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Health and Drug Alerts

Long-acting β_2-agonists in asthma: safety concerns

Reason for posting: Long-acting β_2-agonist (LABA) medications are bronchodilators used in the treatment of asthma and chronic obstructive pulmonary disease. More than a decade ago questions were raised about an excess of asthma-related events, including death, in a study of salmeterol.[1] Randomized trials were completed in recent years of either salmeterol or formoterol to resolve these safety concerns, but serious questions remain.

As reported previously in *CMAJ*,[2] the Salmeterol Multi-center Asthma Research Trial (SMART), a 28-week randomized controlled trial that enrolled more than 26 000 patients, was stopped early because of salmeterol-related safety concerns. The trial data have not been published and instead were submitted to the US Food and Drug Administration (FDA). The FDA recently convened its Pulmonary-Allergy Drugs Advisory Committee to review these and other LABA safety data; the committee decided that the potential risks seen in this salmeterol trial might be shared by other LABA medications. Safety warnings have now been issued by all manufacturers of LABAs in Canada (www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index_e.html).

Table 1: Primary and selected secondary outcomes of SMART trial*

Outcome; ethnic group	Group; no. (%) of patients† Salmeterol MDI *n = 13 176*	Placebo *n = 13 179*	RR (95% CI)
Primary: respiratory-related death or life-threatening experience‡			
All	50 (0.379)	36 (0.273)	1.40 (0.91–2.14)
White	29 (0.312)	28 (0.299)	1.05 (0.62–1.76)
Black	20 (0.845)	5 (0.215)	4.10 (1.54–10.9)
Secondary: asthma-related death or life-threatening experience‡			
All	37 (0.280)	22 (0.166)	1.71 (1.01–2.89)
White	17 (0.183)	16 (0.170)	1.08 (0.55–2.14)
Black	19 (0.803)	4 (0.172)	4.92 (1.68–14.45)

Note: MDI = metered-dose inhaler, RR = relative risk, CI = confidence interval.
*Adapted from Chowdhury BA. Division director memorandum [overview of the FDA background materials prepared for the meeting to discuss the implications of the available data related to the safety of long-acting beta-agonist bronchodilators]. Available: www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4148B1_03_01-FDA-Div-Dir-Memo.pdf (accessed 2005 Sept 22).
†In the salmeterol group, there were 9281 white, 2366 African-American. In the placebo group, there were 9361 white, 2319 African-American.
‡Life-threatening = required mechanical ventilation or intubation.

Table 2: Occurrence of serious asthma-related adverse events and asthma exacerbations in a phase IV trial of formoterol*

Outcome	Group; no. (%) of patients Formoterol 24 μg bid *n = 527*	Formoterol 12 μg bid *n = 527*	Placebo *n = 514*	Formoterol open-label *n = 517*
Serious asthma-related adverse event	5 (0.9)	2 (0.4)	1 (0.2)	1 (0.2)
Serious asthma exacerbation	3 (0.6)	2 (0.4)	1 (0.2)	1 (0.2)

Note: bid = twice daily.
*Adapted from Chowdhury BA. Division director memorandum [overview of the FDA background materials prepared for the meeting to discuss the implications of the available data related to the safety of long-acting beta-agonist bronchodilators]. Available: www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4148B1_03_01-FDA-Div-Dir-Memo.pdf (accessed 2005 Sept 22).

The drugs: LABAs sold in Canada include salmeterol (as Serevent and, in combination with fluticasone, as Advair) and formoterol fumarate (as Oxeze and Foradil and, in combination with budesonide, as Symbicort). They drugs have been shown to improve measures of lung function, disease control and quality of life for people with asthma.[3]

However, safety concerns exist. SMART participants in the salmeterol group experienced an absolute increase in risk of the study's primary end point (respiratory-related death or life-threatening experience) of 0.106% over that seen in the placebo group (Table 1). This gives a number needed to harm (NNH) of 943 (95% confidence interval [CI] 410 to infinity). The NNH for the secondary end point (asthma-related death or life-threatening experience) was similar. However, a post hoc analysis showed that black patients had much higher relative and absolute risks than non-black patients: the NNH among black salmeterol users was only 159 (95% CI 96–468) for respiratory-related death or life-threatening experience and 158 (95% CI 97–433) for asthma-related death or life-threatening experience.

After 3 small phase III studies of formoterol suggested that the risk of asthma exacerbations increased with higher drug doses,[4] a 16-week phase IV study was conducted, enrolling 2307 patients above the age of 12. No deaths occurred in this trial. Although the absolute event rates were low, patients taking higher formoterol doses appeared to experience more serious asthma-related events than those given lower doses of the drug or placebo (Table 2).

What to do: LABAs are indicated for asthma maintenance therapy, and only the lowest effective dose should be used. Recent large trials, particularly of salmeterol, have shown that asthma-

and respiratory-related deaths and life-threatening events occurred more often among patients given this class of drugs than among those given a placebo. The risk appeared to be much higher among black than among non-black patients for reasons that are not yet clear. These risks must be communicated to patients. Although there is interest in attributing differences in outcomes to differences in baseline rates of inhaled corticosteroid use at enrolment, the trials were not adequately designed to assess this. Patients prescribed LABAs should be made aware of the safety issues in Box 1 and told to seek prompt medical attention if their asthma deteriorates (e.g., they require increased use of a short-acting bronchodilator).

Box 1: Safety messages concerning the use of long-acting β_2-agonist (LABA) medications in asthma

- Do not use as monotherapy
- Do not use as "rescue" medication. Patients must also have a short-acting bronchodilator to use as needed for acute asthma symptoms
- Do not initiate in patients with acutely deteriorating asthma
- Do not use as a replacement for inhaled corticosteroids. Patients should be taking optimal doses of inhaled corticosteroids before starting LABA therapy
- Prescribe only the lowest effective dose

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