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[Intervention Review]

Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease

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ABSTRACT

Background

Long-acting beta-agonists and inhaled corticosteroids have both been recommended in guidelines for the treatment of chronic obstructive pulmonary disease. Their co-administration in a combined inhaler may facilitate adherence to medication regimens, and improve efficacy.

Objectives

To assess the efficacy of combined inhaled corticosteroid and long-acting beta-agonist preparations, compared to placebo, in the treatment of adults with chronic obstructive pulmonary disease.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials. The date of the most recent search is April 2007.

Selection criteria

Studies were included if they were randomised and double-blind. Studies could compare any combined inhaled corticosteroids and long-acting beta-agonist preparation with placebo.

Data collection and analysis

Two authors independently assessed study risk of bias and extracted data. The primary outcomes were exacerbations, mortality and pneumonia. Health-related quality of life (measured by validated scales), lung function and side-effects were secondary outcomes. Dichotomous data were analysed as fixed effect odds ratios or rate ratios with 95% confidence intervals, and continuous data as mean differences and 95% confidence intervals.

Main results

Eleven studies met the inclusion criteria (6427 participants randomised). Two different combination preparations (fluticasone/salmeterol and budesonide/formoterol) were used. Study quality was good. Fluticasone/salmeterol and budesonide/formoterol both reduced the rate of exacerbations. Pooled analysis of both combination therapies indicated that exacerbations were less frequent when compared with placebo, Rate Ratio: 0.74 (95% CI 0.7 to 0.8). The clinical impact of this effect depends on the frequency of exacerbations experienced by patients. The patients included in these trials had on average 1-2 exacerbations per year which means that treatment with combination therapy would lead to a reduction of one exacerbation every two to four years in these individuals. There is an overall reduction in mortality,

but this outcome is dominated by the results of TORCH and further studies on budesonide/formoterol are required. The three year number needed to treat to prevent one extra death is 36 (95% CI 21 to 258), using a baseline risk of 15.2% from the placebo arm of TORCH. Both treatments led to statistically significant improvement in health status measurements, although the clinical importance of the differences observed is open to interpretation. Symptoms and lung function assessments favoured combination treatments. There was an increase in the risk of pneumonia with combined inhalers. The three year number needed to treat for one extra case of pneumonia is 13, using a baseline risk of 12.3% from the placebo arm of TORCH. Fewer participants withdrew from studies assessing combined inhalers due to adverse events and lack of efficacy.

Authors' conclusions

Compared with placebo, combination therapy led to a significant reduction of a quarter in exacerbation rates. There was a significant reduction in all-cause mortality with the addition of data from the TORCH trial. The increased risk of pneumonia is a concern, and better reporting of this outcome in future studies would be helpful. In order to draw firmer conclusions about the effects of combination therapy in a single inhaler more data are necessary, particularly in relation to the profile of adverse events and benefits in relation to different doses of inhaled corticosteroids.

PLAIN LANGUAGE SUMMARY

Combination therapy with inhaled corticosteroids and long-acting beta-agonists can reduce exacerbations and improve quality of life in people with chronic obstructive pulmonary disease (COPD) when compared to placebo treatment

Combinations of two classes of medication in one inhaler have been developed to treat people with COPD. Two types of combined inhaler exist currently: budesonide/formoterol (BDF - 'Symbicort'), and fluticasone/salmeterol (FPS - 'Advair' or 'Seretide'). The results of the studies showed that combined inhalers were effective and reduced the frequency of exacerbations compared with placebo medication to a level of three quarters of the previous rates. The patients included in these trials had on average 1-2 exacerbations per year which means that treatment with combination therapy would lead to a reduction of one exacerbation every two to four years in these individuals. Combination therapy led to a reduction in mortality over three years, and also led to improvements in lung function and symptoms. However, there was an increased risk of pneumonia associated with combined inhalers, and further monitoring of this outcome in future trials would provide valuable information for consumers and clinicians. Future research is required to show whether there is a difference between combination inhalers with different strengths of inhaled corticosteroids.