Evidence based answers

Is salmeterol safe in asthma?

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Case history

SW, 21 years of age, presented for a prescription for her salbutamol puffer. She had a long history of chronic persistent asthma usually exacerbated by upper respiratory tract infections (URTIs). These exacerbations had occasionally landed her in hospital but never in intensive care. After a friend died of an asthma attack, SW adhered rigorously to her asthma plan and always used a spacer for her preventer, fluticasone. It therefore surprised me when I noticed that she had had no URTIs yet had been prescribed salbutamol by another general practitioner in the practice only 2 weeks previously. In response to my concern, she admitted that despite using the correct puffer technique, the salbutamol was only lasting a few hours before she became breathless. She found she needed the salbutamol a number of times a day. We decided to add a long acting beta agonist (LABA), salmeterol, to her regimen to help control her symptoms.

SW agreed but asked: 'It will help won't it, I don't want to end up like my friend.'

Obviously SW was worried with her recent increase in symptoms. I assured her that with her current regimen and a good action plan, there should be no cause for concern. She left with her salmeterol prescription feeling reassured. However, a thought nagged me for the rest of the session. Wasn't fenoterol, a LABA, found to cause asthma deaths?

I raised the question of the safety of LABAs at the practice's weekly journal club. Discussion began with the epidemic of asthma mortality in New Zealand between 1976 and 1991[1] and the subsequent case controlled trials that showed an association between fenoterol and asthma death.[2–4] A similar case controlled study found that although there was a significant increase in near fatal asthma associated with salmeterol, this association was likely due to confounding by severity. In other words, patients with severe asthma are preferentially prescribed salmeterol.[5] A colleague had recently read a letter published in *The Lancet* describing unpublished data regarding salmeterol from a large randomised controlled trial (RCT) which would be less prone to confounding and more reliable than a case controlled trial. It suggested that there was a statistically significant four-fold increase in asthma deaths with salmeterol compared to placebo.[6]

This amounted to a number needed to harm of 1000 every 6 months according to the SMART trial data found by looking on the United States Food and Drug Administration (FDA) website. It seemed undesirable that for every 1000 asthmatic patients on salmeterol, one should die every 6 months because of salmeterol. This led to three other questions: is the observed increase in mortality with salmeterol offset by the use of an inhaled corticosteroid, does salmeterol result in better symptom control than salbutamol, and are these effects seen with other forms of LABAs? These questions were formulated using PICO (Patient, Intervention, Comparator, Outcome) to facilitate a literature search by focusing on relevant search terms:

- Do patients with asthma (P) using an inhaled corticosteroid in combination with salmeterol (I) compared to inhaled corticosteroid alone (C) suffer more deaths (O)?
- Do patients with asthma (P) using regular salbutamol (I) compared to regular salmeterol (C) have the same or better symptom relief (O)?
- Do patients with asthma (P) using formoterol or any other LABA (I) compared to placebo (C) suffer more asthma deaths (O)?

Accessing and assessing the information

We decided that systematic reviews followed by RCTs would be the best types of research to answer these

intervention questions. The Cochrane Database of systematic reviews was likely to be the best source of both systematic reviews and RCTs. The search terms: 'asthma', 'inhaled corticosteroid', 'salmeterol', 'deaths', 'regular salbutamol', 'regular salmeterol', 'symptom', 'formoterol', 'LABA', and 'placebo' were typed into the Cochrane search page.

For question one, there were 12 hits in the Cochrane reviews section (which contains both Cochrane systematic reviews and protocols of reviews yet to be completed). One review appeared to address our question directly. This systematic review reported only one RCT by D'Urzo et al[8] looking at the outcome of deaths. There was no significant increase in deaths with LABAs combined with an inhaled corticosteroid (ICS) compared to placebo combined with ICS. The SMART study showed one death per 1000 people with asthma using salmeterol every 6 months.[6] However D'Urzo et al did not recruit enough patients to have enough power to detect this sort of difference.[8] The systematic review concluded that there were no safety concerns nor increase in deaths in asthmatics using LABAs combined with ICS, compared with using ICS alone.[7]

For question two, there were 24 hits in the review section, of which none were relevant, and 13 hits in 'central'. Central is the part of the Cochrane database relating to RCTs (the Cochrane Central Register of Controlled Trials). There are more RCTs listed in this database than in Medline. One of the RCTs addressed our question directly, comparing long term regular salbutamol with long term regular salmeterol. It showed that while regular salbutamol does help day time symptoms, salmeterol is significantly better for symptom control overall, as measured by a combination of peak expiratory flow rate, wheeze, cough, sputum production, and ability to exercise.[9]

For question three, there were 12 hits in the review section. One review directly addressed the question. This systematic review of LABAs in chronic stable asthma included studies of both salmeterol and formoterol. The outcome of death was not reported by this review, although overall adverse effects were more likely in the LABA group with an odds ratio of 1.35 (95% CI: 1.03–1.77).[10] We could not be sure from this evidence if formoterol caused increased asthma deaths or not.

The Cochrane reviews and RCT used to answer these questions were judged to be of high quality.

Applying the evidence

The result of asking these questions, discussing them, and searching for evidence did not reassure my nagging thought about my response to SW's question. The most recent evidence from the largest known RCT (not yet part of a Cochrane review) suggested that I was wrong to completely reassure SW. It did seem reasonable however, to give her an inhaled combination of LABA/ICS. We cannot be completely certain that there is no increased mortality risk with the combination product, but the largest trial available showed no evidence of increased risk. Using the combination product means that SW would get the improved symptom relief of the inhaled LABA and would ensure that it is used only in combination with the ICS which may offset any increased risk of death.

As a result of this investigation, the practice decided to recall all our patients taking inhaled LABAs not in combination with ICS. This recall affected four patients. Under the Pharmaceutical Benefit Scheme, the restricted benefit for prescriptions of combined LABA/ICS indicates that one must use the LABA in isolation first to see if it is effective. As a practice, we adopted a policy of no repeat prescriptions and a 1 month recall on all patients prescribed a LABA in isolation with a view to starting a combination LABA/ICS medication.

This case also highlights the lack of high quality evidence on possible harms of commonly prescribed products.

Conflict of interest: none declared.

Postscript

As this article goes to press, a systematic review has been published confirming our concerns. It indicates that LABAs increase asthma related hospitalisation, increase the risk of life threatening asthma and increase asthma related deaths. This effect is not fully offset by concomitant corticosteroids.[11]

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