

Long-acting beta₂ agonists for childhood asthma

SUMMARY

Long-acting beta₂ agonists are currently overprescribed in children. They are also often used inappropriately as first-line therapy and are not recommended for children aged five years or less.

Due to the paucity of paediatric clinical trials, the evidence for the efficacy and safety of long-acting beta₂ agonists in children is limited. There is little evidence that they reduce the risk of severe exacerbations and some evidence that they may actually increase the risk.

The regular use of long-acting beta₂ agonists may also result in a loss of protection against exercise-induced bronchoconstriction, and the development of tolerance to short-acting beta₂ agonists.

Long-acting beta₂ agonists are only one option for children whose asthma is not adequately controlled with inhaled corticosteroids alone – the other options being an increase of inhaled corticosteroid dose or the addition of a leukotriene receptor antagonist. For children whose major ongoing symptoms are activity related, the addition of a leukotriene receptor antagonist is the preferred option.

Introduction

Australian guidelines for persistent childhood asthma advocate a stepwise approach to therapy with preventer drugs.¹ These guidelines highlight that the vast majority of children requiring preventer therapy will be well controlled on either low-dose inhaled corticosteroids or a leukotriene receptor antagonist. Long-acting beta₂ agonists should be given only to children who remain symptomatic on optimal doses of inhaled corticosteroids.

There is limited evidence for the efficacy of long-acting beta₂ agonists in children,² but combination therapy (inhaled corticosteroids and long-acting beta₂ agonists) is commonly prescribed as first-line when preventer therapy is needed. Combination therapy now represents over 40% of prescribed

preventer therapy in children. Based on the frequency of asthma patterns in children and the stepwise approach advocated by the current National Asthma Council of Australia guidelines,¹ combination therapy should represent no more than 10% of prescribed preventer therapy in children and probably less, given the availability of alternative step-up options.

A greater concern is that combination therapy now represents 20% of **all** prescribed asthma medication (preventers and relievers) in pre-school children.³ This is outside the prescribing indications for combination therapy and no evidence exists for the efficacy or safety of long-acting beta₂ agonists in this age group. Combination therapy is also often inappropriately prescribed for intermittent, rather than regular, use.

Efficacy of long-acting beta₂ agonists in children

A Cochrane review has assessed the addition of long-acting beta₂ agonists to inhaled corticosteroids for persistent asthma in children.² It included 25 randomised trials, representing 31 control-intervention comparisons, in 5572 children. Importantly, no studies included children less than four years of age.

There were 24 comparisons of adding long-acting beta₂ agonists or placebo to a constant dose of inhaled corticosteroids. These trials showed a predictable small and probably not patient-important improvement in lung function. There was no significant reduction in exacerbations in the children taking regular long-acting beta₂ agonists.

Seven studies compared the addition of long-acting beta₂ agonists with an increased dose of inhaled corticosteroids. The children on long-acting beta₂ agonists had significantly improved lung function and short-term linear growth when compared to those on higher dose inhaled corticosteroids. However, there was a non-significant increase in exacerbations requiring oral corticosteroids and hospitalisation (which the authors concluded required further examination).

Another Cochrane review highlighted the difference in the effectiveness of long-acting beta₂ agonists

Peter Paul van Asperen

Head, Department of Respiratory Medicine
The Children's Hospital at Westmead
Sydney Children's Hospitals Network

Macintosh Professor of Paediatric Respiratory Medicine
Discipline of Paediatrics and Child Health
Sydney Medical School
University of Sydney

Key words

inhaled corticosteroids,
leukotriene receptor
antagonists

Aust Prescr 2012;35:111-3

No trials of long-acting beta₂ agonists have been conducted in pre-school children

ARTICLE

Long-acting beta₂ agonists for childhood asthma

in children versus adults.⁴ This review compared the addition of long-acting beta₂ agonists to inhaled corticosteroids versus higher dose inhaled corticosteroids, in both adults and children with suboptimal asthma control despite low-dose inhaled corticosteroids. In adolescents and adults the combination of long-acting beta₂ agonists and inhaled corticosteroids was modestly more effective in reducing the risk of exacerbation requiring oral corticosteroids than a higher dose of inhaled corticosteroids. However, in children, combination therapy did not lead to a significant reduction, but rather a trend toward an increased risk of severe exacerbations and hospital admission.⁴

A further Cochrane review examined the addition of long-acting beta₂ agonists to inhaled corticosteroids versus inhaled corticosteroids alone as first-line therapy for persistent asthma in adults and children who had previously taken steroids. This review concluded that the 'current evidence does not support the use of combination therapy as first-line preventive treatment, without a prior trial of inhaled corticosteroids'.⁵ While the combination of budesonide and eformoterol is approved for patients aged 12 years and over, there are limited paediatric data.

Safety of long-acting beta₂ agonists in children

The Cochrane reviews raised safety concerns about an increased risk of severe exacerbations and hospitalisation with long-acting beta₂ agonists.^{2,4}

These observations are consistent with a recent meta-analysis which found an increased risk of severe and life-threatening asthma exacerbations associated with long-acting beta₂ agonists, even when they were used with concomitant inhaled corticosteroids.⁶ This finding contradicts previous suggestions that the increased risk of severe exacerbations with long-acting beta₂ agonists is only seen in patients treated with long-acting beta₂ agonists alone.

A possible explanation for the increased risk of severe exacerbations is the development of tolerance to short-acting beta₂ agonists, resulting in a diminished response to the child's normal rescue therapy. This assumption is supported by a recent study in children with poorly controlled exercise-induced asthma, despite inhaled corticosteroids. The trial compared montelukast versus long-acting beta₂ agonists as add-on therapy to inhaled corticosteroids. Long-acting beta₂ agonist therapy was associated with the development of tolerance to both protection against exercise-induced bronchoconstriction and the response to short-acting beta₂ agonists.⁷

These safety concerns have led the US Food and Drug Administration (FDA) to recommend that long-acting

beta₂ agonists should only be used as combination therapy to ensure that children continue to receive an inhaled corticosteroid. To limit exposure, the long-acting beta₂ agonist should be withdrawn once good asthma control has been achieved.⁸ More recently the FDA issued a requirement for further trials in children, adolescents and adults, to 'provide data in a timely fashion that will clarify the safety risks associated with long-acting beta₂ agonists when used concurrently with inhaled corticosteroids, and to inform the safe use of these medications for the treatment of asthma'.⁹

Comparison with other treatments

The currently recommended options for children whose asthma is not adequately controlled on inhaled corticosteroids alone are:

- adding a long-acting beta₂ agonist
- adding a leukotriene receptor antagonist
- increasing the dose of inhaled corticosteroids.

Before intensifying the treatment of poorly controlled asthma it is important to first exclude other factors contributing to poor control. These include incorrect diagnosis, poor adherence, inappropriate delivery device and poor inhaler technique.

When comparing the addition of long-acting beta₂ agonists to an increased dose of inhaled corticosteroids, current evidence suggests that while regular use of long-acting beta₂ agonists will predictably improve lung function, the risk of exacerbation appears, if anything, to increase.^{2,4}

A randomised triple crossover study in 182 children aged 6–17 years of age who had uncontrolled asthma on 100 microgram of fluticasone propionate twice daily also provides relevant comparative information.¹⁰ These children received 16 weeks on each of the following therapies, in random order:

- 250 microgram of fluticasone twice daily (inhaled corticosteroid step-up)
- 100 microgram of fluticasone plus 50 microgram salmeterol twice daily (long-acting beta₂ agonist step-up)
- 100 microgram of fluticasone twice daily plus 5 or 10 mg montelukast daily (leukotriene receptor antagonist step-up).

The response was assessed by a composite index comprising exacerbations requiring oral corticosteroids, asthma-control days and forced expiratory volume in one second. Overall the probability of the long-acting beta₂ agonist step-up providing the best response was higher (45%), but the probability of having a best response to leukotriene receptor antagonist (28%) or inhaled corticosteroid

(27%) step-up was also significant. This highlights the variability of children's responses to these drugs, plus the need to regularly monitor and appropriately adjust each child's therapy.⁹

What is clear is that leukotriene receptor antagonists are superior to long-acting beta₂ agonists in protecting against exercise-induced bronchoconstriction as add-on therapy in children already receiving inhaled corticosteroids.⁷ Further, in contrast to regular use of long-acting beta₂ agonists, leukotriene receptor antagonists are not associated with the development of tolerance to either protection against exercise-induced bronchoconstriction, nor responsiveness to short-acting beta₂ agonists.⁷ Montelukast has now been listed in the Australian Pharmaceutical Benefits Scheme for add-on treatment (as an alternative to long-acting beta₂

agonists) for children aged 6–14 years, who despite inhaled corticosteroids, have ongoing activity (exercise)-related asthma.

Recommendations

There are few efficacy trials of long-acting beta₂ agonists in children with asthma, and no trials have been conducted in children under four years of age. There are ongoing safety concerns with long-acting beta₂ agonist use, particularly in children, which require further clarification. Based on current evidence the Thoracic Society of Australia and New Zealand has made recommendations on 'The role of corticosteroids in the management of childhood asthma'¹¹ (see Box).

In brief, there are three step-up options for children not adequately controlled on inhaled corticosteroids:

- adding a long-acting beta₂ agonist
- adding a leukotriene receptor antagonist
- increasing the dose of inhaled corticosteroids.

The addition of a leukotriene receptor antagonist is the preferred option for children with ongoing activity-related asthma. Long-acting beta₂ agonists are not recommended for children five years or younger. ◀

Professor Peter van Asperen is currently a member of the MSD (Aust) Paediatric Respiratory Physician Advisory Board and has received speaker fees from MSD for presentations on management of asthma and wheeze in children. He is a member of the GlaxoSmithKline Paediatric Respiratory Taskforce which has been convened to ensure appropriate prescribing of Seretide in children. His department has received research funding in the past from GlaxoSmithKline, Astra Zeneca, MSD, Boehringer Ingelheim and Altana for involvement in clinical trials but is not currently receiving funding from these companies.

Box Recommendations on step-up options¹¹

In situations where effective control of asthma cannot be achieved with doses of 400 microgram/day budesonide, or 200 microgram/day fluticasone or hydrofluoroalkane-beclomethasone dipropionate or 160 microgram/day ciclesonide, the main step-up options include increasing the inhaled corticosteroids dose or adding a long-acting beta₂ agonist or a leukotriene receptor antagonist. In the absence of evidence of safety and efficacy, the use of long-acting beta₂ agonists is not recommended in children aged five years or younger. (Strong recommendation, moderate quality evidence)

In children with ongoing exercise-induced symptoms, despite inhaled corticosteroids, adding leukotriene receptor antagonists has been shown to be effective and superior to long-acting beta₂ agonists, and does not have the problem of the development of tolerance. (Strong recommendation, moderate quality evidence)



SELF-TEST QUESTIONS

True or false?

1. Long-acting beta₂ agonists may induce tolerance to short-acting beta₂ agonists in children with asthma.
2. In childhood asthma, the combination of a long-acting beta₂ agonist with an inhaled corticosteroid significantly reduces severe exacerbations.

Answers on page 135

REFERENCES

1. Asthma Management Handbook 2006. Melbourne: National Asthma Council Australia; 2006.
2. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009;CD007949.
3. Phillips CB, Toyne H, Ciszak K, Attewell RG, Kljakovic M. Trends in medication use for asthma in school-entry children in the Australian Capital Territory, 2000–2005. Med J Aust 2007;187:10–3.
4. Ducharme FH, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010;CD005533.
5. Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long-acting beta-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naïve adults and children. Cochrane Database Syst Rev 2009;CD005307.
6. Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. Am J Med 2010;123:322–8.
7. Fogel RB, Rosario N, Aristizabal G, Loeys T, Gaile S, Noonan G, et al. Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. Ann Allergy Asthma Immunol 2010;104:511–7.
8. Chowdhury BA, Dal Pan GD. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. N Engl J Med 2010;362:1169–71.
9. Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. N Engl J Med 2011;364:2473–5.
10. Lemanske RF, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma while receiving inhaled corticosteroids. N Engl J Med 2010;362:975–85.
11. Van Asperen PP, Mellis CM, Sly PD, Robertson CF. The role of corticosteroids in the management of childhood asthma. Sydney: Thoracic Society of Australia and New Zealand; 2010.

FURTHER READING

Van Asperen PP, Mellis CM, Sly PD, Robertson CF. Evidence-based asthma management in children – what's new? [editorial]. Med J Aust 2011;194:383–4.

Van Asperen P. What's new in the management of asthma in children? Med Today 2011;12:53–64.