Paediatric Asthma - Some Questions Answered

Abstract:

The prevalence of childhood asthma in Ireland continues to rise, though its causes remain elusive. While traditionally, clinical trials have mainly targeted adult populations, in more recent years, an increased number have been performed in children, which is appropriate and required. Paediatricians have a responsibility to ensure high quality clinical trials are performed in the paediatric population to adequately assess the effect of treatments in the young, independent of adults.

Lemanske's sentinel paper provided evidence, which was previously lacking, to guide step up therapy in children who have uncontrolled asthma despite inhaled corticosteroids (ICS). The BADGER trial reviewed the best add on therapy giving effective response in children (aged 6-17 years, n = 182) with uncontrolled asthma despite fluticasone 100 mcg twice daily. Interestingly nearly all children (96%), had a differential response to add on therapy. This prospective, blinded, triple cross over trial compared increased fluticasone (from 100mcg to 250 mcg), with the addition of a long acting β2 agonist (LABA), (50 mcg of salmeterol twice daily), with a leukotriene receptor antagonist (LTRA), (montelukast). The percentage of children who had a best response was similar with each add on therapy. Step up therapy with LABA was significantly more likely to provide the best response as compared with either ICS or LTRA in children with mild to moderate asthma, but it can be argued, that in the mild group, step up therapy is least likely required. White race predicted a better response to LABA step-up, whereas black patients were least likely to have a best response to LRTA step up. This is a valuable study for paediatricians particularly in light of the ongoing concerns regarding LABA use.

Regarding exercise induced broncho-constriction (EIB) in children, the addition of montelukast or salmeterol to inhaled fluticasone was assessed in a randomised, double blind, double dummy, multi-centre trial (n=145 subjects, aged 6-14 years) attenuating and response of EIB to salbutamol rescue after exercise challenge were significantly better with montelukast than with salmeterol. Montelukast, compared with LABA treated children, had a reduced mean maximum percentage decrease in forced expiratory volume in 1 second (FEV1), (10.6% versus 13.8%), were more responsive to short acting β2 agonists and had a shorter median time to recovery. However, it is not clear why in this study 63% of patients treated with montelukast responded to therapy, when it is known that not all asthmatics are cysteinyl leukotrienes producers and one would have expected more in the region of a 30% response.

Regarding the ongoing concerns about the safety of LABAs, the F.D.A. published a statement again highlighting its concerns regarding the use of these medications, which for a number of years has been carrying a black box warning. They emphasise that it remains unclear if the concomitant use of ICS with LABAs mitigates the risk of asthma related death, associated with LABA treatment alone. They remind us that there is 50 years of evidence demonstrating that short acting β2 agonists (SABAs) can worsen asthma and cause asthma related deaths and that both SABAs and LABAs have the same basic pharmacological activity and clinical effect. They are ensuring that manufacturers of LABAs conduct large clinical trials to evaluate whether the addition of LABA to ICS increases the risk of serious asthma outcomes, comparing ICS plus LABA with ICS alone. Reassuringly, the FDA will have input into these studies. However, though the language employed by the F.D.A. in this statement was stronger than previous, the message is similar, indicating perhaps that it was more of a political statement.

Interestingly, the Cochrane Database systemic review of LABA plus ICS versus higher ICS therapy in children and adults reported that combination therapy in children did not lead to a significant reduction in oral steroid treated exacerbations and hospital admissions, in contrast to adults where a modest reduction was documented. A ban on smoking in public places introduced in Scotland (March 2006) resulted in a mean reduction in the rate of hospital admissions for childhood asthma of 18.2% per year, with a similar change in preschool and school age children. This was the first study to demonstrate that a ban on smoking in public places influenced respiratory disease among people who do not have an occupational exposure to environmental tobacco smoke.

Dr. Jeff Drazen (editor of the NEJM) highlighted the responsibility drug companies have to their patients. A comparative effectiveness trial was set up to compare three treatments in uncontrolled asthma in adults: addition of tiotropium, addition of LABA and doubling of I.C.S appropriately critisised one drug company who declined to give their active drug and matching placebo for the trial. This resulted in an additional cost to the National Institute of Health and ultimately the...
American tax payer, of $900,000. He argued that just as patients put themselves at risk in clinical trials, drug companies should put their products at risk in comparative effectiveness research to determine whether one treatment is superior or non inferior. As paediatricians, we need to continue to be advocates for our patients by supporting high quality clinical trials and comparative effectiveness research in the paediatric population. This is critical to ensure our patients receive the most appropriate and clinically effective treatment.

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References