the evaluation and management of CF but offer same day evaluations—to provide education and instruction about a positive newborn screen, obtain accurate information in making the diagnosis either by a standardized sweat test or genetic (CFTR mutations) testing, and finally treat those patients who ultimately are afflicted with the disease. Furthermore, because of the nature of our practice, we are able to segregate our patients thereby limiting the risk of cross infection with pathogenic and multi-drug resistant organism, a challenge for the large CF Centers. *John F. Spivey, MD*

References:

1. CDC Morbidity and Mortality Weekly Report (MMWR). Newborn Screening for Cystic Fibrosis. October 15, 2004.
2. *Pediatrics.* 1997; 99:819-824.

Be sure to check out our website <http://www.pedpulm.org> for previous issues of *Respirations* as well as information regarding our practice. Order forms for outpatient pulmonary function tests and sleep studies are also available so you could order these directly for your patients.