Airway-stabilizing effect of long-acting beta2-agonists as add-on therapy to inhaled corticosteroids
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CRD summary
This review assessed the bronchoprotective effects of salmeterol or formoterol in patients with asthma who were using corticosteroid inhalers. The authors concluded that the beta2-agonists improved bronchoprotection compared with placebo. The evidence presented appears to support the authors' conclusions, but it is difficult to assess the generalisability of the results and the clinical importance of the findings is unknown.

Authors' objectives
To assess the effect of chronic use of long-acting beta2-agonists on residual bronchoprotection in asthmatic patients.

Searching
MEDLINE, databases on BIDS, and the Cochrane Library were searched from 1990 to June 2002 for reports published in the English language. The keywords were listed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The included studies were either crossover (all but three RCTs) or parallel-group RCTs. The duration of the included studies ranged from one to 52 weeks.

Specific interventions included in the review
Studies that compared long-acting beta2-agonists (salmeterol or formoterol) with placebo were eligible for inclusion. Only studies of treatment lasting at least one week were included.

Participants included in the review
Studies of asthmatic patients who were maintained on inhaled steroids were eligible for inclusion.

Outcomes assessed in the review
Studies that provoked bronchial constriction using direct (methacholine or histamine) or indirect (adenosine monophosphate) stimuli were eligible for inclusion. The primary outcome in the review was the doubling dose or dilution shift (i.e. the doubling dose/dilution of the stimulating agent that led to a 20% reduction in forced vital expiratory volume in one second).

How were decisions on the relevance of primary studies made?
Two authors independently selected potentially eligible studies on the basis of the title and abstract. Four authors then selected studies, according to the inclusion criteria, from the full publications and agreed on the studies selected.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the doubling dose/dilution shift from each study were transformed using logarithms to calculate the doubling dose/dilution. Where necessary, the doubling dose/dilution difference was calculated (equation given).
Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis. The weighted overall protection and 95% confidence interval (CI) of the doubling dose/dilution was calculated for long-acting beta2-agonists compared with placebo. The authors did not report whether they used a fixed-effect or random-effects model.

How were differences between studies investigated?
Statistical heterogeneity was tested using the chi-squared statistic. The mean doubling dose/dilution protection and 95% CIs were plotted graphically for each study. The review also performed separate meta-analyses according to drug (salmeterol and formoterol), timing of the outcome assessment (peak and trough) and type of stimulus (direct and indirect).

Results of the review
Thirteen RCTs with 19 treatment arms were included (596 patients).

Long-acting beta2-agonists significantly increased bronchoprotection compared with placebo; the doubling dose/dilution was estimated to be 0.79 (95% CI: 0.63, 0.96). No significant heterogeneity was detected (P=0.51).

Protection was greater for peak measurements than trough: protection was 1.20 (95% CI: 0.88, 1.53) at peak versus 0.65 (95% CI: 0.46, 0.84) at trough. There was no evidence of a difference for salmeterol compared with fenoterol, or for indirect compared with direct stimulus; the data were presented. There was no evidence of significant heterogeneity within any of these subgroups (P-values ranged from 0.29 to 0.98).

Authors' conclusions
Long-acting beta2-agonists, used as second-line treatment, improved bronchoprotection by about an 0.8 doubling dose/dilution shift compared with placebo.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and the keywords were listed. By limiting the included studies to those published in English, some relevant studies may have been omitted. No attempt was made to locate unpublished studies, thus raising the possibility of publication bias. More than one reviewer independently selected the studies, which reduces the potential for bias and errors. However, the methods used to extract the data were not described; hence, any efforts made to reduce errors and bias in the data extraction cannot be judged. Only RCTs were included but validity was not formally assessed. Limited information on the individual studies was presented. Some indication of the severity of asthma among participants, the age range, drug doses and concomitant treatments would have been useful in judging which populations and which treatment regimens the results of the review might apply to. It was not stated whether the data were extracted on an intention-to-treat basis and the issue of drop-outs was not addressed. Most of the included RCTs were crossover studies, but no comment was made on the adequacy of the washout period in preventing carry-over effects of the first drug. Data for the main outcome were appropriately combined in a meta-analysis and statistical heterogeneity was tested. Subgroup analyses were conducted to explore the influence on the results of drug type, stimulus type and timing of the outcome.

The evidence presented appears to support the authors' conclusions but, given the lack of detail of the patients studied, it is not possible to judge the generalisability of the results. In addition, the outcome is a proxy outcome and the clinical importance of the review's findings is unknown.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.
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