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Risk of pneumonia associated with long-term use of inhaled corticosteroids in COPD: A critical review and update

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Abstract

Purpose of Review—To determine the effects of long-term inhaled corticosteroid use on pneumonia in patients with Chronic Obstructive Pulmonary Disease via systematic searches of MEDLINE, EMBASE, ISI, regulatory documents and manufacturers' trial registries.

Recent findings—Our updated meta-analysis of 24 long term randomized controlled trials involving 23, 096 participants shows a significantly increased risk of pneumonia with the use of inhaled corticosteroids in Chronic Obstructive Pulmonary Disease (RR 1.57, 95% CI 1.41–1.75, $P < 0.0001$). The increased risk of pneumonia is not accompanied by a corresponding increase in mortality. The elderly and those with more severe disease and lower FEV1s are at the highest risk of pneumonia. The trials of currently available inhaled corticosteroids have included participants with varying duration of inhaled corticosteroid exposure and COPD severity, with apparent differences in the proportion of pneumonia ascertained among these trials. The absence of adequately powered long term head- to- head trials precludes any definitive conclusions on intra-class differences in risk.

Summary—Clinicians should consider the long term risks of pneumonia with the use of inhaled corticosteroids in patients with Chronic Obstructive Pulmonary Disease. Adequately powered long term head to head trials with objective pneumonia definitions, active ascertainment and radiologic and microbiologic confirmation are needed to clarify any intraclass differences in the risk of pneumonia.

Keywords

Inhaled corticosteroids; Chronic Obstructive Pulmonary Disease; Pneumonia

Introduction

Inhaled corticosteroids are widely used in patients with Chronic Obstructive Pulmonary Disease. The commonly used inhaled corticosteroids include inhaled fluticasone, inhaled budesonide and inhaled beclometasone.

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According to the Chronic Obstructive Pulmonary Disease Global Obstructive Lung Disease Guidelines, inhaled corticosteroids are indicated in combination with long-acting bronchodilators such as beta-agonists to reduce the frequency of exacerbations in symptomatic patients with severe Chronic Obstructive Pulmonary Disease (Forced Expiratory Volume₁(FEV₁) <50% predicted (Stage III: Severe COPD and Stage IV: Very-Severe COPD) and repeated exacerbations.¹

Recently, several studies have raised the possibility of pneumonia with inhaled corticosteroid therapy in COPD. The Towards a Revolution in COPD Health trial in 2007 reported a higher probability of having pneumonia reported as an adverse event among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group of salmeterol 50/Fluticasone 500 microgram and 18.3% in the fluticasone group 500 microgram) than in the placebo group (12.3%, $P<0.001$ for comparisons between these treatments and placebo) among nearly 6112 participants with COPD for a period of 3 years.^{2,3} Our aim is to critically review, analyze and update the current evidence on the risk of pneumonia associated with the long-term use of inhaled corticosteroids in patients with COPD.

Literature Search and Methodology

As part of our previous meta-analysis,⁴ we set up an automated search on Pub Med to provide weekly notifications on any new publications of (i) trials of budesonide, beclometasone, fluticasone or triamcinolone in COPD (ii) inhaled corticosteroids and pneumonia. Details of the search strategy and methods are outlined in our previous meta-analysis on this topic.⁴ These searches were updated in October 2009. We checked the study registries of Glaxo Smith Kline, and Astra Zeneca. We extracted data from the published study manuscript when available and from pharmaceutical company reports when published data were unavailable.

Recent Findings

The studies reporting on the risk of pneumonia with the use of inhaled corticosteroids include observational studies and meta-analysis of randomized controlled trials.

Observational Studies

In 2007, a case-control study epidemiological study in Quebec, Canada compared the rates of inhaled corticosteroid use in elderly COPD patients who were hospitalized due to pneumonia versus 95,768 controls in 2007. Inhaled corticosteroids were associated with a dose-dependent increased risk of hospitalization for pneumonia (RR 1.70; 95%CI, 1.63–1.77) and an increase in pneumonia related mortality at 30 days (RR, 1.53 95%CI 1.30–1.80). Limitations of this study were the possibility of residual confounding, lack of lung function data, and the reliance on dispensing records which may not reflect patient's actual utilization of these inhalers.⁵

Two unpublished observational studies in the Glaxo Smith Kline clinical trials register have reported on pneumonia with inhaled corticosteroids.^{6,7} A retrospective cohort study of 10,918 newly diagnosed COPD patients in the General Practice Research Database (GPRD) in the UK reported no increase in pneumonia risk for the first three years after initiation of an inhaled corticosteroid. However, a doubling in the risk of pneumonia was seen four years after inhaled fluticasone exposure (Odds Ratio [OR] 2.08, 95%CI, 1.01–7.77). A second unpublished study evaluated 15,614 adults with newly diagnosed COPD in the GPRD. Both the retrospective cohort analysis and the case-control analysis failed to find a significant association for pneumonia with inhaled corticosteroid exposure of up to 24 months, with or

without long acting beta-agonists, when compared to short acting β -agonists. However, the highest risk for pneumonia associated with inhaled corticosteroids in combination with a long acting β -agonist was seen in the 18–24 month categories (OR 1.82, 95%CI, 0.95–3.47, $p=0.07$), and a larger study may have had sufficient power to detect a significant difference. Both these studies were limited by the recruitment focusing on incident (newly-diagnosed) COPD cases, and the uncertainty around whether the diagnosis of pneumonia was validated by chest radiographs in the GPRD.

Meta-analysis of randomized controlled trials

Our previous systematic review and meta-analyses,⁴ another industry supported pooled analysis,⁸ have evaluated pneumonia as a pre-specified primary outcome of interest. Another systematic review and meta-analysis has evaluated pneumonia alongside the primary outcome of overall mortality.^{9,10} Several additional reviews have also performed secondary analyses on the adverse effects of pneumonia associated with inhaled corticosteroids.^{11–13}

In 2008, Drummond et al evaluated mortality and pneumonia with inhaled corticosteroids limited to 11 published clinical trials.⁹ They found a significantly increased risk of pneumonia (RR 1.34; 95% CI, 1.03–1.75; $P=.03$) with substantial statistical heterogeneity ($I^2=72\%$). The limitations of this analysis include the extraction of lower respiratory serious adverse events as ‘pneumonia’ events and the inclusion of potentially ineligible trials which provided for a confounded comparison of salmeterol/fluticasone versus tiotropium.¹⁰ A re-analyses of the data addressing the above removes the estimates of substantial statistical heterogeneity and show a consistently increased risk of pneumonia.¹⁰ The results of several additional reviews are also consistent with the overall evidence showing a significantly increased risk of pneumonia with inhaled corticosteroids.^{11–13}

In early 2009, we reported a trial level meta-analysis on pneumonia (adverse events and serious adverse events, and pneumonia-related mortality).⁴ Eighteen long-term (>24 weeks) trials with 17,000 participants with COPD were included in the analysis which showed a RR of 1.60 (95 % CI 1.33 –1.92, $p < 0.001$) for pneumonia with inhaled corticosteroids. The increased risk of pneumonia was not accompanied by an increase in mortality. This increased risk was consistent irrespective of whether inhaled corticosteroids were used alone, or in combination with long-acting beta-agonists. Our analysis was limited by the paucity of information on inhaled budesonide because only two trials reported on pneumonia with inhaled budesonide whereas 16 trials evaluated fluticasone. There was a lack of information on how pneumonia adverse events were ascertained in the respective trials.

In 2009, Sin et al. pooled individual patient data provided by AstraZeneca on the risk of pneumonia in 7 budesonide trials. The strengths of the meta-analysis included the availability of patient level data. However, their analysis had several methodological limitations. Firstly, the analysis censored patient data at one year and this relatively short definition of the exposure period removed their ability to detect any long term effect of inhaled budesonide on the risk of pneumonia, despite there data being available from trials extending up to three years.⁸ Secondly, the analysis may have been biased by inclusion of a trial which did not meet their prespecified eligibility criteria of a 10 pack year smoking history, but was the only long-term study demonstrating a lower rate of pneumonia with budesonide compared to placebo.¹⁴ Thirdly, part of the pooled data involved a confounded comparison of budesonide/formeterol vs placebo by including the placebo arm as comparator despite the absence of a budesonide arm in one trial.¹⁵ Fourthly, there was an inadequate exploration of statistical heterogeneity ($I^2=23\%$). Finally, they lacked the ability

to detect seasonal variations in pneumonia incidence. Despite these limitations which limited their ability to detect any significant difference, the study reported a hazard ratio of 1.05 (95% CI 0.81 – 1.37) with relatively wide confidence intervals, indicating they could not rule out the possibility of as much as a 37% increase in the risk of pneumonia with inhaled budesonide.⁸

An updated meta-analysis

To address these limitations, we report an updated meta-analysis of 24 RCT involving 23,096 participants with COPD based on an updated literature search, including data from previous meta-analysis,^{4,8} and all pneumonia events reported throughout the duration of the budesonide trials. The safety database of inhaled budesonide still remains extremely limited with a smaller sample size than fluticasone (n=7 trials with budesonide vs n=16 trials with fluticasone) and only $\approx 2/5$ the number of participants. The inadequacy of the limited sample size is further compounded by the relatively lower proportion of pneumonia events in the budesonide trials ($\approx 3.5\%$ in budesonide vs $\approx 6.2\%$ in fluticasone trials), reflecting lower rates of ascertainment of pneumonia and shorter duration of inhaled budesonide exposure.

Our updated meta-analysis shows a significantly increased risk of pneumonia with inhaled corticosteroids (RR 1.57, 95% CI 1.41–1.75, $P<0.0001$) (Figure 1). Inhaled fluticasone and mometasone exposure remain significantly associated with an increase in the risk of pneumonia. The evidence on whether budesonide is different from other inhaled corticosteroids in the risk of pneumonia remains inconclusive. In subgroup analysis the *magnitude* of risk of pneumonia associated with inhaled budesonide appears to be lower, and does not meet the threshold for statistical significance. However, the *direction* of effect on pneumonia suggests the possibility of an increased risk of pneumonia with inhaled budesonide. Such subgroup analysis for intraclass differences should be only interpreted for their *direction* of effect.

The exclusion of the single trial which recruited patients with the mildest severity of COPD and the highest FEV1 of $\approx 80\%$ ¹⁴ which was supposed to be ineligible for Sin's primary analysis⁸ demonstrates a statistically significantly increased risk of pneumonia with inhaled budesonide (Pooled RR 1.34, 95% CI 1.01 – 1.79, $p=0.04$) and removes the statistical heterogeneity ($I^2=0\%$) in a sensitivity analysis (Figure 2). There was one trial where exposure to budesonide (1500 patient years) was almost twice as long compared to the relatively short duration of all the other budesonide trials, and our analysis showed a significant doubling in the risk of pneumonia (RR 2.02, CI 1.13–3.64) with this long-term study.¹⁶ Thus, only head to head adequately powered long term trials with objective pneumonia definitions can clarify any doubts and determine whether there are genuine intraclass differences in the risk of pneumonia.

Risk factors for Inhaled Corticosteroid Associated pneumonia

A posthoc analysis of the TORCH trial has identified a number of risk factors including age above 55 years, FEV1 $<50\%$, recent history of exacerbations, and those with worse dyspnoea scores and lower Body Mass Indexes.³ The authors reported an increase in pneumonia which was discernible 6 months after treatment with inhaled corticosteroids.

Does Increased Risk of Pneumonia translate into Increased Mortality?

Observational studies reported an increase in 30 day mortality associated with pneumonia secondary to inhaled corticosteroid use. However the available evidence from randomized trials suggests that the increased risk of pneumonia associated with inhaled corticosteroids is

not associated with an increased risk of pneumonia related mortality or overall mortality. These differences between the results of randomized trials and observational studies can be explained by the inclusion of different study populations, the limited ability of the trials to detect differences in pneumonia mortality and the possibility that the pneumonia associated with inhaled corticosteroids has a milder severity.

The precise biological mechanism underlying the increased risk for pneumonia with inhaled corticosteroids and within class differences in risk are uncertain. Inhaled corticosteroids achieve locally high concentrations in the lung which may lead to immunosuppressive effects.⁴ Patients with advanced COPD who are at the highest risk of colonization with pathogenic bacteria may be uniquely susceptible to these local immunosuppressive effects. Any possible differences in the risk of pneumonia between fluticasone and budesonide may relate to decreased bioavailability and lesser potency of inhaled budesonide.⁸

Conclusion

The consistency of the available clinical, biological and epidemiological evidence suggests that long term inhaled corticosteroid use in patients with Chronic Obstructive Pulmonary Disease is associated with a significantly increased risk of pneumonia. The evidence for any intraclass differences in the risk of pneumonia remains inconclusive. Robust head to head trials of sufficient duration, sample size and active ascertainment of pneumonia events along with radiologic and microbiologic confirmation are required to address these uncertainties. Clinicians should remain particularly vigilant for the development of pneumonia with inhaled corticosteroids in these patients, as the signs and symptoms of pneumonia may closely mimic that of COPD exacerbations. They should discuss the risks and benefits of long term inhaled corticosteroid therapy with their patients.

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None

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Annotation Special (*) or Outstanding (**) interest

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Figure 1.
Meta- Analysis of Inhaled Corticosteroids and the risk of Pneumonia in COPD

Figure 2.
 Sensitivity analysis of Inhaled Budesonide and the Risk of Pneumonia in COPD