Antiinflammatory effects of long-acting beta2-agonists in patients with asthma: a systematic review and meta-analysis

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CRD summary
Long-acting beta2-agonists did not decrease inflammatory cell numbers in the airways of adults and children with asthma; any clinical synergy between long-acting beta2-agonists and inhaled corticosteroids was unlikely to be related to an anti-inflammatory effect of the long-acting beta2-agonists. Overall, the conclusions of this review should be considered as reliable.

Authors' objectives
To determine the anti-inflammatory effects of long-acting beta2-agonists in patients with asthma.

Searching
The following databases were searched between 1966 and December 2006, without any language restrictions: MEDLINE, EMBASE, CINAHL, AMED, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, DARE and ACP Journal Club. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared long-acting beta2-agonists (salmeterol or formoterol) with placebo, or compared a combination of long-acting beta2-agonists plus inhaled corticosteroids with inhaled corticosteroids alone, in children or adults diagnosed with asthma, were eligible for inclusion. Trials were required to report change in an inflammatory marker as a primary outcome. Relevant markers were detailed for the large airways, small airway and tissue. Trials where inflammation was induced by a controlled allergen were excluded.

The included trials evaluated the anti-inflammatory effect of long-acting beta2-agonists versus placebo, or long-acting beta2-agonists plus inhaled corticosteroids versus inhaled corticosteroids alone. Trial designs included parallel and crossover. Inflammatory markers reported included cell counts, markers of cell activation in sputum, bronchoalveolar lavage fluid, bronchial biopsy specimens, serum and exhaled nitric oxide. The duration of the trials ranged from one to 52 weeks.

Studies were selected by two independent reviewers; it was unclear how disagreements were resolved.

Assessment of study quality
The Cochrane criteria for allocation concealment and the five-point Jadad scale were used to assess validity.

Studies were assessed by two independent reviewers; disagreements were resolved by recourse to a third reviewer.

Data extraction
Trial outcomes were extracted as post-treatment mean differences. Authors were contacted for details where necessary.

Data extraction was performed by two independent reviewers.

Methods of synthesis
Fixed-effect and random-effects models were used to calculate standardised mean differences (SMDs) according to level of heterogeneity (assessed using $\chi^2$ and I$^2$ statistics). Subgroup analyses were performed where possible according to trial population (paediatric or adult).

Results of the review
Thirty-two RCTs (1,105 participants) were included in the review. Twenty-one trials evaluated long-acting beta2-agonists versus placebo (729 participants); 11 trials compared long-acting beta2-agonists plus inhaled corticosteroids with inhaled corticosteroids alone (376 participants).
Long-acting beta2-agonists versus placebo: There was no effect of long-acting beta2-agonists therapy on sputum, bronchoalveolar lavage fluid or mucosal inflammatory cells in adults or children. There was a significant reduction in serum eosinophils with long-acting beta2-agonists therapy, largely due to the effect on children (SMD 1.52, 95% CI -2.67 to -0.36).

Long-acting beta2-agonists plus inhaled corticosteroids versus inhaled corticosteroids alone: Meta-analyses found no significant additive anti-inflammatory effect of long-acting beta2-agonists on serum eosinophil cationic protein, sputum eosinophil cationic protein or sputum eosinophil.

Authors' conclusions
Long-acting beta2-agonists did not decrease inflammatory cell numbers in the airways of patients with asthma; any the clinical synergy between long-acting beta2-agonists and inhaled corticosteroids was unlikely to be related to an anti-inflammatory effect of the long-acting beta2-agonists.

CRD commentary
This review addressed a clear clinical question with relevant inclusion criteria, with comprehensive database and grey literature searches. The review methods were detailed. The use of two reviewers for study selection, validity assessment and data extraction was likely to have reduced the chance of reviewer error/bias impacting on the review.

Validity assessment was carried out and reported, although the use of summary scores may have obscured useful information on quality. The meta-analyses appeared to be appropriate, although heterogeneity tests were not reported.

Overall, the conclusions of this review should be considered as reliable.

Implications of the review for practice and research
Practice: The authors stated that the addition of a long-acting beta2-agonist in patients whose eosinophilic inflammation is uncontrolled by inhaled corticosteroids is not recommended.

Research: The authors did not make any recommendations for research.

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