Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis

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CRD summary
The review concluded that high-dose formoterol administered via dry powder inhaler was well tolerated and provided rapid and effective bronchodilation, similar to high-dose salbutamol or terbutaline via metered dose inhaler or nebuliser. Given the variable quality of the included trials and the high level of variation between them, some caution is warranted when interpreting the authors’ conclusions.

Authors' objectives
To evaluate the efficacy and safety of inhaled formoterol compared with short-acting beta2-agonists for the emergency department treatment of patients with acute asthma.

Searching
MEDLINE, EMBASE and Cochrane Register of Controlled Trials (CENTRAL) were searched from January 1980 to October 2009 for articles in any language. Search terms were reported. AstraZeneca and Novartis websites were also searched.

Study selection
Parallel-group randomised controlled trials (RCTs) that compared single or repeated doses of formoterol (alone or in combination with inhaled corticosteroids) with a short-acting beta2-agonist in children or adults with short-term exacerbations of asthma, presenting to an emergency department or its equivalent, were eligible for inclusion. The short-acting beta2-agonists could be delivered by dry powder inhaler, metered-dose inhaler, or nebuliser.

The relevant primary outcomes were spirometric measures, forced expiratory volume in one second (FEV$_1$) or peak expiratory flow (PEF), as absolute or change from baseline to 30 to 40 minutes after the first treatment, at the end of treatment, and 60 to 90 minutes after the last dose of treatment. Secondary outcome measures included heart rate, electrocardiac results, total withdrawals and final serum potassium levels.

The included RCTs primarily compared formoterol (12μg to 90μg total dose) with inhaled salbutamol (200μg to 7.5mg total dose) or terbutaline (1.5mg to 10mg total dose), but also considered formoterol (36μg total dose) in combination with budesonide (1,280μg total dose) compared with salbutamol. Formoterol was mainly given via a dry powder inhaler, but was also given as a nebuliser. Salbutamol was mainly given via metered-dose inhaler or nebuliser, whilst terbutaline was given via a dry powder inhaler. The mean age of included patients ranged from 8.7 to 56 years (where reported); the proportion of male patients ranged from 20 to 61%. The trial sample size ranged from 34 to 103 participants, and the trial duration varied from 45 minutes to 4 hours. The mean baseline predicted FEV$_1$ varied from 32 to 78.5%.

Two authors independently undertook the selection process and disagreements were resolved by team discussion.

Assessment of study quality
Quality assessment was undertaken independently by two reviewers and disagreements were resolved by team consensus. Four quality factors were considered: sequence generation, allocation concealment, patients blinded, and data collection blinded.

Data extraction
Two authors independently extracted data on spirometric outcomes and other secondary outcomes, and used the data to calculate standardised mean differences (SMDs) or odds ratios (ORs), together with 95% confidence intervals (CIs).

Methods of synthesis
The pooled odds ratios or weighted mean differences (WMDs), together with 95% confidence intervals, were
calculated using a random-effects meta-analysis. Statistical heterogeneity was assessed using the $I^2$ statistic. The number needed to treat was planned where significant differences between groups were found. Sensitivity and subgroup analyses were also undertaken.

Publication bias was assessed using funnel plot analysis.

**Results of the review**

Nine RCTs were included in the review (n=576 participants). The trial quality was generally poor, with only one trial fulfilling all four quality criterion. There was no evidence of publication bias using visual inspection of the funnel plot of spirometric outcomes.

**Primary outcome:** In terms of the primary spirometric outcomes, formoterol did not show any statistically significant difference compared with salbutamol or terbutaline at 30 to 40 minutes of treatment (SMD -0.19, 95% CI -0.56 to 0.17; $I^2$=75%; eight RCTs), at the end of treatment (SMD -0.25, 95% CI -0.62 to 0.13; $I^2$=80%; nine RCTs), or at 60 to 90 minutes after completed treatment (SMD -0.13, 95% CI -0.55 to 0.28; $I^2$=80%; eight RCTs). The substantial heterogeneity within the analyses was found to be related to two trials; exclusion of these trials from the analysis did not significantly alter the results.

**Secondary outcomes:** Formoterol did not show any statistically significant difference compared with salbutamol or terbutaline in terms of final heart rate per minute (WMD -2.97, 95% CI -7.32 to 1.30; $I^2$=55%; six RCTs), electrocardiac QT intervals (WMD -8.1 milliseconds, 95% CI -19.79 to 3.58; $I^2$=0%; three RCTs), final serum potassium (WMD -0.0mmol/L, 95% CI -0.15 to 0.14; $I^2$=34%; five RCTs), hospitalisations (OR 0.50, 95% CI 0.21 to 1.22; $I^2$=0%; three RCTs), or withdrawals (OR 0.64, 95% CI 0.31 to 1.34; $I^2$=0%; six RCTs).

**Sensitivity and subgroup analyses:** Formoterol did not show any statistically significant difference compared with salbutamol or terbutaline when the type of model was varied (fixed-effect versus random-effects), the dose of short-acting beta2-agonist to formoterol was varied, when children were separated from adults, when severe asthma was separated from mild/moderate asthma, or when pharmaceutical sponsored trials were analysed separately. There was evidence of statistical heterogeneity ($I^2>80\%$) within many of the subgroup analyses.

**Authors’ conclusions**

High-dose formoterol administered via dry powder inhaler was well tolerated and provided rapid and effective bronchodilation, similar to high-dose salbutamol or terbutaline via metered dose inhaler or nebuliser.

**CRD commentary**

Inclusion criteria for the review were clearly defined. Several relevant databases were searched for articles in any language. Publication bias was assessed and was not detected, although the low number of included trials made assessing publication bias difficult. There was no attempt to locate unpublished trials and only full-text papers were included, which increased the potential for missed trials. Attempts were made to minimise error and bias in the process of study selection, data extraction and quality assessment.

Trial quality was formally assessed, included appropriate criteria, and the results were clearly reported. The quality assessment indicated the variable quality of the included trials, which the authors acknowledged. Relevant trial details were summarised in text and tables, and (where possible) trials were combined using meta-analysis. Statistical heterogeneity was explored, but substantial statistical heterogeneity remained in several of the analyses.

Given the variable quality of the included trials and the high level of statistical heterogeneity, some caution is warranted when interpreting the authors’ conclusions.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further trials are needed to assess the comparison of formoterol with short-acting
beta2-agonists in patients with acute life-threatening asthma and to examine the use of formoterol plus inhaled corticosteroids in acute asthma.

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