Salmeterol (Serevent) asthma trial halted early

Reason for posting: A large, placebo-controlled trial of Serevent (salmeterol), a long-acting β_2-receptor agonist (LABA), was recently stopped early amid concerns that the drug may be associated with life-threatening asthma episodes and asthma-related deaths. Although details of the trial have not been published, a recent Dear Healthcare Professional letter posted on the US Food and Drug Administration's Web site describes some interim findings (www.fda.gov/medwatch/SAFETY/2003/serevent.htm).

The drug: Salmeterol is a long-acting (12 hours) agonist of β_2-adrenoreceptors with a slow onset of action (10–20 minutes).[1] It is indicated for use in patients with asthma and chronic obstructive pulmonary disease (COPD)[1] and may also prevent high-altitude pulmonary edema.[2] Salmeterol is marketed as Serevent, and is combined with fluticasone in the Advair Diskus.[3]

With hopes of resolving controversy about the safety of LABAs,[4–7] the Salmeterol Multi-center Asthma Research Trial (SMART) was initiated in 1996. In addition to their usual asthma therapy, patients were given either salmeterol (42 µg twice daily) or a placebo for 28 weeks. The primary end point was the combined number of respiratory-related deaths and life-threatening events (requiring intubation and mechanical ventilation). Secondary end points included asthma-related events (including deaths). In a routine interim analysis of data for nearly 26 000 patients in late 2002, the salmeterol group showed a nonsignificant trend toward more asthma-related life-threatening events (including deaths) than did the placebo group.

Among the black patients (17% of the study population), there were significantly more primary and secondary outcomes in the salmeterol group than in the placebo group. No such difference was seen among the white patients (71% of the study population). No other ethnic subgroup data were analyzed owing to small numbers. The black patients had more frequent symptoms and worse peak expiratory flows at baseline and more intubations, emergency department visits and hospital admissions before study entry.

Fifty percent of white and 38% of black patients were using inhaled corticosteroids at baseline. Among the patients using inhaled corticosteroids, there was no significant difference between the salmeterol and placebo groups in primary or secondary outcomes. However, among patients not using inhaled corticosteroids, there were significantly more asthma-related deaths in the salmeterol group than in the placebo group.

What to do: Ethnicity may be a factor in asthma-related death[8] and asthma care.[9] Regardless, the SMART findings appear to reinforce Canadian asthma recommendations,[10] which state that LABAs should play a role as "additional therapy" for those already managed with appropriate doses of inhaled corticosteroids. Salmeterol is not a substitute for inhaled asthma anti-inflammatory therapy and should not be initiated in patients with acutely deteriorating asthma. For patients already using the drug, acute symptoms should not be treated with salmeterol in place of short-acting β_2-agonists. Patients with increasing requirements for short-acting β_2-agonists may have deteriorating asthma and require prompt reassessment. Abrupt discontinuation of salmeterol is not advisable, as this can lead to serious asthma or COPD exacerbation.

Eric Wooltorton
CMAJ

References

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