Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis

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CRD summary
This well-conducted review assessed the risks of pneumonia associated with long-term inhaled corticosteroid use in patients with chronic obstructive pulmonary disease (COPD). The authors concluded that there is a significantly increased risk of pneumonia associated with these treatments, without a concomitant increase in mortality. This conclusion was based on the evidence of the review and is likely to be reliable.

Authors' objectives
To determine the risk of pneumonia with long-term inhaled corticosteroid use in patients with chronic obstructive pulmonary disease (COPD).

Searching
PubMed, EMBASE and the Cochrane Database of Systematic Reviews were searched up to June 2008. Search terms were reported. The websites of the US Food and Drug Administration, the European regulatory authorities and manufacturers' information materials and clinical trials registers were also consulted. References from reviews and the Web of Science citation index were also checked.

Study selection
Randomised controlled trials (RCTs) assessing the use of inhaled corticosteroids (fluticasone, beclomethasone or budesonide) with at least 24 weeks follow-up in patients with COPD were eligible for inclusion in the review. Acceptable comparisons were corticosteroids versus placebo or corticosteroids plus a long-acting β-agonist versus a long-acting β-agonist alone. Primary outcomes were pneumonia reported as an adverse event and serious pneumonia. Secondary outcomes were pneumonia-related mortality and overall mortality. Trials in patients with asthma were excluded from the review.

Included studies employed a range of different formulations and doses of inhaled corticosteroids and concomitant medications. A majority of patients were male and mean ages ranged from 59.0 to 67.6 years.

Two reviewers independently selected the studies for inclusion and discrepancies were resolved through discussion and consultation with a third reviewer.

Assessment of study quality
Two reviewers independently assessed the studies for validity using the following criteria: randomisation, allocation concealment, blinding and reporting of loss to follow-up. The strength of adverse event monitoring was also assessed following the recommendations of the Cochrane handbook. Discrepancies were resolved through discussion and consultation with a third reviewer.

Data extraction
Two reviewers independently extracted intention-to-treat (ITT) data on incidence of pneumonia as an adverse event. Discrepancies were resolved through discussion and consultation with a third reviewer. Authors were contacted for clarification where required.

Methods of synthesis
Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated using a random effects meta-analysis. Numbers needed to harm (NNH) with 95% confidence intervals were calculated. Heterogeneity was assessed using $I^2$, with greater than 50% considered indicative of substantial heterogeneity. Analyses of the impact of comparison subgroups and individual studies were planned to explore such heterogeneity. Sensitivity analyses using fixed effect models, the exclusion of individual trials and restriction to studies considered to be at low risk of bias were conducted.
The fail-safe numbers were calculated in order to assess publication bias.

**Results of the review**

Eighteen RCTs (n=16,996 patients) were included in the review. Sample sizes ranged from 186 to 6,184 patients. Trial quality varied with nine RCTs judged to be at low risk of bias and nine RCTs where this was unclear. Trial duration ranged from 24 weeks to three years.

There was a statistically significantly higher incidence of pneumonia (pooled RR 1.60, 95% CI 1.33 to 1.92; 18 RCTs) and serious pneumonia (RR 1.71, 95% CI 1.46 to 1.99; 16 RCTs) in the inhaled corticosteroid groups. Subgroup analyses of trials with long-acting beta-agonists and placebos showed a similar effect for the outcome of serious pneumonia. There was no statistically significant difference between the groups for the outcomes of pneumonia-related mortality and overall mortality. Statistical heterogeneity was low in all analyses. Sensitivity analyses did not significantly affect the findings. The number needed to harm for the outcome of serious pneumonia was 47 (95% CI 34 to 73). The failsafe number was calculated as 16 trials with a mean N=945.

**Authors’ conclusions**

Inhaled corticosteroid use for at least 24 weeks is associated with a significantly increased risk of serious pneumonia, without a significantly increased risk of death, in patients with COPD.

**CRD commentary**

The review question and the inclusion criteria were clear. The authors searched a number of relevant databases and other sources without reported restrictions, reducing the chances of relevant studies being excluded from the review. Rigorous methodology was employed at all stages of the review process and an appropriate validity assessment was conducted, which was used to inform the synthesis. The decision to employ meta-analyses appeared appropriate and suitable explorations of clinical heterogeneity were undertaken. The authors’ conclusions clearly reflected the results of the review and are likely to be reliable.

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

**Practice:** The authors stated that clinicians should be vigilant for the development of pneumonia in COPD patients using inhaled corticosteroids and should re-evaluate the benefit-harm profile of their use in this patient group.

**Research:** The authors stated that manufacturers of inhaled corticosteroids need to make source data available for independent external analysis and that prospective trials of inhaled corticosteroids need to monitor pneumonia as a pre-specified outcome using objective definitions. They also stated that additional cost-benefit analysis is needed to determine optimal steroid use in the COPD population.

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