β₂-adrenergic agonists have been the mainstay treatment for relief of acute asthma exacerbations since its introduction in the 1960’s. The introduction of long-acting β₂-adrenergic agonists (LABAs) in the 1990’s subsequently provided clinicians with another ‘tool’ in the management of uncontrolled asthma. LABAs have not been without their fair share of controversy however. This article aims to review the controversy surrounding LABAs as well as their physiology and current recommended use in the pediatric population.

Physiology:

The β₂-receptor is a G-protein coupled receptor widely distributed throughout the body. It is most densely located in airway smooth muscle. The bronchodilating effect occurs when the β₂-agonists bind to and stabilize the β₂-receptor in its activated form. The β₂-receptor is in the activated form when it is associated with the α-subunit of the G-protein, together with guanosine triphosphate (GTP). This leads to an increase in cyclic adenosinemonophosphate (cAMP). Although the mechanism by which an increase in cAMP leads to bronchodilation is not fully understood, it is thought that it catalyzes the activation of protein kinase A (PKA), which in turn phosphorylates key regulatory proteins involved in the control of muscle tone.

LABAs:

Formoterol fumarate is moderately lipophilic and is taken up into the cell membrane. It acts like a “depot” and progressively releases into the aqueous environment to interact with the β₂-receptor. Its onset is 2-3 minutes. This is due to some of the drug remaining in the aqueous phase outside of the cell allowing it to interact immediately with the β₂-receptors. Its duration is approximately 12 hours.

Salmeterol xinafoate is even more lipophilic and as such has a longer time of onset (30 minutes) as compared to formoterol. It diffuses laterally in the cell membrane to approach the activity site of the β₂-receptor. Its duration is also approximately 12 hours.

Controversy:

The US Food and Drug Administration (FDA) black box warning on LABAs was issued in 2006 following several studies which showed an increase in serious adverse events (SAEs) with the use of LABAs. The mechanism by which LABAs could potentially cause harm were postulated to be due to its cardiac side effects, desensitization of the β₂-receptors, delay in seeking help due to the masking of the severity of the exacerbation and/or reduction in the use of inhaled corticosteroids (ICS). The controversy at the time was due to the fact that the black box warning was issued for both monotherapy and combination ICS/LABA use. Although the evidence was quite clear that there was a significant increase in SAEs with LABA monotherapy, the evidence against combination ICS/LABA use was not as clear. Criticisms for the studies used leading to the FDA warning include undertreatment with ICS and differential dosing of ICS.
in many of the trials. As an example, in the SMART study which was the largest study conducted at the request of the FDA to examine LABA safety, less than 50% of their study population were on an ICS at baseline. Since then, various meta-analyses have struggled to clearly identify a significant increase in SAEs with the use of combination ICS/LABA therapy, as the majority of the study populations were either not on ICS at baseline or were not assigned to consistent ICS plus LABA use. Subsequently, the FDA re-issued an updated warning in 2010 stating that LABAs should always be used with an ICS in the treatment of asthma. Furthermore, in the pediatric and adolescent population, the medication should be delivered in a fixed-dose combination product to ensure that LABA monotherapy does not occur. The latest Cochrane Review examining the safety of LABAs in children estimates that there are probably an additional three children per 1000 over three months who suffer a non-fatal SAE on combination therapy in comparison to ICS use alone. The authors emphasized that this estimated risk needs to be balanced against the symptomatic benefit obtained by each child. They also stated that there was insufficient information to make any conclusion in relation to the risks of mortality in children on regular LABA therapy.

Current Recommendations:

Currently, the Canadian Thoracic Society (CTS) 2012 Asthma guideline update recommends the use of combination ICS/LABA use in those >/= 12 years whose asthma is not controlled on low-dose ICS and upon review of adherence, technique and avoidance of triggers. ICS/LABA use is recommended in children 6-11 years whose asthma is uncontrolled on moderate-dose ICS and upon review of adherence, technique and avoidance of triggers. Although salmeterol is approved for patients as young as four, use of a combination ICS/LABA in the preschool group should probably be reserved for those whose asthma is uncontrolled despite the use of moderate to high-dose ICS and leukotriene receptor antagonist and in consultation with a specialist. The CTS has also commented that the FDA statement to “Stop [the] use of the LABA, if possible, once asthma control is achieved and maintain the use of an asthma-controller medication, such as an inhaled corticosteroid,” is not evidence-based and that withdrawing the LABA may result in loss of symptom control.

Future directions:

Ultra-long β2-adrenergic agonists (uLABAs) such as indacaterol have now entered the market in Canada as of 2012 although it is not indicated for asthma. The duration of uLABAs are approximately 24 hours and would only require once daily dosing which may help improve adherence to the medication. Since LABA monotherapy is contraindicated in asthma, perhaps it will not be too long before a combination ICS/uLABA product may be seen in the future for the treatment of asthma.

Conclusion:

It is clear that LABA monotherapy should not be used in any age group for the treatment of asthma. There is a role however for LABAs as add-on therapy in asthma, in combination with ICS as recommended in the CTS guidelines. As clinicians, we must continue to weigh the benefits with the risks of using any therapy. Until there is stronger evidence to suggest the contrary, for some patients the risks of uncontrolled asthma outweigh the potential risk of using ICS/LABA therapy.
References:


8. Kovesi T et al, Achieving Control of Asthma in Preschoolers, CMAJ March 9, 2010 vol. 182 no. 4