

Update on the use of LABAs for the treatment of Asthma

The current literature regarding the use of LABAs in asthma can only be described as 'busy'. Central to the debate are two issues – firstly how safe are LABAs in the treatment of asthma and secondly how should exacerbations be managed in patients currently using combination LABA/ICS inhalers.

Key Points

- Long acting beta agonists (LABAs) are not indicated as first-line therapy for any asthmatic patient.
- Adverse reactions to LABAs such as hyper-responsiveness, bronchospasm and respiratory arrest are rare but patients should be closely monitored for the first 6 – 12 weeks after the initiation of treatment.
- LABAs should only be prescribed for people who are already on inhaled corticosteroids (ICS).
- LABAs may be indicated as add-on therapy if symptoms do not respond to low to moderate doses of ICS (e.g. in adults 400 - 800 micrograms beclomethasone or equivalent).
- Patients on LABAs should be counselled and reminded on the importance of continuing their ICS.
- LABAs should be discontinued after a trial period if no benefit is seen.
- Patients with acutely deteriorating asthma should not be started on a LABA.
- Review the asthma management plans of people on combination LABA/ICS inhalers.

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Adding a LABA improves symptom control, lung function and reduces the need for rescue medication

Randomised controlled trials (RCTs) have found that adding a LABA improves symptom control, lung function and reduces the need for rescue medication compared with placebo in people with asthma that is poorly controlled by ICS. There was no significant difference in the exacerbation rates between the two groups in any of the RCTs (Clinical Evidence, 2006).

Furthermore, adding regular doses of LABA improves lung function and symptoms, decreases exacerbation episodes and reduces the need for rescue medication compared with increasing the dose of ICS (Clinical Evidence, 2006).

Adding a LABA is more effective than doubling the dose of ICS (at a dose of 400 micrograms beclomethasone per day or equivalent) and should always be considered if a dose of ICS greater than 800 micrograms per day is required (NZGG, 2002). In this regard LABA can be considered to have two advantages; improved symptom control along with a steroid sparing effect.

Adverse respiratory reactions to LABA possible

There have been occasional reports of deterioration in asthma control, impairment of response to short acting bronchodilators and even respiratory arrest following commencement of a LABA. Several mechanisms may be implicated including paradoxical bronchospasm, increased bronchial responsiveness and tolerance, but none of these have been identified in prospective trials. Prescribers need to be aware of the possibility of these rare adverse reactions and monitor patients closely especially during the first 6 – 12 weeks after starting a LABA (Taylor, 1999).

Peak flow monitoring should be encouraged and patients should be advised to seek advice if they perceive a lack of benefit from using their reliever (short acting bronchodilator) medication. When people are put on a LABA symptoms often improve and compliance with ICS may be reduced. It is therefore important to remind patients to continue to take their inhaled steroids regularly in addition to the LABA. The LABA should be withdrawn if asthma control continues to deteriorate in the absence of other explanations (Taylor, 1999).

Latest trials question safety of LABA

Two recent trials have raised awareness of the possible safety concerns regarding the use of LABAs, and prompted regulatory authorities in some countries to reiterate warnings about their appropriate use, especially the need for concurrent use of an ICS.

Salpeter et al conducted a meta-analysis of 19 RCTs involving almost 34,000 asthmatic patients. The primary objective was to estimate the risk of serious adverse events associated with LABA use. The use of LABA was associated with increased asthma exacerbations and asthma related deaths. In addition, statistically significant increases in hospitalisations occurred in both adults and children with salmeterol or formoterol, compared with placebo (Salpeter, 2006). It was estimated that LABAs cause an excess of approximately one death per 1000 years of patient use.

The Salmeterol Multicentre Asthma Research Trial (SMART) compared the addition of salmeterol or placebo to existing asthma treatment in over 26,000 patients aged 12 years and over (mean age 39 years) (Nelson, 2006). All patients had a current diagnosis of asthma and were receiving asthma medication. Exclusion criteria included the previous use of inhaled LABA and a history of adverse reactions to sympathomimetic amine drugs. The intervention group received 42 micrograms of salmeterol twice daily by metered dose inhaler and the control received a matched placebo inhaler. All subjects were followed for 28 weeks and continued to use their current asthma drugs.

The composite primary end point was respiratory related death or life threatening experience (i.e. intubation and mechanical ventilation). Secondary endpoints included all cause mortality, asthma related death, respiratory related death, life threatening experiences and combinations of these.

The trial was stopped early after the interim analysis due to enrolment problems and preliminary findings from a subgroup analysis which indicated a significant risk of harm in African-Americans. In this group there were more respiratory deaths (24 vs 11) and asthma related deaths (13 vs 3) in the salmeterol group than the placebo group (Table 1).

Table 1: SMART trial results: addition of salmeterol vs placebo to usual pharmacotherapy in patients with asthma

Outcomes at 28 weeks	Salmeterol	Placebo	RRI (95% CI)	NNH (95% CI)
Combined respiratory related death or life threatening experience	0.4% (n = 50)	0.3% (n = 36)	40% (-9 – 114)	NS
Asthma related death	0.1% (n = 13)	0.02% (n = 3)	337% (25 – 1434)	1239 (705 - 5126)
Respiratory related death	0.2% (n = 24)	0.1% (n = 11)	116% (6 – 341)	965 (515 - 7861)
Combined asthma related death or life threatening experience	0.3% (n + 37)	0.2% (n = 22)	71% (1 – 189)	810 (415 - 16050)

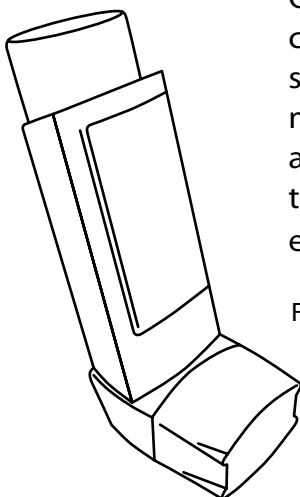
RRI = Relative Risk Increase, CI = Confidence Interval, NNH = Number Needed to Harm (Lipchik, 2006)

As the trial was stopped early there are insufficient data to indicate whether the apparent increased risk in African-Americans applies to other populations.

Taken together SMART and the meta-analysis indicate that LABAs may be responsible for a small increase in the absolute risk of asthma related deaths and serious exacerbations. In both trials the number of adverse events was small and it is not possible to ascertain if inappropriate use of LABAs (e.g. monotherapy, poor adherence to ICS use or continued use of LABAs despite lack of response) was a contributing factor.

The important messages are to ensure that LABAs are prescribed and used in accordance with current recommendations; ensure concurrent use of ICS, monitor for adverse reactions (especially early in treatment) and discontinue if there is a lack of or inadequate response.

There is now more choice and wider access for subsidised asthma inhalers



On 1 August 2006 some significant changes occurred to the range of subsidised asthma inhalers. The changes mean that you will be able to prescribe a wider range of asthma inhalers, while there is now also wider access to some existing treatments.

For further details visit <http://snipurl.com/12asq> or see your latest schedule

Role of combination LABA/ICS inhalers

The combination of a LABA and ICS in one inhaler provides a convenient and effective dose form in a single inhaler and also ensures the concurrent use of an ICS with the LABA. However they do not allow flexibility in adjusting the doses of individual components and their use in asthma exacerbations is unclear. They are most suitable for people who are already established on a moderate dose of ICS and a LABA in separate inhalers.

LABA/ICS combination in asthma exacerbation

There is currently significant controversy and debate on optimal treatment of early asthma exacerbations in those patients who are already taking a combination LABA/ICS preparation.

Budesonide and fluticasone share similar anti-inflammatory characteristics but there are differentiating features between salmeterol and eformoterol which affect how they can be used in worsening asthma. Salmeterol should not be given at doses greater than the maximum maintenance dose, but the dose of eformoterol can be temporarily increased with the potential of quadrupling the lowest recommended dose (Fitzgerald, 2006).

In the management of early exacerbations the patient should follow an individual management plan and for those on combined LABA/ICS options include temporary additional ICS doses provided via a separate inhaler, a short course of oral prednisone or a temporary increase in the dose of eformoterol/budesonide (Symbicort®).

A LABA should not be started during worsening asthma and the dose of either of the LABAs alone or salmeterol/fluticasone combination (Seretide®) should not be increased during exacerbation.

References

- Clinical Evidence (BMJ publishing) 2006.
- Fitzgerald JM, Gibson PG. Asthma Exacerbations. *Thorax* 2006;61:992-999.
- Lipchik RJ. Addition of salmeterol to usual asthma pharmacotherapy may increase reparatory related deaths or life threatening experiences. *Evid Based Med* 2006;11:139.
- Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005;60:730-34.
- Nelson HS, Weiss ST, Bleecker ER et al. The Salmeterol Multicenter Asthma Research Trial; a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; 129:15-26.
- New Zealand Guidelines Group. Diagnosis and treatment of adult asthma. 2002 available from <http://snipurl.com/127p0>.
- Salpeter SR, Buckley NS, Ormiston TM et al. Meta-analysis: effect of long acting beta agonists on severe asthma exacerbations and asthma related deaths. *Ann Intern Med* 2006; 144:904-12.
- Taylor D R. Adverse respiratory reactions to long acting beta agonists. *Prescriber Update* 1999;18;24-28. Available from; <http://snipurl.com/120il> (Accessed October 2006).

Indications for LABA

The addition of a LABA to inhaled corticosteroids can be considered:

- For younger children (under 12 years) where asthma is poorly controlled despite using ICS for at least three months at total daily doses of 200 micrograms beclomethasone or budesonide or 100 micrograms fluticasone.
- For adults and older children (12 years and over) despite using ICS for at least three months at total daily doses of 400 micrograms beclomethasone or budesonide or 200 micrograms fluticasone.

Source: Current PHARMAC Schedule. This is consistent with current evidence (Masoli, 2005, Fitzgerald, 2006).