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Inhaled Corticosteroids Cause Pneumonia . . . or Do They?

You might be surprised if an intervention or therapy that, on the one hand, reduced the overall frequency of exacerbations of chronic obstructive pulmonary disease (COPD), at the same time increased the frequency of pneumonia. Prepare, then, to be surprised!

This was exactly what was found in a recent 3-year, prospective, randomized, placebo-controlled comparison of an inhaled corticosteroid with a long-acting β-agonist and the inhaled corticosteroid/long-acting β-agonist combination (1). Compared with placebo, there were 49 and 60% increases in the rate of pneumonia in the inhaled corticosteroid and inhaled corticosteroid/long-acting β-agonist arms, respectively, while at the same time a reduction of 18 and 25% in moderate or severe exacerbation frequency. At first sight, this appears paradoxical, and indeed it may be. The study was not designed to study pneumonia frequency and so neither an objective definition nor radiographic confirmation of pneumonia was used. Added to the high drop-out rate in the study, these features might reasonably lead to the conclusion that the pneumonia findings could have been spurious. Similar findings in other studies might, on the other hand, suggest that the results are real.

In this issue of the *Journal* (pp. 162–166), a study with a different design, a population-based cohort study, with a nested case-control analysis, has also found a similar increase in pneumonia frequency in patients receiving inhaled corticosteroids (2). Ernst and coworkers used a large health database to identify patients with COPD and to study the frequency of inhaled corticosteroid use in those admitted to hospital because of pneumonia compared with matched control subjects. Current use of inhaled corticosteroids was associated with an increase of 70% in the rate of hospital admission for pneumonia. The admission rate was greatest with the highest doses of corticosteroids used, and a reduction in risk once inhaled corticosteroids were stopped was observed. A 53% increase in pneumonia death within 30 days of admission with inhaled corticosteroids was also found. The strengths of this study are as follows: (*1*) the completeness of the database, (*2*) that the inhaled corticosteroid–pneumonia relationship was the specific goal of the study, and (*3*) that a more objective pneumonia definition was used (although radiographic confirmation was presumed rather than demanded). Weaknesses are as follows: (*1*) the absence of radiographic confirmation of pneumonia; (*2*) that an accepted definition for COPD was not used, with COPD being defined by age over 65 plus repeated inhaled medication prescription in the absence of any mention of asthma; (*3*) COPD severity was presumed according to number of respiratory medications and oral corticosteroid prescription and hospital admission; (*4*) medication intake was based on prescription rather than actual use; and (*5*) measures of pulmonary function were not included. Compared with the above-mentioned study, patients were older (mean age, 77 vs. 65 yr), had a lower frequency of males (50 vs. 75–76%), and had a higher pneumonia mortality (7.4–8.2 vs. 2.7–4.6%). Neither study specified that pneumonias were community acquired, nor documented the frequency of vaccination against influenza or pneumococcal infection—interventions that could have affected pneumonia frequency. A further smaller, prospective study of inhaled corticosteroid/long-acting β-agonist versus long-acting β-agonist alone has also recently found an excess of pneumonia (again undefined) in the patients receiving inhaled corticosteroids (3).

What else do we know about COPD and corticosteroid use in relation to pneumonia? Previous studies have identified COPD as a risk factor for pneumonia occurrence in the community (4, 5), as a cause of hospital admission (6), and, in the elderly, as a risk factor both for occurrence and hospital admission (7). COPD is also a risk factor for invasive (8) and noninvasive pneumococcal disease (9). Only one of these studies, which were performed before inhaled corticosteroid use in COPD was as widespread as it is today, attempted to separate the influence of the disease from the treatments used for it (4). In that study, only 10% of cases used inhaled corticosteroids and their use was not associated with pneumonia occurrence. Similarly, no study has sought a relationship between inhaled corticosteroid use and pneumonia in patients with asthma, although patients with asthma have been identified to have an increased risk of pneumonia (7) and invasive pneumococcal disease (8, 10). In two studies, no relationship was found between use of corticosteroids (route unspecified) with pneumococcal infection (9) or oral corticosteroids with pneumonia (4), but conversely, an oral corticosteroid dose–response relationship with pneumonia frequency has been found in patients with rheumatoid arthritis (11).

So where does all of this leave us? Studies of pneumonia are bedeviled by the lack of correlation between clinical findings and radiographic information. The latter is the gold standard

for pneumonia definition, but may not be easily available for large community-based studies. Maybe this criticism has been overplayed? Computed tomography studies have shown that pulmonary infiltrates may be present even though absent on the chest radiograph (12). Also, the clinical behavior of patients with radiographic pneumonia may be similar to those with clinical pneumonia, not confirmed on chest radiograph (13). Absence of radiographic confirmation may, therefore, not be such a big fault of the above studies.

Is a different effect of inhaled corticosteroids on pneumonia and COPD exacerbation biologically plausible? Most pneumonias are bacterial in origin. Bacteria are important in COPD exacerbations, but we are now increasingly aware of the importance of viral infections in up to 56% of cases (14). Maybe a differential effect on viral compared with bacterial infections could explain the difference?

So, do inhaled corticosteroids increase the risk of pneumonia? The finding of an association between pneumonia frequency and inhaled corticosteroid use in studies of different design, in different populations, and with evidence of a dose–response relationship means that the findings may be real and that these observations cannot simply be dismissed. The issue requires prospective evaluation in further large studies of inhaled corticosteroids using objective pneumonia definitions. Maybe more surprises await us?

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