REVIEW ARTICLE

Is it safe to use long-acting β-agonists in asthma and chronic obstructive pulmonary disease? Implications of recent trials and meta-analyses

Malcolm R. Sears

Firestone Institute for Respiratory Health, St. Joseph's Healthcar, McMaster University, Hamilton, ON, Canada

KEY WORDS

inhaled corticosteroids, long-acting β-agonists, meta-analyses, monotherapy, mortality, safety, serious adverse events

ABSTRACT

The safety of long-acting β-agonists (LABAs) has been hotly debated for several years, with surveillance studies suggesting increased risk of mortality, especially with use of LABA without inhaled corticosteroid (ICS). Meta-analyses of selected trials, especially those dominated by one large study, report significantly increased risks for mortality and Serious Adverse Events (SAEs). Review of all of the available evidence from clinical trials, and meta-analyses using different selection criteria, suggests that LABA with ICS in fact significantly reduces SAEs. The risk of mortality is more difficult to assess, but post-hoc analyses suggest the risk is increased with LABA monotherapy and not with concomitant use of ICS. In both asthma and chronic obstructive pulmonary disease, concomitant use of ICS should be considered best practice whenever LABAs are used.

Correspondence to:
Prof. Malcolm R. Sears, MB, FRACP, FRCPC, FAAAAI, McMaster University, Firestone Institute for Respiratory Health, St. Joseph's Healthcare Hamilton, 50 Charlton Avenue East, Hamilton, ON L8N 4A6, Canada, phone: 001-905-522-1155, fax: 001-905-521-6132, e-mail: searsm@mcmaster.ca
Received: November 3, 2008.
Accepted: November 12, 2008.
Conflict of interest: Malcolm R. Sears has reveived research funding from AstraZeneca, Merck Frosst Canada and Merck Sharpe Dohme, and has acted as consultant for AstraZeneca, GlaxoSmithKline, Merck Frosst Canada, Nycomed and Schering-Plough. He holds the Chair in Respiratory Epidemiology jointly endowed by AstraZeneca and McMaster University.
Pol Arch Med Wewn. 2008; 118 (12): 761-766

Questions regarding the safety of bronchodilators in asthma go back to a report in 1948 of increased mortality associated with use of nebulized epinephrine.[1] Concern became widespread in the 1960s when England and Wales, Australia and New Zealand experienced an increase in asthma mortality among young people, associated in time with introduction of a high dose formulation of isoprenaline.[2] A further epidemic of asthma mortality occurred in New Zealand from 1976 through the 1980s,[3] and case-control studies suggested a relationship to prescription of fenoterol, a more potent and slightly longer acting β-agonist than salbutamol.[4] A randomized placebo-controlled clinical trial demonstrated that regular use of fenoterol could increase asthma severity.[5] Asthma mortality in New Zealand decreased abruptly when fenoterol was severely restricted,[6] just as mortality in the UK, Australia and New Zealand had decreased in the late 1960s when use of high dose isoprenaline was discouraged. An accompanying substantial reduction in asthma morbidity with restriction of fenoterol suggested the epidemic was more likely mediated through increased asthma severity rather than through cardiac adverse effects, perhaps through down-regulation of β-receptors.[3]

Long-acting β-agonists (LABAs) were introduced in 1990, and over time have become a very common treatment in both asthma and chronic obstructive pulmonary disease (COPD). In both diseases, LABAs have been used as monotherapy or added to inhaled corticosteroid (ICS). This latter strategy was shown in large randomized controlled trials in asthma to provide overall better outcomes (symptom control, improved lung function, and reduced exacerbations) than doubling the dose of ICS.[7,8] Some have interpreted these findings as indicating LABAs have anti-inflammatory activity, for which evidence is in fact weak, but most regard LABAs as providing stability of airway function, increasing asthma control and thus accounting for their "steroid-sparing" properties in asthma. Notably, in one large study, the most substantial impact on reducing both mild and severe exacerbations in asthma

occurred in the group given both increased ICS and formoterol.[8]

Concerns regarding LABAs in asthma – original studies

With the background of concern regarding adverse effects of regular or high-dose or potent short-acting β-agonists, it was not surprising that the introduction of LABAs was accompanied by questions regarding their potential for adverse effects, leading to a number of surveillance and clinical studies addressing safety issues.

Castle et al. studied 25,180 patients who were considered to require regular bronchodilator therapy, 69% of whom used ICS.[9] Patients were randomized 2:1 to salmeterol 50 μg b.i.d. or regular salbutamol 200 μg q.i.d. in addition to their usual therapy for 16 weeks. There was a non-significant but disconcerting numeric increase in deaths (0.07% vs. 0.02%, odds ratio [OR] 3.0, 95% CI 0.7–20.0, p = 0.105) in the salmeterol group. The authors considered lack of adequate ICS a likely contributor to death, stating "for 10 of the patients who died from asthma, the independent consultants considered that their asthma could possibly have been more appropriately treated by earlier or higher doses of inhaled corticosteroid."

Meanwhile, given the proven benefits of combination therapy, LABAs were seen as steroid-sparing, and lower ICS doses were recommended for regular use. The concern that inflammation might increase because of insufficient ICS while concomitant LABA maintained apparent control of asthma was addressed by McIvor et al.[10] Salmeterol effectively masked the clinical effects of inflammation by controlling symptoms and maintaining stable lung function as the sputum eosinophil count increased during steroid reduction. While taking salmeterol, the mean sputum eosinophil count increased to over 20% before an exacerbation was evident. In contrast, exacerbation occurred at a mean eosinophil count of only 9% while taking placebo.

Because of the inconclusive findings in the post-marketing study of Castle et al. in the UK,[9] a large study of salmeterol vs. placebo added to usual therapy was conducted in the US, powered on death as the primary outcome.[11] The study was terminated prematurely, in part because of preliminary findings of a higher proportion of deaths and serious adverse events with salmeterol. The OR for respiratory-related deaths was 2.16 (95% CI 1.06–4.41), and for asthma related deaths 4.37 (95% CI 1.25–15.34). African Americans in this study appeared to be at higher risk, and the question arose regarding the possible impact of β-receptor genotype, as African Americans have a higher prevalence of Arg-Arg at position 16. However the apparent higher risk in African Americans reflected their higher baseline risk of mortality, as the actual mortality rate in the study in both African-Americans and Caucasians was about 3-fold higher than that expected in their age- and race-matched population. A more likely factor was the lack of ICS, as post hoc analysis showed that deaths were dominantly among those not prescribed ICS at baseline. ICS use was not recorded throughout the study, but at baseline, only 38% of African Americans and 49% of Caucasians used ICS. Among those not using ICS at baseline, there were 9 deaths in the salmeterol arm and none in the placebo arm, whereas among those using ICS at baseline, no difference was seen in the risk of mortality (4 vs. 3 deaths).

Mann et al.[12] reported safety data from a review of published[13,14] and unpublished formoterol studies conducted by Novartis for which the data had been provided to the Food and Drugs Administration (FDA). There were no deaths in the 2 adult studies and one pediatric study reviewed, each of about 500 individuals. Each study reported an increased risk of SAEs with exposure to the highest dose of formoterol (24 μg b.i.d.), particularly the pediatric study which reported 6.3% SAEs with formoterol vs. 0% with placebo.[14] The authors of that pediatric study had however carefully explained in the discussion of their paper the reason for this unusual finding – in essence that children were withdrawn from the placebo arm when symptoms worsened making it virtually impossible to have SAEs in that arm. A subsequent multi-dose study by Wolfe et al. to address these concerns showed no dose-response relationship between formoterol and SAEs, but rather there were fewer SAEs with all formoterol doses compared with the placebo arm.[15] The use of ICS by patients in these studies was not clearly reported.

The "black-box" warning

The US Salmeterol study,[11] together with the earlier salmeterol studies and consideration of data from the formoterol trials conducted by Novartis in the US, led the FDA to impose a "black-box" warning on both salmeterol and formoterol, both as monotherapy and in combination with ICS.[16] This action, and the safety concerns leading to it, has resulted in a number of reviews of published data and meta-analyses examining safety of LABA therapy in both asthma and COPD.

Concerns regarding LABAs in asthma – meta-analyses and reviews

In a high-impact meta-analysis, Salpeter et al. assessed the effect of LABAs on severe asthma exacerbations requiring hospitalization, life-threatening asthma attacks, and asthma-related deaths in adults and children.[17] Randomized, placebo-controlled asthma trials of LABAs (salmeterol, formoterol, and eformoterol) with duration of more than 3 months were included, but those without placebo control groups were excluded. Of the 33,826 subjects included, some 80% (26,353) were participants in the US salmeterol study[11]. ICS was used at baseline by 53% of included patients. The OR for asthma-related deaths for LABA compared to placebo over 6 months was 3.5 (95% CI

1.3–9.3), p = 0.013, primarily reflecting data from the study of Nelson et al.[11] The OR for hospitalization for asthma for LABA was 2.6 (95% CI 1.6–4.3), p <0.001, based on 5091 subjects in 12 studies (the study of Nelson et al.[11] was excluded from this analysis since it did not collect data on hospitalizations related to exacerbations). Subgroup analyses within this dataset found significantly increased risks associated with LABA use in children (OR 3.9, 95% CI 1.7–8.8), adults (OR 2.0, 95% CI 1.0–3.9), salmeterol (OR 1.7, 95% CI 1.1–2.7) and formoterol (OR 3.2, 95% CI 1.7–6.0). The risk of life-threatening asthma exacerbation for LABA over 6 months (based on 29,981 subjects in 7 studies including Nelson et al.)[11] was 1.8 (95% CI 1.1–2.9). The authors suggested, based on these data, that up to 80% of the 5000 asthma deaths reported annually in the USA might be due to the introduction of LABAs.

Major criticisms of this meta-analysis were the dominance of the study of Nelson et al.,[11] the exclusion of pivotal studies on the addition of LABAs to ICS because these studies did not have a placebo controlled arm, and the lack of verification of concomitant use of ICS during therapy with LABAs. Ernst et al. from the Canadian Asthma Guidelines committee compared the analysis of Salpeter et al. with that reported in previous Cochrane reviews, and concluded that LABA used with ICS was safe.[18]

A Cochrane review was published in 2008 examining serious adverse events during regular treatment with salmeterol versus placebo or short-acting β_2-agonists, after excluding trials that included randomization to treatment containing ICS.[19] An increased risk of serious adverse events was reported with regular salmeterol compared with placebo. The increased risk of asthma-related mortality in patients not using ICS was driven primarily by the studies of Castle et al.[9] and Nelson et al.[11] Although the increase in asthma-related mortality was smaller in patients taking ICS at baseline, the authors could not conclude that ICS abolished the risks of salmeterol therapy.

In response, Bateman et al.[20] reported data from 20,966 participants in 66 studies of >1 week duration conducted by GlaxoSmithKline involving use of ICS with or without salmeterol in standard dosage (50 μg b.i.d.) examining asthma-related serious adverse events including hospitalizations and exacerbations requiring oral corticosteroids. Only one death and one intubation were reported, both in patients using salmeterol with ICS, but there was no difference in hospitalizations (35 among 10,400 using salmeterol plus ICS vs. 34 among 10,566 using ICS alone, p = 0.84). Among US trials in which data on exacerbations requiring oral corticosteroids was available, exacerbations were significantly reduced.

Safety data relating to formoterol exposure in all AstraZeneca randomized, controlled, parallel-group asthma trials of 3–12 months duration involving formoterol were recently reported by Sears et al.[21] There were 8 asthma-related deaths (0.34 per 1000 patient-years) among 49,906 formoterol-randomized patients (92% using ICS), and 2 (0.22 per 1000 patient-years) among 18,098 patients (83% using ICS) not randomized to formoterol (relative risk [RR] 1.57, 95% CI 0.31–15.1). Asthma-related SAEs, over 90% of which were hospitalizations, were significantly lower among formoterol-randomized patients (0.75% vs. 1.10%, RR 0.68, 95% CI 0.57–0.81). There was no increase in asthma-related SAEs with increased daily doses of formoterol (9 vs. 18 vs. 36 μg) but rather a significant trend in the opposite direction. There was no statistically significant difference in cardiac mortality (RR 0.34, 95% CI 0.12–1.02) or non-cardiac, non-asthma-related mortality (RR 2.35, 95% 0.69–12.5). Examining data in those studies in which ICS was mandated, OR for mortality was 2.32 (95% CI 0.30–150) but for SAEs was reduced (OR 0.63, 95% CI 0.52–0.76) indicating protection from SAEs by formoterol with ICS. The authors concluded that, despite reviewing data on over 68,000 patients, the power was insufficient to conclude no increased mortality with formoterol, but that cardiac-related SAEs were not increased, and asthma-related SAEs were significantly reduced with formoterol.

A meta-analysis of all studies in which formoterol or salmeterol was used with concomitant ICS was completed by Jaeschke et al.[22] Based on 62 studies with over 29,000 participants, the authors concluded that in patients with asthma using ICS, LABA use did not increase the risk of asthma-related hospitalizations. There were 3 asthma-related deaths and 2 asthma-related non-fatal intubations (all in LABA groups, no more than 1 event per study), too few to establish the effect of LABA on these outcomes. Decreases in asthma-related hospitalizations (OR 0.74, 95% CI 0.53–1.03) and asthma-related serious adverse events (mostly hospitalizations, OR 0.75, 95% CI 0.54–1.03) failed to reach statistical significance. The OR for total mortality was 1.26, 95% CI 0.58–2.74, reflecting 14 deaths in LABA groups and 8 deaths in control groups respectively.

A further meta-analysis by Jaeschke et al. specifically examined the safety of formoterol with ICS.[23] Among over 11,000 participants (6405 taking formoterol with over 4000 patient-years observation) there were 2 asthma-related deaths (both in formoterol groups) and no asthma-related non-fatal intubations. Asthma-related hospitalizations were significantly reduced (OR 0.58, 95% CI 0.37–0.92) as were asthma-related serious adverse events which were mainly hospitalizations (OR 0.56, 95% CI 0.36–0.87). The OR for total mortality was 1.22, 95% CI 0.38–3.90, reflecting 7 deaths in formoterol groups and 3 deaths in control groups respectively.

A contrasting Cochrane review of formoterol was also recently published examining rates of serious adverse events during regular treatment with formoterol versus placebo or short-acting β_2-agonists.[24] In 22 studies, 3 deaths were identified on formoterol treatment compared

with none on placebo. Non-fatal serious adverse events were significantly increased (by 57%) when formoterol was compared with placebo, but not when compared with regular short-acting β-agonists. The authors estimated that for every 1000 patients treated, there would be an expected 16 adverse events with formoterol compared with 10 with placebo. However this review excluded all trials in which patients were randomized to ICS-containing treatment, making it more difficult to address the issue of whether ICS protected against any adverse effect of LABA.

What can we make of these discordant reviews of LABA safety in asthma? The risks reported appear to be highly dependent on the selection criteria for the reviews and meta-analyses. Those in which use of ICS was considered in the analysis suggest no increased risk of LABA used with concomitant ICS, and even a protective effect in reducing exacerbations. This is particularly evident when the use of ICS was part of the randomization process, or when ICS use was mandated in the study. Monotherapy with LABA may increase the risks of both mortality and SAEs in asthma.

Concerns regarding LABAs in COPD There are fewer trials indicating the efficacy of LABAs in chronic obstructive pulmonary disease (COPD) than in asthma. Use of LABA without ICS has been more common in COPD, particularly as trials of ICS in COPD have shown relatively unimpressive benefits.[25,26] Guidelines for management include anticholinergic or β-adrenergic bronchodilator therapy as the primary treatment in COPD without mandating concomitant use of ICS.

Concerns about mortality associated with use of LABAs in COPD were raised in 2 meta-analyses by Salpeter et al., who reported an increased risk of respiratory death in COPD with use of LABA vs. placebo or vs. anticholinergic therapy,[27] while anticholinergic therapy in COPD reduced hospitalizations by 30% and mortality by 70%.[28] More recently Rodrigo et al. reported a meta-analysis of 27 studies in which LABA was compared with placebo in patients with COPD.[29] In some trials ICS was also prescribed, and some studies also involved the long-acting anticholinergic tiotropium. These authors came to different conclusions to those of Salpeter et al.[27,28], reporting no increased risk in COPD patients of mortality with use of LABAs. Salpeter et al. included studies of at least 3 months duration, whereas Rodrigo et al. analyzed more studies by including studies of at least 1 month duration and also excluded some duplicate studies which had been included by Salpeter et al. Rodrigo et al. found that LABA with ICS was associated with lower mortality compared with LABA without ICS (RR 0.35, 95% CI 0.14–0.93), and that tiotropium decreased the incidence of severe COPD exacerbations compared with LABAs (RR = 0.52, 95% CI 0.31–0.87). The authors concluded that LABA was safe in COPD compared with placebo. However an accompanying editorial highlighted the finding that while LABA did not increase adverse events compared with placebo, LABA accompanied by ICS decreased adverse events compared with LABA monotherapy.[30] Furthermore, COPD and asthma may not be well differentiated in practice, and treating both diseases with concomitant ICS should add to the margin of safety if a patient with "COPD" in fact has unrecognized asthma.

CONCLUSION The dominant conclusion to draw from these original studies, meta-analyses and reviews of clinical trial data in asthma and COPD is that questions remain regarding use of LABA as monotherapy. Used with ICS, LABAs are not only very effective in controlling asthma in the more severe patient, but reduce asthma-related SAEs. In the view of the writer, in both asthma and COPD, LABA should always be accompanied with adequate ICS. Use of a combination inhaler in all circumstances has been advocated to ensure that the patient cannot use LABA alone.[31]

REFERENCES

1 Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy. 1948; 19: 129-140.

2 Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. BMJ. 1968; 1: 335-339.

3 Sears MR, Taylor DR. The beta 2-agonist controversy: observations, explanations, and relationship to asthma epidemiology. Drug Saf. 1994; 11: 259-283.

4 Grainger J, Woodman K, Pearce N, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax. 1991; 46: 105-111.

5 Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet. 1990; 336: 1391-1396.

6 Sears MR. Epidemiological trends in asthma. Can Respir J. 1996; 3: 261-268.

7 Greening AP, Wind P, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet. 1994; 344: 219-224.

8 Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. New Engl J Med. 1997; 337: 1405-1411.

9 Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ. 1993; 306: 1034-1037.

10 McIvor RA, Pizzichini E, Turner MO, et al. Potential masking effects of salmeterol and airway inflammation in asthma. Am J Respir Crit Care Med. 1998; 158: 924-930.

11 Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial. A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006; 129: 15-26, and erratum Chest. 2006; 129: 1393.

12 Mann M, Chowdhury B, Sullivan E, et al. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. Chest. 2003; 124: 70-74.

13 Bensch G, Lapidus RJ, Levine BE, et al. A randomized, 12-week, double-blind study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. Ann Allergy Asthma Immunol. 2001; 86: 19-27.

14 Bensch G, Berger WE, Blokhin BM, et al. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. Ann Allergy Asthma Immunol. 2002; 89: 180-190.

15 Wolfe J, LaForce C, Friedman B, et al. Formoterol 24 mcg bid, and serious asthma exacerbations. Chest. 2006; 129: 27-38.

16 Murphy S, Roberts R. "Black-box" 101: How the Food and Drug Administration evaluates, communicates, and manages drug benefit/risk. J Allergy Clin Immunol. 2006; 117: 34-39.

17 Salpeter SR, Buckley NS, Ormiston TM, et al. Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med. 2006; 144: 904-912.

18 Ernst P, McIvor A, Ducharme FM, et al. Safety and effectiveness of long-acting inhaled beta-agonist bronchodilators when taken with inhaled corticosteroids. Ann Intern Med. 2006; 145: 692-694.

19 Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events (Review). The Cochrane Library. 2008, Issue 3.

20 Bateman E, Nelson H, Bousquet J, et al. Meta-analysis: Effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med. 2008; 149: 33-42.

21 Sears MR, Ottosson A, Radner F, Suissa S. Long-acting beta-agonists: a review of formoterol safety data from asthma clinical trials. Eur Respir J. 2008; Sept 3 [Epub ahead of print].

22 Jaeschke R, O'Byrne PM, Mejza F, et al. The safety of long acting beta-agonists among patients with asthma using inhaled corticosteroids. AJRCCM Articles in Press. 2008: 10.1164/rccm.200804-494OC.

23 Jaeschke R, O'Byrne PM, Nair P, et al. The safety of formoterol among patients with asthma using inhaled corticosteroids. Systematic review and meta-analysis. Pol Arch Med Wewn. 2008; 118: 627-635.

24 Cates CJ, Cates MJ, Lasserson TJ. Regular treatment with formoterol for chronic asthma: serious adverse events (Review). The Cochrane Library. 2008, Issue 4.

25 Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med. 1999; 340: 1948-1953.

26 The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000; 343: 1901-1909.

27 Salpeter SR. Bronchodilators in COPD: Impact of beta-agonists and anticholinergics on severe exacerbations and mortality. Int J Chron Obstruct Pulmon Dis. 2007; 2: 11-18.

28 Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: Anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med. 2006; 21: 1011-1019.

29 Rodrigo GJ, Nannini LJ, Rodriguez-Roisin R. Safety of long-acting beta-agonists in stable COPD: A systematic review. Chest. 2008; 133: 1079-1087.

30 Sears MR. Long-acting bronchodilators in COPD. Chest. 2008. 133: 1057-1058.

31 Wijesinghe M, Perrin K, Harwood M, et al. The risk of asthma mortality with inhaled long acting beta-agonists. Postgrad Med J. 2008; 84: 467-472.