COPD: risk of pneumonia with inhaled corticosteroids

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A large Canadian observational study provides evidence that taking inhaled corticosteroids (ICS) increases the risk of serious pneumonia in people with chronic obstructive pulmonary disease (COPD). This risk appears to be sustained with long-term use, but declines after stopping ICS, and disappears after 6 months of no use. Fluticasone was associated with a greater risk of serious pneumonia than budesonide, but this might be due to differences between the people who were assigned to each drug. The study reinforces MHRA advice to be vigilant for the development of pneumonia and other infections of the lower respiratory tract when using inhaled corticosteroids to treat people with COPD, and to follow NICE guidance for the care of people with COPD.

Overview and current advice

NICE guidance on the management of COPD recommends inhaled corticosteroids (ICS) in combination with other inhaled therapies for selected patients, as part of the range of treatment options. The guidance advises practitioners to be aware of the potential risk of side effects (including non-fatal pneumonia) in people with COPD treated with ICS, and to be prepared to discuss this risk with patients.

The MHRA has advised that treatment with an ICS in COPD – either alone or in combination with a long-acting beta-agonist (LABA) – significantly increases the risk of pneumonia. In the TORCH randomised controlled trial (RCT) the probability of pneumonia was 19.6% in the fluticasone propionate/salmeterol group and 18.3% with fluticasone propionate alone compared with 12.3% in the placebo group. The MHRA recommends that ICS should not be used alone in COPD. Although in all trials combination therapy was more effective than monotherapy, the benefit is variable and not always clinically relevant and the MHRA advises that ICS should be introduced only when COPD progresses to severe disease, in line with NICE guidance.

Only ICS in combination inhalers are licensed for treating COPD. Three products are currently licensed for this indication: Seretide Accuhaler (fluticasone propionate with salmeterol), Symbicort (budesonide with formoterol) and Relvar Ellipta (fluticasone furoate with vilanterol), the latter being the subject of a NICE Evidence Summary New Medicine.
It is unclear whether the risk of pneumonia varies between different ICS. A meta-analysis of RCTs found more reports of pneumonia with fluticasone than with budesonide in people with COPD. However, firm conclusions are limited by the smaller numbers and shorter durations of budesonide RCTs published in this area and other differences between studies. A recent large observational study (PATHOS) found that use of fluticasone/salmeterol in people with COPD was associated with a greater risk of pneumonia, and of death associated with pneumonia, than budesonide/formoterol. (See previous Medicines Evidence Commentary for a discussion of this study and its limitations).

See the NICE Evidence topic page on COPD and the Clinical Knowledge Summary for a general overview of the condition. The NICE Pathway: COPD brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A Canadian population-based cohort study of 163,514 people receiving new treatment for COPD attempted to assess whether ICS (budesonide or fluticasone in particular) vary in their propensity to increase the risk of pneumonia and to evaluate the dose-response effects.

The investigators used health-insurance databases to identify people who had been dispensed at least one prescription for any form of beta-agonist, theophylline, ipratropium or tiotropium bromide, or ICS between 1999 and 2005. To identify people with COPD, the authors included those with 3 or more prescriptions for these medications (except ICS) in any 1 year and on at least 2 different dates. The authors attempted to exclude people with asthma by excluding anyone with a mention of asthma (including hospital admission for this before the third prescription) and anyone using nedocromil, ketotifen, cromolyn or antileukotrienes. The cohort included in this study were considered to be new users of respiratory medications (no respiratory medications during the 2 years before the first of their 3 prescriptions) and had a mean age of 72 years (50% men). They were followed up for up to 18 years, or until first hospitalisation for pneumonia or death.

Over a mean follow-up of 5.4 years, 20,344 patients had serious pneumonia (defined as hospital admission n=19,667; or death n=677). These patients were matched by age to 197,705 controls who did not have pneumonia. After adjusting for various factors such as age, sex, severity of respiratory disease and other diseases that can increase the risk of pneumonia, current use of ICS was associated with a 69% relative increase in the rate of serious pneumonia (rate ratio [RR] 1.69, 95% confidence interval [CI] 1.63 to 1.75). This risk appeared to increase with the dose of ICS, ranging from a 24% relative increase in the rate of serious pneumonia (RR 1.24, 95% CI 1.13 to 1.36) with low doses (equivalent to less than 500 micrograms/day of fluticasone propionate) to 86% (RR 1.86; 95% CI 1.77 to 1.94) with high doses (equivalent to at least 1000 micrograms/day of fluticasone propionate). Looking at time after stopping ICS, the risk of serious pneumonia diminished with time and disappeared after 6 months (RR in the first 6 months 1.19, 95% CI 1.13 to 1.26; RR from 6 to 9 months 1.08, 95% CI 0.99 to 1.17; RR from 9 months to 1 year 1.08, 95% CI 0.99 to 1.18).

When the effect of different ICS was considered on the rates of serious pneumonia compared with controls, current use of fluticasone was associated with double the rate (RR 2.01, 95% CI 1.93 to 2.10), but budesonide was only associated with a 17% relative increase in the rate (RR 1.17, 95% CI 1.09 to 1.26). This might be due to differences between people who were assigned to each drug (see Commentary below). In another group who were mostly receiving beclometasone, there was a 41% relative increase in the rate of serious pneumonia (RR 1.41, 95% CI 1.33 to 1.51). For fluticasone, the rate of serious pneumonia increased with the dose, but this was not the case for budesonide.

The authors also modelled duration of current use of ICS; this suggested that the risk of serious pneumonia peaks in the first year and then remains stable and elevated over the long-term, even up to 5 years of continuous use.
**Commentary**

This study's strengths include its size (163,514) and the duration of follow-up over several years (mean 5.4 years). In addition, being an observational study it was based on usual practice and so is more naturalistic than a RCT. However, the data come from Canada and may not completely reflect current prescribing practices in the UK. Furthermore, in an observational study, observed differences in outcomes may be due to differences among the patients, not only the different treatments. The authors did attempt to adjust for several confounding factors. For example, they adjusted for differences in COPD severity based on variables such as the numbers of prescriptions for respiratory medicines and previous hospitalisation. However, they acknowledge that residual confounding might still remain. In particular, the difference seen in risk of pneumonia between fluticasone and budesonide might reflect prescription of budesonide to people with a lower risk of pneumonia, such as those with asthma or less severe COPD. The definition of COPD in this study may not be robust as it was not based on a physician diagnosis or objective criteria.

This observational study supports earlier RCTs and meta-analyses in showing an increase in the risk of pneumonia with ICS in COPD, which may be dose-related. There appears to be a higher risk of serious pneumonia reported with fluticasone than with budesonide in this study, which is consistent with previous published data. Large head-to-head RCTs over several years, with accurate and objective definitions of COPD and pneumonia, are needed before firm conclusions can be made on the differences in risk between these 2 ICS.

Prolonged use of high doses of ICS carries a risk of systemic side effects, including adrenal suppression, decrease in bone mineral density, cataracts and glaucoma. ICS have also been associated with a dose-related increased risk of diabetes onset and diabetes progression, and with an increased risk of fracture. The MHRA has reminded health professionals to remain vigilant for the development of pneumonia and other infections of the lower respiratory tract when using ICS to treat people with COPD, because the clinical features of such infections and exacerbations frequently overlap.

This study reinforces the need for healthcare professionals to follow NICE guidance and be aware of the potential risk of side effects in people with COPD treated with ICS and be prepared to discuss these with patients. Because of the risk of systemic side effects, patients who require prolonged high-dose ICS should be issued with a steroid treatment card. Practitioners may wish to bear in mind the results of this study when discussing treatment options with patients.

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**References**

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