Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events

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CRD summary
This review concluded that salmeterol combined with inhaled corticosteroids decreased the risk of severe exacerbations, had a comparable risk for asthma-related hospitalisations and may not alter risk for asthma-related deaths or intubations compared with inhaled corticosteroids alone in people with persistent asthma. Despite some minor limitations in the review, the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the effect of salmeterol and inhaled corticosteroids compared with inhaled corticosteroid treatment alone on the incidence of severe asthma-related events in patients with persistent asthma.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Database of Systematic Reviews were searched from 1982 to September 2007. The GlaxoSmithKline Clinical Trials Registry was also searched up to September 2007. The search was not restricted by language and search terms were reported. References from published reviews were also checked.

Study selection
Randomised, double-blind, parallel-design, long-term dosing studies that compared the use of inhaled corticosteroids plus salmeterol (50 μg twice daily) with inhaled corticosteroids alone in people with asthma were eligible for inclusion in the review. Of the included studies, median trial duration was 12 weeks (range 1 to 52 weeks), the mean age of included participants was 38 years, 44% were male, 82% were white, and most had moderate to severe persistent asthma. Key outcomes included hospitalisation, intubation or death.

Three reviewers selected studies from the GlaxoSmithKline database. The authors did not state how papers were selected or how many reviewers performed the study selection for the other databases.

Assessment of study quality
The quality of the included trials was not systematically assessed.

Data extraction
Study personnel asked standardized open-ended questions about any changes in participants' health status at regular interviews in order to solicit information about any adverse events. Participants could also spontaneously report any adverse event. The interval for these interviews varied by study protocol but generally did not exceed four weeks. Case narratives reporting serious adverse events from GlaxoSmithKline trials were sent to three physicians. They independently reviewed the narratives, blinded to drug assignment, and adjudicated the asthma relationship for hospitalisation, intubation or death in each case. Any disagreements were resolved by consensus. The primary outcome measures for the trials were not the same as the review outcomes.

One reviewer extracted data from the GlaxoSmithKline sponsored trials and another reviewer checked this extraction. For the non-GlaxoSmithKline sponsored trials, one reviewer extracted data.

Methods of synthesis
Two methods were used to pool studies.

Firstly, risk differences and 95% confidence intervals (CI) were calculated. A treatment group continuity correction for trials in which at least one of the treatment groups had no events was applied. Sensitivity analyses were performed using 0.01, 0.001 and 0.0001 continuity corrections.
Secondly, odds ratios (OR) and 95% CI were calculated using Peto odds ratio method. This excluded trials with no events.

Studies were pooled in a meta-analysis using a fixed-effects model. The Cochrane Q test and the $I^2$ test were used to evaluate statistical heterogeneity.

**Results of the review**

Sixty-six GlaxoSmithKline trials were included in the review (n=20,966); 10,400 participants received inhaled corticosteroids plus salmeterol; 10,566 participants received inhaled corticosteroids alone. Sample sizes ranged from 12 to 3,416. The overall rate of withdrawal was about 14% among participants receiving inhaled corticosteroids plus salmeterol and about 17% in participants receiving inhaled corticosteroids alone. Lung function was the primary endpoint in most included trials. Seven non-GlaxoSmithKline sponsored trials met eligibility criteria but were not included in the analysis as none of these studies reported asthma related hospitalisations, intubations or mortality.

**Asthma-related hospitalisations:**

The number of events reported for participants receiving inhaled corticosteroids plus salmeterol and inhaled corticosteroids alone was 35 and 34, respectively. The majority of studies (40/66) did not record any hospitalisations. The risk difference attributed to inhaled corticosteroids plus salmeterol compared with inhaled corticosteroids alone was 0.0002 (95% CI: -0.0019, 0.0023). Sensitivity analyses yielded similar results. No statistically significant difference was found between the two treatment groups (OR 1.07, 95% CI: 0.66, 1.73).

Of six trials involving children (4 to 17 years, n=1,575), two participants (one in each treatment group) had an asthma-related hospitalisation.

When study duration was considered; trials at 12 weeks duration reported 16 events in the salmeterol group and 7 events in the inhaled corticosteroids alone group (28 trials, n=7,059); trials with duration greater than 12 weeks reported 19 events in the salmeterol group and 27 events in the inhaled corticosteroids alone group (26 trials, n=12,720); trials of less than 12 weeks did not record any events (12 trials, n=1,187).

A comparable number of events were found where participants received a similar dose of inhaled corticosteroid dose in the salmeterol group and the inhaled corticosteroids alone group (21 versus 22; 41 trials, n=11,859). Where participants received a higher dose (usually double) of inhaled corticosteroids alone compared to inhaled corticosteroid plus salmeterol, 13 and 14 events were reported, respectively.

Studies were also grouped by fluticasone propionate plus salmeterol administered in a single device versus inhaled corticosteroids alone (26 versus 23 events), and inhaled corticosteroids plus salmeterol administered in separate devices versus inhaled corticosteroids alone (9 versus 11 events).

**Asthma-related intubations:**

One event occurred in a participant receiving beclomethasone dipropionate plus salmeterol.

**Asthma-related deaths:**

One asthma-related death was reported approximately three months after the start of the study in a participant receiving inhaled fluticasone propionate (250 μg twice daily) plus salmeterol by use of separate devices. An autopsy confirmed that death was asthma-related. Six deaths (all-cause) were reported in participants receiving inhaled corticosteroids plus salmeterol (4 used a single device and 2 used separate devices) and six deaths (all-cause) were reported in participants receiving inhaled corticosteroids alone (1 receiving triamcinolone and 5 receiving fluticasone propionate).

**Severe asthma-related exacerbations:**

The summary risk difference for a severe asthma-related exacerbation for inhaled corticosteroids plus salmeterol, in a single or separate device, compared with inhaled corticosteroids alone, was -0.025 (95% CI: -0.036, -0.014) (24 trials,
n=7,549). Risk differences for comparisons of delivery (use of single or separate devices) of corticosteroids and salmeterol found similar results.

Authors’ conclusions
Salmeterol combined with inhaled corticosteroids decreases the risk of severe exacerbations and has a comparable risk for asthma-related hospitalisations compared with inhaled corticosteroids alone. Combination therapy with salmeterol may also have an equivalent risk for asthma-related deaths or intubations compared with inhaled corticosteroids alone.

CRD commentary
This review question was supported by clear inclusion criteria. Several relevant databases were searched without language restriction and the authors searched for unpublished trials. Methods used to select papers and extract data relating to the GlaxoSmithKline trials were likely to minimise reviewer error or bias. However, it would have been better if the selection and extraction of all studies had used comparable methods. The quality of the included studies does not appear to have been assessed limiting any interpretation of the results. Methods used for the adjudication of adverse events from the case narratives were likely to have minimised bias. Appropriate methods were used for pooling studies and statistical heterogeneity was assessed, although results were not reported for all analyses. The authors highlighted that the included trials involved selected patients who received careful follow-up, that few trials were longer than 12 weeks in duration, and that the small number of asthma related-deaths or intubations limited the ability to measure these outcomes.

Whilst the authors' conclusions follow from the results presented, they appear to be based on a relatively small number of events and one small, although statistically significant, effect size and thus might be overstated.

Implications of the review for practice and research
Practice: The authors stated that the review supports national and international asthma treatment guidelines recommending that long-acting beta-agonists always be used with concurrent inhaled corticosteroids.

Research: The authors did not state any implications for research.

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