

Safety concerns with salmeterol

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The introduction of long-acting beta₂ agonists, such as salmeterol and eformoterol, has been an important development in the management of asthma. For patients with persistent symptoms of asthma, despite treatment with inhaled corticosteroids, the addition of a long-acting beta₂ agonist results in improved lung function, fewer symptoms, a reduced need for 'rescue' medication and a reduction in acute exacerbations.¹ The recommendation that these patients add a long-acting beta₂ agonist to their inhaled corticosteroid therapy has resulted in salmeterol or products containing salmeterol becoming the second most frequently prescribed group of drugs for asthma in Australia. It is therefore of great significance that the US Food and Drug Administration (FDA) has issued advice about long-acting beta agonists that states 'these medicines may increase the chance of severe asthma episodes, and death when those episodes occur'.²

Safety concerns regarding beta agonists are not new. Overuse of the potent short-acting beta agonist fenoterol, in New Zealand in the 1980s, was associated with increased asthma mortality.³ Similar concerns have arisen over reported cases of severe asthma exacerbations associated with the use of

long-acting beta₂ agonists. In the 1990s a UK trial compared 'add-on' salmeterol to regular salbutamol in 25 000 patients. Those on salmeterol appeared to have a three times greater risk of death. There was one death for every 650 patient years of salmeterol treatment. As there were only 14 asthma-related deaths in the 16-week study, the difference between salmeterol and salbutamol was not statistically significant.⁴

The FDA then requested the makers of salmeterol to clarify these findings and this resulted in the Salmeterol Multicenter Asthma Research Trial (SMART). Patients with persistent symptoms of asthma had salmeterol 42 microgram twice a day or placebo added to their usual treatment and were followed for 28 weeks. In the previous 12 months 26% of these patients had reported emergency room visits and only 47% regularly used inhaled corticosteroids. An interim analysis was performed after 26 335 patients had completed the study. The composite primary outcome of respiratory-related deaths and life-threatening episodes was uncommon and did not show a statistically significant effect. However, there were significant increases in asthma-related deaths in the salmeterol group (Table 1). The risk appeared greater in African Americans, but as this group had more severe disease at baseline this may have been a confounder rather than indicative of a genetic effect.⁵ These results led to the FDA announcement and to a change in labelling to include a warning about 'a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths'.

It is unclear whether this is an effect unique to salmeterol. There are no published trials similarly assessing the safety of eformoterol. However, in data submitted to the FDA there did appear to be an increase in adverse events. Eformoterol was associated with 5.2 adverse events per 100 patient years compared to 0.6 with placebo and 0 with albuterol (salbutamol).⁶ Again this event rate appears low but suggests a real clinical finding that could be a class effect of long-acting beta₂ agonists.

Although the events are rare, the association between salmeterol and serious asthma-related episodes and asthma-related deaths appears compelling. How therefore do we explain these results and can we identify those individuals at risk?

Unfortunately the data so far do not give us conclusive answers and data in children are lacking. It is clear that inhaled

In this issue...

Critical appraisal is a useful method for assessing the results of trials. However, Michael Lowe and Bradleigh Hayhow remind us that the information must be considered in a clinical context. Providing health professionals with independent information about drugs is essential for the quality use of medicines. It is therefore unfortunate that an Australian appraisal of a product has been blocked by legal action.

Disseminating drug information is particularly important if there is a question of safety, such as the concerns about salmeterol discussed by Peter Wark.

With warmer weather approaching, Australian snakes will be on the move. Geoffrey Isbister therefore provides a timely review on how to manage snake bites.

Table 1

Relative risks of adverse outcomes with salmeterol³

Outcome	Relative risk (95% confidence interval)	Number of events	
		Salmeterol (13 176 patients)	Placebo (13 179 patients)
Respiratory-related deaths and life-threatening experiences	1.40 (0.91, 2.14)	50	36
Respiratory-related deaths	2.16 (1.06, 4.41)	24	11
Asthma-related deaths	4.37 (1.25, 15.34)	13	3
Asthma-related deaths or life-threatening experiences	1.71 (1.01, 2.89)	37	22

corticosteroids are highly successful in improving asthma control and reducing serious asthma-related events. In the SMART study a mixture of poorly controlled asthma and a lack of use of inhaled corticosteroids may have resulted in the adverse outcomes. Inhaled corticosteroids suppress airway inflammation. This disease modification is thought to be central to the way inhaled corticosteroids exert their effect. One hypothesis is that inhaled corticosteroids may also be needed to prevent the serious asthma-related episodes associated with long-acting beta₂ agonists. If this is found to be true, patients will need to take inhaled corticosteroids with long-acting beta₂ agonists. A combination inhaler may be advantageous, but the safety of combinations of inhaled corticosteroids and long-acting beta₂ agonists needs to be defined.

How will the findings about salmeterol affect Australian practice? Currently, long-acting beta₂ agonists are recommended as add-on therapy to an appropriate dose of inhaled corticosteroid. The importance of inhaled corticosteroid use and its rationale still needs to be reinforced to patients and health professionals. Non-compliance with inhaled corticosteroids however remains a danger as these drugs, by their preventive nature, do not directly improve asthma symptoms. The Pharmaceutical Benefits Scheme restricts the use of combination inhalers to those who have first been stabilised on inhaled corticosteroids and long-acting beta₂ agonists given from separate inhalers. Combination inhalers may be a better insurance against non-compliance with inhaled corticosteroids and the possible adverse outcomes of long-acting beta₂ agonists given alone. Long-acting beta₂ agonists should not be used to treat acute asthma.

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Further reading

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Dr Wark has received sponsorship in the form of unrestricted educational grants from GlaxoSmithKline and AstraZeneca to attend conferences. He has spoken at events sponsored by these companies, though not in direct relation to their products. Dr Wark also serves on an advisory board for AstraZeneca.

Schedule of Pharmaceutical Benefits – 'the yellow book'

From December 2006 the Schedule of Pharmaceutical Benefits ('the yellow book') will be available online and updated monthly. Readers will be able to search the online version for information on medicines, brands and prices.

As part of the transition, a printed version of the December 2006 issue will be sent to users who currently receive a printed copy. For more information and to subscribe to email updates of the Schedule, go to www.health.gov.au/pharmbiz