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EBM COMMENTARY

ARE INHALED LONG-ACTING BETA-AGONISTS (LABA) REALLY HARMFUL IN ADULT ASTHMATICS?

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Case scenario

Mr. SS, a 32 year old Chinese male, is a known case of moderately severe persistent asthma since the past 17 years. He is a palm oil plantation worker for the past 6 years. He is a non- smoker, non-hypertensive and has no history of diabetes mellitus. There is a family history of bronchial asthma in both his mother and maternal grandfather. On examination, the patient appears tachypnoeic, with a respiratory rate of 30 breaths per minute. His pulse rate is 110 beats per minute. Peak expiratory flow done at the time of clinical examination is 200 L/min. He is currently on a combination of fluticasone propionate (250 mcg) and salmeterol (50 mcg) administered by an inhaler device twice a day. He has heard that the use of inhaled long-acting beta agonists (LABA) is considered controversial and potentially damaging and is therefore concerned about further usage of this therapy.

Question

Is it safe to use inhaled long acting beta-adrenergic agonists (LABA), on a prolonged basis in patients with moderately severe persistent asthma?

EBM commentary

Asthma is a chronic inflammatory disorder of the air passages that is rapidly increasing in incidence in both adults and children. In these patients, it is important to prevent frequent exacerbations in order to prevent progression to irreversible obstructive airway disease, later in life. If left untreated, an acute exacerbation of bronchial asthma can even lead to respiratory failure and death. Long acting inhaled beta agonists have been widely used by pulmonologists all over the world and have also been recommended by the British Thoracic Society (BTS) in their guidelines on the management of asthma, but their safety has recently been doubted. The Food and Drug Administration (FDA) approved new safety labelling on March 2, 2006 for medication containing salmeterol, a LABA, because of data suggesting an increased risk of fatal or potentially fatal asthma episodes. The "black box" warning and public health advisory for salmeterol, salmeterol-fluticasone combination, and formoterol has heightened the concerns of both, patients and their treating physician, regarding the risk-to-benefit ratio and consequently the medico-legal implications of prescribing these agents for patients with bronchial asthma.

Contrary to these doubts being raised, several clinical trials,[1,2] have shown that patients who received LABA combined with inhaled corticosteroids had fewer symptoms (including nocturnal awakening), improved lung function, better health-related quality of life and reduced frequency of severe exacerbations than patients who received inhaled corticosteroid as monotherapy at the same or higher doses.

The much publicized Cochrane review by Walters *et al*.[3] has conclusively shown that LABA are significantly more effective when compared with a placebo in improving morning and evening PEFR and quality of life. Several other meta-analyses[4,5] have also found significantly lower rates of acute exacerbations with the combined use of an inhaled corticosteroid and a LABA as compared to inhaled corticosteroid monotherapy. Neither cohort studies[6] nor case-controlled studies[7] have found any evidence linking LABA use to an increased risk of fatal or near-fatal asthma. Jenkins et al.[8] found that the combination of fluticasone propionate 250 mcg and salmeterol 50 mcg twice a day was superior to therapy with budesonide 800 mcg twice a day while treating moderate persistent bronchial asthma.

After salmeterol was approved in the United Kingdom, the Serevent Nationwide Surveillance (SNS) trial[9] enrolled 25,180 asthma patients, who were randomized in a two-to-one ratio to receive either salmeterol 50 mcg twice a day or salbutamol 200 mcg four times a day, added to their current asthma therapy for 16 weeks. More than two thirds (69%) of the patients took inhaled corticosteroids concurrently. Twelve of the 16,787 patients in the salmeterol group died of asthma or other respiratory causes, compared with 2 of 8,393 patients in the salbutamol group; the difference was not statistically significant (relative risk [RR] =3.0, P = 0.105). However, the

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Salmeterol Multicenter Asthma Research Trial (SMART), conducted by Nelson et al.[10] in the United States, showed that the patient group which was treated with salmeterol, particularly African-Americans, had significantly higher rates of respiratory-related deaths (RR 2.16, 95% CI 1.06-4.41), asthma-related deaths (RR 4.37, 95% CI 1.25-15.34) and combined asthma-related deaths or life threatening experiences (RR 1.71, 95% CI 1.01-2.89). There were 13 asthma-related deaths and 37 combined asthma-related deaths or life threatening experiences in the salmeterol group, compared with 3 and 22, respectively, in the placebo group.

A recent meta-analysis of randomised double blind studies in which LABA therapy was compared with placebo by Salpeter *et al*,[11] found significantly higher rates of death from bronchial asthma and hospitalization for asthma exacerbations with salmeterol or formoterol than with placebo. The odds ratio for hospitalization with LABA was 2.6 (95% CI 1.6-4.3) for both adults and children. Salpeter *et al*,[11] asserted that the asthma death rate has increased in the United States in the past decade and states that "salmeterol may be responsible for approximately 4,000 of the 5,000 asthma-related deaths that occur in the United States each year".

Is the problem really with inhaled long-acting beta-adrenergic agonists or is there another reason?

There appear to be several potential explanations for the greater rate of untoward outcomes with salmeterol in the SMART trial.

- ***Genetic polymorphism.*** An asthma sub-group homozygous for the Arg/Arg 16 genotype of the $_2$-adrenergic receptor may be predisposed to adverse events with the regular use of LABA. Genetic polymorphisms of the β_2-adrenergic receptor could influence the clinical response in these patients.[12] Many studies have focused on amino acid 16, which may be either arginine (Arg) or glycine. With the regular use of shot-acting beta agonists, patients with the Arg/Arg genotype appear to be predisposed to adverse effects,[12,13] including a reduction in the morning peak expiratory flow rate (PEFR) and an increased rate of acute exacerbations, which improve after the regular use of short-acting β_2-agonists is stopped. Racial variation in the distribution of genetic polymorphisms, such as the gene encoding the β_2-adrenergic receptor, places African-Americans at a greater risk for asthma exacerbations when they take short-acting β_2-agonists regularly. It is not yet known whether this risk also applies to LABA. Wechsler *et al*[13] reported that the morning PEFR declined in Arg/Arg 16 patients receiving salmeterol monotherapy, thereby providing support for this contention.
- ***"Masking" of airway inflammation.*** It is believed that LABA monotherapy may mask airway inflammation and thereby heighten the risk of fatal and near-fatal respiratory events. The findings of the Salmeterol or Corticosteroids (SOCS) study indicate that monotherapy with a LABA may improve symptoms and lung functions while masking unchecked airway inflammation.[14] Consequently, such patients are at greater risk of serious asthmatic exacerbations. In another study, in a small group of young adults with a history of asthma but no clinical evidence of asthma for over a year, bronchial biopsy specimens confirmed on-going evidence of airway inflammation.[15] Moreover, low dose exposure to allergens in a group of patients with mild asthma under controlled research conditions showed worsening airway inflammation without significant change in asthma symptoms.[16] These findings indicate that perhaps absent or minimal symptoms may not truly reflect disease activity. It has been noted that near-fatal and fatal episodes of asthma occur in patients with seemingly mild disease; it is therefore possible that in these patients an assessment of airway inflammation, rather than symptoms and lung function, would have indicated more severe disease.[17] This could probably explain the increased incidence of fatal and potentially near-fatal asthma episodes in patients using LABA, thereby deflecting blame from these medications.

Conclusion

Asthmatic patients such as Mr. SS should be explained that:

- FDA recently issued a black box warning regarding use of LABA for management of asthma. This warning was based on results of the Salmeterol Multicenter Asthma Research Trial (SMART), which found a statistically significant increase in episodes of fatal and near-fatal asthma attacks in patients randomized to salmeterol compared with placebo, primarily affecting African-Americans.
- There is a fair difference of opinion regarding the role of LABA in treatment of bronchial asthma, and based on the interpretation of evidence in the medical literature, it is for the treating doctor to decide whether the potential for benefit with use of inhaled corticosteroids combined with LABA far outweighs the potential for risk.
- Alternatives to inhaled corticosteroids combined with LABA, include higher-dose inhaled corticosteroids, or inhaled corticosteroids at lower dose in combination with another "controller" (anti-leukotrienes, theophylline, nedocromil, or cromolyn); however, compared with these alternatives, the evidence indicates that outcomes are superior with the combination of inhaled corticosteroids and LABA.
- In light of the FDA actions, the decision to prescribe or continue to prescribe LABA should be based on a determination of risks and benefits made by the asthma patient in partnership with his or her physician.

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In the October 16 issue of BMJ, a new study has cast doubt on the role of aspirin in diabetic patients. Diabetic patients were randomised to receive either aspirin or antioxidant or both or none (the so-called 2x2 factorial design). The current ADA guideline advised all diabetic patients to be on aspirin since it is considered a "cardiac equivalent".

This RCT from UK found that neither aspirin alone or antioxidant or combination actually reduce the risk of major CV events after seven years.

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