Long acting beta agonists and asthma

JEANIE LEONG MB BS

QUENTIN SUMMERS MB BS, DM, FRACP

These bronchodilators are a useful add-on therapy to inhaled corticosteroids for the treatment of persistent asthma.

Figure. Long acting beta agonists are particularly useful for exercise-induced and nocturnal asthma.

Long acting beta agonists (LABAs) are a major therapeutic development in the management of asthma. They cause significant sustained bronchodilatation, thereby providing superior symptom control and improved lung function when added to inhaled corticosteroids.

Pharmacology

There are two LABAs currently available in Australia, eformoterol (Foradile, Oxis Turbuhaler) and salmeterol (Serevent). Both of these drugs are well-tolerated, β_2-selective adrenoceptor agonists that result in significant bronchodilation for at least 12 hours.[1,2] The molecular structures of these agents are very different, giving rise to their distinctly different timing of onset of action.

Eformoterol, when inhaled, is deposited in the aqueous biophase overlying the smooth muscle, allowing immediate interaction with β_2-receptors.[2] Consequently it has a rapid onset of action, exerting its effect in one to three minutes[3] – which is at least as fast as salbutamol (a short acting beta agonist [SABA]).[1]

Dr Leong is Registrar and Dr Summers is Respiratory Physician, Royal Perth Hospital, Perth, WA.

Being moderately lipophilic, the drug can also enter the cell membrane and be retained.[2] It is purported that small amounts of eformoterol are released over time, enabling a continued interaction with β_2-receptors and thus accounting for the long duration of action following a single inhalation (the diffusion microkinetic model).[1]

Salmeterol is highly lipophilic and readily partitions into the cell membrane.[2] It activates β_2-receptors by diffusing laterally into the receptors from the cell membrane, thereby giving a slow onset of action – a bronchodilatory effect within 30 minutes.[3]

Few other clinical differences have been observed between the two LABAs.[3,4]

Indications

Asthma is an inflammatory disorder and thus requires effective anti-inflammatory treatment. Inhaled corticosteroids are the basis of maintenance therapy in patients who need more than an occasional inhalation of a SABA.[3,5,6] If asthma is not controlled on inhaled corticosteroids, a LABA may be introduced. Their long duration of action make LABAs particularly useful in the management of nocturnal and exercise-induced asthma.[3,4]

The addition of a LABA should be considered if a patient's asthma symptoms persist while on a daily dose of 250 μg beclomethasone (Qvar), 400 μg budesonide (Pulmicort) or 250 μg fluticasone (Flixotide). The combination of an inhaled corticosteroid with a LABA has been clearly shown to decrease asthma symptoms, improve lung function and decrease the frequency of exacerbations in patients with persistent mild, moderate and severe asthma.[3,5,7]

The benefits of adding a LABA to an inhaled corticosteroid are greater than those seen with increasing the dose of the inhaled corticosteroid alone.[5,6] Inhaled corticosteroids have a fairly flat dose–response curve, with the majority of their effects seen in the lower dose range.[6]

Regular use of a SABA does not confer the same benefits as use of a LABA.[4] Using a SABA four times a day as add-on therapy to inhaled corticosteroids in patients with persistent asthma is no different from using a placebo.

LABAs must be considered as 'symptom controllers', and should always be used as add-on therapy to inhaled corticosteroids.[3] As they have essentially no anti-inflammatory effect, they must not be used as monotherapy. The mechanism(s) responsible for the additive effect of LABAs are yet to be clearly identified. They appear to decrease plasma exudation, and, in the presence of inhaled corticosteroids, also seem to modulate the function of inflammatory cells.[1]

LABAs are not indicated for acute attacks of asthma and should not be commenced in patients with acutely deteriorating asthma.[3]

Dosage

The initial recommended dose of eformoterol is 6 to 12 μg twice daily. A total daily maintenance dose of 48 μg/day in adults and 24 μg /day in children over the age of 12 years should not be exceeded unless guided by a specialist respiratory physician.[8]

Because of its rapid onset of action, eformoterol can be used for symptom relief as well as for maintenance therapy. The recommended total daily dose for symptom relief should not exceed 120 μg. Below this total dose, eformoterol is at least as safe and well tolerated as SABAs. Furthermore, using eformoterol on an as-needed basis is more effective in reducing disease exacerbations than using a SABA.[9] Prolonged (i.e. more than three consecutive days') use of doses exceeding 48 μg/ day reflects suboptimal asthma control, and asthma management therefore needs to be reviewed.

The starting dose of salmeterol is 25 to 50 μg twice daily. A maintenance dose of 200 μg/day should not be exceeded unless advised by a specialist respiratory physician.[8] Because of its slow onset of action, salmeterol is not suited for rescue inhalation.

No dosage adjustments are necessary if LABAs are used in patients with renal or hepatic impairment.

The safety of LABAs in pregnancy has not been fully established and their use should be avoided unless there is no safer alternative. As it is unknown whether these drugs pass into breast milk, mothers taking LABAs should be advised against breastfeeding.

Both LABAs are available singly or in combination with an inhaled corticosteroid – eformoterol with budesonide (Symbicort Turbuhaler) and salmeterol with fluticasone (Seretide). There is no significant difference between single and combination inhalers in terms of clinical outcomes; however, compliance may be improved with a combination inhaler.

Monitoring

A patient's response to a LABA should be monitored both clinically and with spirometry. A good response to the addition of a LABA to the asthma treatment regimen will be shown by:

- decrease in the use of short acting reliever medications
- less nocturnal awakenings due to asthma symptoms
- increasing values for morning and evening peak expiratory flow rates (PEFR)
- less diurnal variation in PEFR
- improved FEV_1.

If there is no significant response after one month, the LABA should be stopped.

Tolerability and safety

LABAs have an excellent safety profile.[2] Side effects are more likely with higher dosages.[5] Tremor, headache and palpitations are the more common side effects (but still occur in fewer than 10% of patients); however, they tend to be transient and become less troublesome with regular therapy. As with all inhalation therapies, paradoxical bronchospasm can occur, but does so very rarely.

LABAs should be used with care in patients with pre-existing cardiovascular disease as these patients are at greater risk of adverse cardiovascular side effects.[10] Undesirable cardiovascular side effects may be potentiated by concomitant use of drugs such as monoamine oxidase inhibitors, tricyclic antidepressants and cardioactive drugs. Patients with cardiovascular disease should be monitored with ECG (for QT prolongation) and measurement of serum potassium level (for hypokalaemia).

Conclusion

There is clear evidence to recommend the use of LABAs in patients with persistent asthma who are already taking inhaled corticosteroids. Eformoterol and salmeterol are safe and potent bronchodilators that can improve symptoms, lung function and rates of disease exacerbation without long term loss of asthma control. MT

References

1. Anderson GP. Formoterol: pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective beta 2-adrenoceptor agonist bronchodilator. Life Sci 1993; 52: 2145-2160.
2. Anderson GP, Linden A, Rabe KF. Why are long-acting beta-adrenoceptor agonists long-acting? Eur Respir J 1994; 7: 569-578.
3. National Asthma Campaign. Long-acting $beta_2$ agonists or 'symptom controllers'. http://www.nationalasthma.org.au/publications/beta2/beta2.html.
4. Nightingale JA, Rogers DF, Barnes PJ. Comparison of the effects of salmeterol and formoterol in patients with severe asthma. Chest 2002; 121: 1401-1406.
5. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994; 344: 219-224.
6. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. Eur Respir J 2002; 19: 182-191.
7. Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997; 337: 1405-1411.
8. Palmqvist M, Ibsen T, Mellén A, Lötvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. Am J Respir Crit Care Med 1999; 160: 244-249.
9. Pauwels RA, Sears MR, Campbell M, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J 2003; 22: 787-794.
10. Chervinsky P, Goldberg P, Galant S, et al. Long-term cardiovascular safety of salmeterol powder pharmacotherapy in adolescent and adult patients with chronic persistent asthma: a randomized clinical trial. Chest 1999; 115: 642-648.

DECLARATION OF INTEREST: Dr Leong: None. Dr Summers has received conference support from GlaxoSmithKline and AstraZeneca, and consultancy fees from AstraZeneca.