Inhaled corticosteroids should not be prescribed to all chronic obstructive pulmonary disease patients

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Corticosteroids are one of many therapeutic modalities that pose a clinical dilemma in the treatment of stable chronic obstructive pulmonary disease (COPD). Years ago, the rationale for using corticosteroids in COPD was in part due to the unquestionable benefit in the treatment of asthma. As physicians, we have tended to transfer proven therapies from asthma to COPD. The hope has always been that inhaled corticosteroids will exert a similar effect in COPD patients as in asthma patients by suppressing inflammation reactions. The question of efficacy is of great importance, because long term use of corticosteroids, especially systemic or even high doses of inhaled corticosteroids, can potentially cause systemic adverse effects (1). As well, the cost associated with prescribing inhaled corticosteroids is far from negligible.

SHORT TERM CLINICAL STUDIES

Early studies have suggested that there are no benefits of short term inhaled corticosteroids (2-8). However, many of these studies had a limited sample size. In the occasional studies in which a benefit was shown (9-11), patients were poorly defined (9) or the study included asthma patients (10). Outcomes were also limited to the measurement of forced expiratory volume in 1s (FEV₁) with questionable clinical relevance.

LONG TERM CLINICAL STUDIES

Recently, four long term studies – the European Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) (12), the Copenhagen City Heart Study (13), the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study (14) and the Lung Health Study II (15) – provided evidence that inhaled corticosteroids do not slow the decline in lung function that occurs in patients with COPD. The hope has always been that inhaled corticosteroids will exert a similar effect in COPD patients as in asthma patients by suppressing inflammation reactions. However, the uncertainty of benefits of inhaled corticosteroids in suppressing airway inflammation in COPD patients (16-19) contrasts with the well-documented and consistent benefits in patients with asthma.

A reduction in the frequency of exacerbations was demonstrated in the ISOLDE study (14), but not in the EUROSCOP (12) and Copenhagen City Heart Study (13), in which patients had mild disease. In the ISOLDE study, the effect on the annual exacerbation rate could not be demonstrated in patients with an FEV₁ greater than 1.5 L. More recently, a meta-analysis (20) was also able to confirm a beneficial effect of inhaled corticosteroids in reducing COPD exacerbations. The test for heterogeneity was significant, indicating that the effects of corticosteroids on exacerbations varied among the studies. The beneficial effect on exacerbations was driven largely by the ISOLDE study (14), in which the use of inhaled corticosteroids (fluticasone 1000 µg/day or beclometasone equivalent 2000 µg/day) led to a 30% reduction in exacerbations.

Epidemiological Studies

A recent study by Sin and Tu (21) using health care databases showed that among subjects 65 years of age or older who were discharged from hospital with a diagnosis of COPD, any prescription of inhaled corticosteroids dispensed within 90 days of hospital discharge was associated with a marked reduction in all-cause mortality. Similarly, Soriano et al (22), using the same study methodology, showed a marked reduction in all-cause mortality with increased doses of fluticasone in combination with salmeterol or fluticasone alone. These findings from pharmacoepidemiology studies using similar research methodologies should be interpreted cautiously and cannot be considered definitive. Although pharmacoepidemiology studies are useful complements to randomized clinical trials, randomized clinical trials have not been able to show a reduction in mortality for those patients treated with inhaled corticosteroids. As part of a recent meta-analysis (20), five of nine studies that looked at mortality as a secondary outcome found that there was no reduction in all-cause mortality in patients taking inhaled corticosteroids compared with those not taking inhaled corticosteroids.

BENEFIT TO RISK RATIOS

It remains uncertain whether using high dose inhaled corticosteroids for long periods of time is associated with a favourable risk-benefit ratio. Local adverse effects have been well docu-
The results of a recent systematic review and meta-analysis by Lipworth (1) have shown that marked adrenal suppression occurred with high doses of inhaled corticosteroids (beclomethasone equivalent higher than 1500 µg/day) in patients with asthma, although there is a considerable degree of interindividual susceptibility. Inhaled corticosteroids in doses higher than 1500 µg/day of beclomethasone equivalent can be associated with a significant reduction in bone density, although the risk for osteoporosis can be obviated by post-menopausal estrogen replacement therapy. Furthermore, long term, high dose inhaled corticosteroid exposure can increase the risk of posterior subcapsular cataracts, and, to a much lesser degree, ocular hypertension and glaucoma. Because COPD patients are generally older than asthmatic patients, the prolonged use of high dose inhaled corticosteroids may pose a greater risk in this group.

REFERENCES