Systemic Bioactivity Profiles of Oral Prednisolone and Nebulized Budesonide in Adult Asthmatics*

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Study objective: Because nebulized budesonide may be used as an alternative to maintenance oral prednisolone in the treatment of severe chronic asthma, it is important to compare these two drugs to determine their relative systemic bioactivity profiles in terms of effects on adrenal, bone, and hematologic markers.

Design: Twelve asthmatic patients (mean age; 34.7 years; mean FEV₁; 88.3% predicted; mean forced expiratory flow between 25% and 75% of FVC, 54.8% predicted) were studied in a double-blind, double-dummy, randomized crossover design to compare placebo, low, medium, and high doses of nebulized budesonide given bid (1, 2, and 4 mg/d, respectively), and oral prednisolone given qd (5, 10, and 20 mg/d). All treatments and both placebos were given for 4 days at each dose level with a 7-day washout period between each treatment block with budesonide or prednisolone. All measurements were made at 8 AM after the last dose of each dose increment for plasma cortisol, serum osteocalcin, and blood eosinophil count.

Results: Regression analysis showed significant dose-related suppression with prednisolone for 8 AM plasma cortisol (p<0.0001), osteocalcin (p<0.05), and blood eosinophil count (p<0.0005), but not with budesonide. Compared with placebo, there were significant differences only with prednisolone, at the medium- and high-dose levels for all three markers.

Conclusions: For all three systemic bioactivity markers (8 AM plasma cortisol, serum osteocalcin, and blood eosinophils), there was significant dose-related suppression with prednisolone but not with budesonide. Further long-term studies are required in more severe asthmatics in order to evaluate the therapeutic index.

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Key words: adrenal suppression; asthma; budesonide; cortisol; prednisolone

Abbreviations: CI = confidence interval; FEF25–75 = forced expiratory flow between 25% and 75% of FVC; pMDI = pressurized metered-dose inhaler

Corticosteroid therapy is regarded as the first line anti-inflammatory medication in the treatment of asthma. Current management guidelines suggest that high doses (>800 μg/day) of inhaled corticosteroids are preferable to maintenance oral prednisolone for patients with chronic severe asthma.1,2 In order to obviate compliance problems with multiple actuations of pressurized metered-dose inhalers (pMDIs), nebulizers are an alternative option for the delivery of high doses of inhaled corticosteroids to the lung. The problem of poor inhaler technique, which often occurs with pMDIs, is also avoided with nebulizers as there is no need to coordinate actuation with inhalation. Budesonide (Pulmicort Respules; Astra Pharmaceuticals; King’s Langley, UK) is currently the only suspension formulation of corticosteroid licensed in Europe for delivery via a nebulizer in the treatment of asthmatic patients.

In many patients with chronic severe asthma or chronic obstructive airways disease, their disease is not adequately controlled with conventional inhaled corticosteroid therapy and they require maintenance treatment with oral corticosteroids such as prednisolone. However, long-term systemic adverse effects are a problem, even when the minimal effective maintenance dose of oral prednisolone is used. Although all inhaled corticosteroids are associated with dose-related systemic adverse effects,3 it is assumed that high-dose inhaled corticosteroids have a better

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therapeutic index than oral prednisolone. For these reasons, high-dose nebulized budesonide has been advocated as an alternative for patients who would otherwise be treated with maintenance daily oral prednisolone.4,5

There are few dose-response studies in asthmatics comparing the systemic bioactivity of inhaled corticosteroids with other inhaled corticosteroids or with placebo.6-8 There are also few dose-response data comparing systemic bioactivity of oral and inhaled medication. Two such studies have been performed comparing inhaled budesonide with oral prednisolone, one in asthmatics9 and the other in healthy volunteers.10 In both of these studies, budesonide was given via a large volumatic spacer. Therefore, we felt it was important to perform a direct comparison of oral prednisolone and nebulized budesonide, which are commonly used to treat chronic severe asthmatics.

In the studies mentioned above, the milligram equivalent potency ratio for cortisol suppression for prednisolone vs budesonide was calculated to be 7.6:1 for steroid-dependant asthma9 and 5.1 for healthy volunteers.10 We therefore chose a putative dose ratio of 5:1 for comparing nebulized budesonide and oral prednisolone.

Because glucocorticoid receptors are ubiquitous in bodily tissues, their systemic effects can be measured using different tissue-specific markers.11 Two widely used sensitive markers of the systemic bioactivity of corticosteroids are the suppression of adrenocortical activity and blood eosinophil count.9 Another important long-term side-effect of corticosteroids is that of altered bone metabolism and the associated fracture risk from osteoporosis. The dominant effect of corticosteroids on bone turnover is a reduction in osteoblast activity, which can be evaluated by measuring serum osteocalcin levels.

MATERIALS AND METHODS

Patients

Twelve stable patients with mild to moderate asthma12 (six men, six women) were recruited into the study. Their mean age (±SD) was 34.7±10.1 years, mean FEV1 was 88.3±13.2% predicted, and mean forced expiratory flow between 25% and 75% of FVC was 54.8±18.4% predicted. All patients were receiving ≤1,000 μg/d of inhaled corticosteroid; nine were taking beclomethasone dipropionate; one took fluticasone propionate; and two took budesonide (median dose; 400 μg/d, range; 100 to 1,000 μg/d). No patient had taken oral corticosteroids within the previous 6 months. All subjects had normal full blood counts, biochemical profiles (including urea and electrolytes, liver function tests, and bone markers), and urinalysis results. Approval for the study was obtained from the Tayside medical ethics committee, and all subjects gave written informed consent. Unfortunately, we were unable to evaluate ACTH (Systane; Novartis; Frinley, UK) stimulation response in our study because it is contraindicated in the UK data sheet for use in asthmatic or atopic subjects because of reports of potentially fatal anaphylactic reactions.

Study Design

A double-blind, double-dummy, placebo-controlled, randomized crossover design was used (Table 1). During an initial screening visit, FEV1 and FEF25-75 were measured using a Vitalograph Compact Spirometer (Vitalograph Ltd; Buckingham, UK); subjects were eligible for inclusion if their FEV1 was greater than 70% predicted. Spirometry was also measured at each subsequent visit, although efficacy was not an end point because of the short duration of treatment. Patients were randomized to receive either oral prednisolone (enteric-coated tablets), 5 mg, or nebulized budesonide (as Pulmicort Respules), 0.25 and 0.5 mg/mL, via a Ventstream Nebulizer (Medic-aid Ltd; Pagham, UK) with a mouthpiece with a Portamed compressor (Medic-aid Ltd) delivering air at 6 L/min. Each dose was nebulized to residual volume (approximately 0.5 to 1.0 mL) associated with spluttering over a period of 10 min. Patients were instructed to breathe at tidal volume until delivery was complete.

Each drug sequence was given over a total of 12 days with six patients receiving budesonide first in sequence and the other six patients receiving prednisolone first in sequence. Budesonide was given twice daily, divided doses at 8 AM and 10 PM; prednisolone was given once daily at 8 AM. The doses were given sequentially as follows, with each dosage given for 4 days: prednisolone, one tablet qd, two tablets qd, and four tablets qd (ie, 5, 10, and 20 mg/d, respectively); and budesonide, 2 mL of 0.25 mg/mL bid, 2 mL of 0.5 mg/mL bid, and 4 mL of 0.5 mg/mL bid (ie, 1, 2, and 4 mg/d, respectively). All of the doses of nebulized budesonide were within the licensed recommended dose range. Patients received placebo tablets while taking nebulized budesonide and nebulized placebo (0.9% sterile saline) when taking oral prednisolone, using the corresponding number of tablets or volume of solution in order to make the trial double-dummy. Prior to each 12-day drug sequence with either budesonide or prednisolone, patients received one placebo tablet per day and a 2-mL vial of 0.9% saline via nebulizer for four days. The patients’ usual inhaled corticosteroid therapy was discontinued during the placebo and treatment periods. There was also a 7-day washout period between each of the 12-day treatment sequences, during which patients received their usual maintenance inhaled corticosteroid therapy.

At the beginning of the trial, the nebulizer vials and tablets

<table>
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<tr>
<th>Treatment</th>
<th>PL-I</th>
<th>BUD 1 mg/d</th>
<th>BUD 2 mg/d</th>
<th>BUD 4 mg/d</th>
<th>Washout</th>
<th>PL-II</th>
<th>Pred 5 mg/d</th>
<th>Pred 10 mg/d</th>
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<tr>
<td>Days</td>
<td>4</td>
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*PL-I/II=first/second placebos; BUD=nebulized budesonide; Pred=oral prednisolone.
were masked and sealed by a pharmacist in envelopes with instruction sheets in order to make the trial investigator-blind. Before the study and at each visit, subjects were given detailed training by a third party in how to use their nebulizer and compressor. Each subject received a written instruction sheet to follow while using the inhaler at home and a simple check list was used as an aid to compliance. Compliance was checked by counting the number of returned tablets and empty nebulizers.

**Measurements**

The subjects attended the laboratory at 7:30 AM, 9½ h after taking the eighth dose of inhaled medication or placebo (at 10 PM) and 21½ h after taking the fourth dose of oral medication at each dose level. A cannula was inserted into an antecubital fossa vein to permit blood sampling, and subjects then rested supine for 30 min. After the rest period, blood samples were taken at 8 AM for measurement of plasma cortisol, serum osteocalcin, and blood eosinophils.

**Assays**

All assays were performed in duplicate in a blinded fashion by a separate technician. Plasma cortisol was measured using a commercial radioimmunoassay kit with 11% cross-reactivity for prednisolone (Instar Ltd, Wokingham, Berkshire). The coefficient of variability for analytical imprecision was 4.3% within the assay and 7.2% between assays. Plasma osteocalcin was measured using an Instar radioimmunoassay kit with a within-assay coefficient of variability of 5.9%. The eosinophil count was measured using a SE-9000 Haematology analyzer (Sysmex UK Ltd, Bucks, UK). The lower limit of the normal reference range for 8 AM plasma cortisol, in our laboratory, is 150 nmol/L.

**Statistical Analysis**

The study was designed with sample size of 12 with 90% power (beta error = 0.2) to detect a 20% difference in 8 AM cortisol levels (the primary end point) between treatments, with the alpha error set at 0.05 (two-tailed). All data were analyzed using the Statgraphics software package (STSC Software Group, Rockville, MD). Serum osteocalcin levels and blood eosinophil counts were analyzed geometrically in order to normalize their distributions. The presence of dose-related suppression was determined using least-squares regression analysis to evaluate the overall effects of all three dose levels for each drug.

All active treatments and both placebos were compared by an overall multifactorial analysis of variance using treatments, doses, subjects, and periods as factors, followed by Bonferroni’s multiple-range testing to obviate multiple pair-wise comparisons. The Bonferroni’s multiple-range test was set with 95% confidence intervals (CIs), and hence any significant differences are reported at the p<0.05 level. At the highest dose level (i.e., prednisolone 4 mg vs prednisolone 20 mg), the difference between the mean values and 95% CIs was calculated. The number of individual values of 8 AM plasma cortisol with an abnormal low level (<150 nmol/L) were analyzed with the χ² test.

**Results**

There were no significant carryover effects between the first and second placebos given in sequence using any of the parameters measured: 8 AM plasma cortisol (420.0 vs 373.4 nmol/L), eosinophils (0.35 vs 0.31×10⁹/L), or serum osteocalcin (0.62 vs 0.55 nmol/L). There were also no significant differences between the placebos given prior to each active treatment in 8 AM plasma cortisol (406.9 vs 386.6 nmol/L), eosinophils (0.36 vs 0.31×10⁹/L), or serum osteocalcin (0.61 vs 0.56 nmol/L).

There were no significant differences between the FEV₁ or FEF₂₅₋₇₅ values (as percent predicted) when placebo was compared with low, medium, and high doses of each drug. The FEV₁ was 86.8% for placebo; 84.3%, 78.1%, and 85.4% for low, medium, and high doses of prednisolone, respectively; and 89.6%, 90.4%, and 92.3% for low, medium, and high doses of budesonide, respectively. The FEF₂₅₋₇₅ values were 48.5% for placebo; 47.1%, 42.6%, and 47.7% for low-, medium-, and high-dose prednisolone, respectively; and 52.3%, 51.2%, and 56.3% for low-, medium-, and high-dose budesonide, respectively.

**Plasma Cortisol:** Regression analysis showed that, for 8 AM plasma cortisol, there was significant dose-related suppression with prednisolone (p<0.0001) but not with budesonide (p=0.53) (Fig 1). Compared with placebo, there were significant differences with medium and high doses of prednisolone (p<0.05), but not with any dose of budesonide. There were significant differences between the two drugs at the medium- and high-dose levels. At the highest dose, this amounted to a 3.11-fold difference (95% CI, 2.02 to 4.78). For all dose levels, the number of individual patients with an abnormal cortisol value of <150 nmol/L (<5.4 μg/dL) was significantly higher with prednisolone (13 of 36) than with budesonide (1 of 36; p<0.0005) (Fig 2).

**Eosinophils:** Regression analysis showed there was a significant dose-related suppression of eosinophils with prednisolone (p<0.001) but not with budesonide (Fig 1). There were significant differences from placebo with medium and high doses of prednisolone (p<0.05) but not with any dose of budesonide. There were significant differences between the two drugs only at the highest dose level, amounting to a 1.87-fold difference (95% CI, 1.16 to 3.00).

**Osteocalcin:** Regression analysis showed there was a significant dose-related suppression of osteocalcin with prednisolone (p<0.05) but not with budesonide (Fig 1). There were significant differences from placebo for medium and high doses of prednisolone (p<0.05) but not for any dose of budesonide. There were significant differences between the two drugs at the medium- and high-dose levels. At the highest dose, there was a 1.62-fold difference (95% CI, 1.21 to 2.16).
blood eosinophils, and serum osteocalcin). However, such was not the case for nebulized budesonide, which showed no significant dose-related suppression. It can be seen from the graphs of dose-response curves that for all of the end points, nebulized budesonide caused very little suppression, even at the highest dose of 4 mg per day. If we had used higher doses of budesonide, it might have been possible to detect systemic activity, but the doses chosen represented those most commonly used in clinical practice. Although it is sometimes necessary to prescribe doses greater than 4 mg/d, and indeed nebulized Pulmicort is licensed as such, this is rarely done in normal practice. Budesonide is only licensed up to 1.6 mg/d when given via a pMDI; had we given the highest dose via a pMDI, this would have required 20 puffs per day.

We would advise a degree of caution in extrapolating our data to what happens in more severe asthma, where narrower peripheral airway caliber might conceivably reduce the bioavailable dose absorbed from the lung. In other words, any possible systemic activity of nebulized budesonide would be even less in patients with more severe airflow obstruction as compared with the results of the present study. Also, we did not measure clinical efficacy as we looked at patients with milder asthma and administered the treatments for only a relatively short period of time. Although the prednisolone-sparing effects of nebulized budesonide have been reported in chronic severe asthmatics, there are no dosering studies looking at antiasthma efficacy.

The results of our study for prednisolone are in keeping with those of Toogood et al and Jennings et

**FIGURE 1.** Geometric means with standard errors for pooled placebo (PL), budesonide (BUD) at 1, 2, and 4 mg/d; and prednisolone (Pred) at 5, 10, and 20 mg/d for 8 AM plasma cortisol (top), blood eosinophils (middle), and serum osteocalcin (bottom). Regression analysis showed significant dose-related suppression with prednisolone for plasma cortisol (three asterisks: p<0.0001) for blood eosinophils (two asterisks: p<0.001), and for osteocalcin (asterisk: p<0.05), but no significant dose-response effect with budesonide.

**FIGURE 2.** Individual values for 8 AM plasma cortisol with each treatment. The interrupted line represents the lower limit of the normal reference range at ~150 nmol/L (5.4 μg/dL). Abbreviations as in Figure 1.

**DISCUSSION**

We have shown in this study that, as expected, oral prednisolone produced dose-related suppression for all the measured parameters (8 AM plasma cortisol,
al., who also showed dose-related suppression for the same end points we measured. In our study, however, we found no significant suppression with budesonide, even at a dose of 4 mg/d. The explanation for this discrepancy is unlikely to be related to asthma severity in our subjects, as the previous studies involved both patients with severe, steroid-dependent asthma and healthy volunteers. The duration of treatment was shorter in our study, but because the effects of corticosteroids on adrenal suppression may become detectable within 12 h of a single dose, it is unlikely to account for the observed differences. Furthermore, steady-state blood levels would be achieved within the 4-day dosing period. Our patients received budesonide via a nebulizer because this is a common way of delivering high doses of inhaled medication; in the previous studies, a pMDI plus large-volume spacer was used. The lack of detectable systemic activity with steroids delivered by a nebulizer has previously been reported; a single 4-mg dose of inhaled budesonide given via a Sidestream nebulizer (Medic-aid Ltd) had no effect on 9 AM serum cortisol.

We specifically chose to use the Ventstream nebulizer because of its superior in vitro and in vivo performance characteristics compared with other conventional jet nebulizers. Indeed, we have shown that the Ventstream produces 80% of respirable particles with a diameter of less than 5 μm, as well as increasing the lung dose to the patient by boosting respiratory delivery and minimizing expiratory wastage. For example, in comparison to a Hudson Updraft II nebulizer (Hudson RCI; Temecula, CA), the Ventstream nebulizer produces 25% more respirable particles in vitro and a two-fold improvement in lung delivery in vivo. Thus, we cannot justifiably explain the lack of systemic bioactivity with budesonide solely on the basis of poor nebulizer performance, although it is likely that the lung dose, and hence systemic bioavailability, would probably be greater from a large-volume spacer. We have also previously shown that chronic dosing with 2 mg/d of budesonide given by metered-dose inhaler to asthmatics produces no significant detectable activity on 8 AM plasma cortisol or the more sensitive overnight urinary cortisol/creatinine excretion. The favorable profile with inhaled budesonide probably reflects its high degree of hepatic first-pass metabolism (90%) for the swallowed fraction, short elimination half-life (2.3 h), short glucocorticoid receptor residency half-time (3.7 h), and relatively low degree of lipophilicity. All of these factors result in a relatively low degree of systemic drug exposure when given at steady state with repeated twice-daily dosing.

Linear regression analysis and interpretation of the mean data provide information about the relative effects of the two drugs studied. It is, however, also relevant to consider the patients as individuals, as we do in everyday clinical practice. By looking at the scatter plot of individual results for 8 AM plasma cortisol, it is evident that there is a large individual variability in response to corticosteroids. For example, even at a high dose of 20 mg/d of prednisolone, some patients are relatively insensitive to adrenal suppression. The reason for this effect is not clearly understood but it may be related to effects of glucocorticoid receptor polymorphism or individual differences in glucocorticoid metabolism.

From the scatter plot of individual values (Fig 2) it can also be seen that a number of individuals receiving prednisolone had an abnormally low 8 AM cortisol level of <150 nmol/L (≤5.4 μg/dL). It is clinically important to consider such individuals when prescribing corticosteroids as it is known that patients with abnormally low basal cortisol levels will usually fail to respond satisfactorily to dynamic stimulation tests. These patients will, therefore, have impaired adrenal reserve and may be unable to mount an adequate stress response. An abnormally low cortisol level occurred in one patient taking 4 mg/d of budesonide. Unfortunately, we were unable to evaluate ACTH (tetracosactrin) stimulation response in our study because it is now contraindicated in the UK data sheet for use in asthmatic or atopic subjects because of reports of potentially fatal anaphylactic reactions.

The patients recruited into the study were all taking up to 1,000 μg/d of inhaled corticosteroid, representing their lowest effective maintenance dose. These patients can therefore be considered as having mild to moderate asthma (with an average FEV₁ of 88% predicted and FEF₂₅₋₇₅ of 55% predicted) and would not regularly require the high doses that were studied. However, it is conceivable that such patients may experience exacerbations of their asthma and require a course of oral prednisolone and subsequently require higher doses of maintenance inhaled steroid. However, it is reassuring to know that even in asthmatics without severely impaired airway caliber, we found only minimal systemic response to high-dose nebulized budesonide.

Glucocorticoids have effects on all glucocorticoid receptors in all bodily tissues. We have measured these effects by changes in markers of three different tissues (adrenal, bone, and blood). It is known that systemic tissues exhibit a differential degree of sensitivity to the relative effects of corticosteroids; therefore, it may not be possible to infer the changes in one tissue based on the effects in another. In this respect, we observed greater differences (in re-
response ratios) between nebulized budesonide and oral prednisolone for effects on the hypothalamic-pituitary-adrenal axis compared to bone or eosinophils.

In conclusion, we found dose-related suppression with oral prednisolone for markers of adrenal, bone, and blood tissues, but not with nebulized budesonide. Further comparative dose-ranging studies looking at both efficacy and adverse effects are required to evaluate whether this translates into a beneficial therapeutic index.

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