A comparison of nebulized budesonide with oral prednisolone in the treatment of exacerbations of obstructive pulmonary disease

Nebulized corticosteroids in acute bronchospasm may offer topical anti-inflammatory activity while minimizing undesirable systemic effects. We compared the side-effect profile of nebulized budesonide (2 mg twice daily) with that of oral prednisolone (30 mg once daily) in a randomized parallel-group study of 19 adults with severe acute airway obstruction. Over the 5 days of the study, baseline forced expiratory volume in 1 second (FEV₁) increased from 1.8 (95% confidence interval [CI], 0.7) to 2.1 (95% CI, 0.7) L in the group that received oral corticosteroids compared with 1.9 (95% CI, 0.7) to 2.0 (95% CI, 0.7) L in the group that received nebulized corticosteroid. All biochemical variables were similar at day 1. Comparison of budesonide treatment with prednisolone on day 5 showed that urinary corticosteroid metabolites were significantly higher (2012 [95% CI, 812] compared with 1079 [95% CI, 346] mg/24 hr [p < 0.05]), urinary androgen metabolites were not different, serum osteocalcin was elevated (2.3 [95% CI, 1.4] compared with 0.6 [95% CI, 0.6] ng/ml [p < 0.05]), and 24-hour urinary calcium to creatinine ratios were lower (0.28 [95% CI, 0.1] compared with 0.53 [95% CI, 0.2]), whereas urinary hydroxyproline to creatinine ratios were similar. The biochemical markers associated with corticosteroid side effects improve in patients treated with nebulized corticosteroids compared with patients who receive conventional treatment. (Clin Pharmacol Ther 1996;60:675-8.)

Alyn H. Morice, MD, David Morris, MB, ChB, and Peter Lawson-Matthew, PhD
Sheffield, England

Inhaled corticosteroids are a safe and effective treatment of chronic asthma and steroid-responsive chronic obstructive pulmonary disease (COPD). Their efficacy has been shown in numerous studies. Inhaled corticosteroids not only cause improvement in objective measures of lung function but also diminish symptoms and reduce episodes of acute bronchospasm. Their mode of action is thought to be a reduction of inflammation, thus diminishing cellular infiltration and swelling and exudation within the airways. Inhaled corticosteroids are relatively free from systemic effects because, although the majority of any inhaled dose is swallowed, rapid first-pass hepatic metabolism ensures little systemic bioavailability.

All international guidelines for the treatment of acute asthma and exacerbations of COPD recommend the use of parenteral corticosteroids. Such therapy for infrequent exacerbations is unlikely to have serious systemic effects. Unfortunately, many patients with severe disease receive repeated courses and are potentially at risk from corticosteroid-induced side effects.
Osteoporosis and bone fracture have been reported with long-term administration, and evidence suggests that even short-term administration may adversely alter markers of bone turnover. In severe acute bronchospasm the efficacy of inhaled corticosteroids has not been tested, although an increase in the inhaled dose has been shown to be an effective means of inhibiting more slowly developing deterioration. We hypothesized that inhaled corticosteroid therapy may be an effective method of treatment for many patients with obstructive lung disease who have an acute exacerbation. Unfortunately, the efficacy of parenteral steroids in acute asthma has previously been difficult to demonstrate. Indeed, some placebo-controlled studies have shown no effect.

Conventional therapy of severe acute asthma includes the use of nebulized bronchodilators. Recently high-dose nebulized corticosteroids have become available in the United Kingdom and have a potential role in the treatment of acute bronchospasm. Because any difference in efficacy between systemic administration of corticosteroids and topical administration by nebulizer is likely to be small, any trial attempting to differentiate effects on recovery would require large numbers of patients. We therefore performed a preliminary study to test the hypothesis that treatment of acute bronchospasm with nebulized corticosteroids is associated with an improvement in the biochemical profile characteristic of corticosteroid side effects.

PATIENTS AND METHODS

The trial was approved by the hospital’s Ethics Review Committee. Nineteen consecutive adult patients who had been admitted after a deterioration in their obstructive airway disease gave informed consent to participate. Patients (eight men; mean age, 50 years) had all been previously diagnosed with asthma or COPD responsive to corticosteroids. All were required to be taking inhaled corticosteroids (mean dose, 850 µg; range, 100 to 2000 µg) and inhaled β-agonists before admission. Patients were ineligible for study if they had received oral corticosteroid treatment in the 3 months before the study. Patients received conventional treatment for acute bronchospasm by their family practitioner and in the hospital’s Accident and Emergency Department before randomization. Prestudy corticosteroid medication was similar in the two treatment groups and consisted of either 30 or 40 mg oral prednisolone or 200 mg intravenous hydrocortisone.

The day after admission (day 1), written consent was obtained and each patient was randomized to receive 30 mg oral prednisolone once daily (n = 10) or 2 mg nebulized budesonide twice daily (n = 10), one patient having been studied twice in separate treatment arms with 6 months between exacerbations. Nebulized corticosteroids were delivered with an R252 nebulizer (Intersurgical Respiration Systems, Wokingham, Berkshire, England) with a Medix HiFlow compressor and mouthpiece (Medix Ltd., Lutterworth, Leicestershire, England). In addition, patients received 5 mg nebulized albuterol four times daily. Patients with profound hypoxemia (PO2 < 5 kPa) or significant hypercarbia (PCO2 > 7 kPa) were excluded.

On study day 1 patients performed lung function using a Vitalograph Compact (Vitalograph, Buckingham, England); 10 ml blood was withdrawn, which was immediately centrifuged and the plasma stored at −20°C. A 24-hour urine collection was performed for steroid metabolites. On the fifth study day (day 5) these investigations were repeated at the same time of day. Analysis of biochemical markers was performed without knowledge of treatment allocation.

Urinary steroid measurements were performed by capillary gas liquid chromatography. The interassay coefficient of variation for cortisol metabolites was 14% (normal range for men, 8891 to 4178 mg/24 hr; normal range for women, 6531 to 2968 mg/24 hr). The interassay variation in the calcium creatinine ratio was 8.4%. Osteocalcin was measured in a single batch with use of the BGP IRMA kit (Mitsubishi Petrochemical Co. Ltd., Tokyo, Japan). The normal range is 3.1 to 12.7 ng/ml (mean, 6.2 ng/ml). The intraassay coefficient of variation was 6.4%.

Results are expressed as a mean value (95% confidence interval). A statistical comparison of the primary end points was performed with use of a two-tailed student t test for unpaired samples. The study had an 80% power to detect a difference of 1000 mg/24 hr in 24-hour urinary cortisol metabolites at a 5% significance level.

RESULTS

All patients tolerated the treatment well without obvious adverse effects, and there were no further acute exacerbations that needed emergency treatment or withdrawal from the trial during the study period. Mean baseline forced expiratory volume in 1 second (FEV1) was similar in both groups (1.8 and 1.9 L for prednisolone and budesonide, respectively). There was no significant difference in response to treatments: FEV1 increased to 2.1 and 2.0 L, respectively.
There were no significant differences between any of the biochemical variables at day 1. On day 5, mean urinary corticosteroid metabolites were significantly higher after nebulized budesonide: 2012 (95% CI, 812) mg/24 hr compared with prednisolone treatment 1079 (95% CI, 346) mg/24 hr (p < 0.05). Urinary androgen metabolites were similar in both treatment groups: 831 (95% CI, 304) mg/24 hr on budesonide compared to 759 (95% CI, 287) mg/24 hr on prednisolone. The effect of treatment on serum osteocalcin was also significant 2.3 (95% CI, 1.4) ng/ml on budesonide compared to 0.6 (95% CI, 0.6) ng/ml on prednisolone (p < 0.05). Twenty four hour urinary calcium to creatinine ratios were significantly lower on budesonide 0.28 (95% CI, 0.1) compared with 0.53 (95% CI, 0.2) on prednisolone. There was no significant difference between urinary hydroxyproline to creatinine ratios 23.7 (95% CI, 7.5) on budesonide compared with 20.6 (95% CI, 5.5) on prednisolone.

DISCUSSION

The widespread use of inhaled corticosteroids in the management of chronic airflow obstruction has revolutionized the treatment of asthma and COPD. The inhaled route allows the delivery of a potent anti-inflammatory agent direct to the airway, and because of the rapid hepatic metabolism of these drugs there is little systemic effect even at relatively high doses. At very high concentrations of inhaled corticosteroids, some systemic activity is to be expected because the drug is absorbed directly from the lung into the pulmonary circulation, thus avoiding first-pass liver metabolism. In this study we have investigated whether twice-daily doses of 2 mg nebulized budesonide given to patients with acute bronchospasm causes fewer systemic effects than conventional therapy with oral prednisolone. Our results clearly show an improvement in the biochemical markers associated with systemic corticosteroid activity when nebulized budesonide is compared with oral prednisolone treatment. This occurred despite probable suppression of these markers caused by initial treatment with systemic corticosteroids by family practitioners or in the Accident and Emergency Department.

It may be questioned whether biochemical changes such as those shown in this study are of clinical significance. We have assessed the most frequently used markers of bone turnover to reflect bone formation, resorption, and net bone turnover. Osteocalcin is produced by osteoblasts and is recognized as a more specific and sensitive marker of bone formation than serum alkaline phosphatase activity. Both hydroxyproline and calcium excretion may be expressed as a ratio to creatinine measured in a 2-hour collection of urine after an overnight fast. Hydroxyproline and creatinine are used to reflect bone resorption, and calcium and creatinine are used as a marker of net bone turnover being the result of calcium incorporation into bone during formation and calcium release during bone resorption.

Histomorphometric studies of patients receiving oral corticosteroids have shown reduction in bone formation and increase in bone resorption. Such changes are thought to underlie the pathologic process that leads to corticosteroid-induced osteoporosis. Although long-term oral corticosteroid therapy has clearly linked with biochemical changes, reduced bone mineral density, and osteoporotic bone fractures, the evidence for such effects with the use of inhaled corticosteroids, even at high doses, is limited.

Suppression of osteocalcin has been reported in some studies, particularly with the use of beclomethasone (beclometasone), but interpretation of longer-term studies in patients is complicated by concomitant administration of short-term oral corticosteroid rescue medication.

In the treatment of severe airflow obstruction, many patients receive frequent short courses of oral corticosteroid for acute exacerbations. In the study by Packe et al., such patients had a significantly reduced bone density that was similar to those receiving long-term oral corticosteroids, after adjustments for age and sex differences. Repeated short-term high-dose oral corticosteroids may be injurious to bone as low-dose maintenance treatment. Our finding that short-term oral corticosteroid medication produces an early reduction in markers of bone formation confirms earlier studies. These biochemical changes are associated with the period of maximal bone loss, as shown in longitudinal bone density studies. It appears that bone loss occurs with the initiation of treatment, but no study has yet prospectively compared the effects of intermittent and continuous oral corticosteroid treatment on bone density or fracture rate.

In conclusion, our study has shown that the use of short-term parenteral corticosteroids in the treatment of severe bronchospasm causes a detrimental effect on the biochemical markers related to side effects. Nebulized budesonide treatment, compared
with oral prednisolone, produced a significant improvement in these markers without significantly affecting recovery. Larger studies will be needed to confirm these findings.

We thank Dr. R. Forrest and Mrs. D. A. Rodgers, who performed the steroid assays, and Dr. L. Coulton, who performed the osteocalcin assay.

References

7. Malo JL, Cartier A, Merland N. Four times a day dosing frequency is better than twice a day regimen in subjects requiring a high dose inhaled steroid, budesonide, to control moderate to severe asthma. Am Rev Respir Dis 1989;140:624-8.