

Effects of dose and dosing schedule of inhaled budesonide on bone turnover

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To assess whether the use of larger than usual doses of inhaled steroid to treat severe asthma may adversely affect bone turnover and whether such an effect may be mitigated by altering the dose schedule, we investigated the effects of budesonide (BUD) on serum osteocalcin and the urinary output of hydroxyproline and calcium. Healthy adults were administered 1.2 or 2.4 mg of BUD per day (N = 40) or placebo (N = 8) in a crossover, double-blind comparison of morning versus diurnal dosing schedules for 1 month each. Both BUD doses reduced the 24-hour urinary free-cortisol output ($p < 0.001$) and serum osteocalcin ($p < 0.001$). The larger dose reduced the morning serum cortisol levels ($p = 0.002$). Neither dose increased the 8 AM urinary calcium or hydroxyproline output. Osteocalcin and plasma cortisol levels were higher on morning than on diurnal dosing ($p = 0.01$). The 24-hour urinary free-cortisol output was the same with either schedule ($p = 0.96$). Additional study is required to assess the clinical importance of the inhibitory effect of BUD on bone formation, as evidenced by the reduction in osteocalcin levels. Of concern is the possibility of serious bone complications resulting from the long-term use of inhaled steroid, particularly in growing children or patients in whom other risk factors for osteoporosis are present. The clinical advantage, if any, of morning dosing remains questionable. (J ALLERGY CLIN IMMUNOL 1991;88:572-80.)

Key words: Adrenocortical function, asthma, bone Gla protein (β -glycerolphosphatase), bone metabolism, budesonide, corticosteroids, hydroxyproline, inhaled steroids, osteocalcin, osteoporosis

Low-dose inhaled steroid therapy for asthma appears to be devoid of clinically important systemic adverse effects.¹ However, the safety of intermediate and large dosages of inhaled steroid is as yet incompletely defined.¹ In particular, the possible adverse effects of these dosages on skeletal metabolism remain largely unknown.¹

Abbreviations used

BUD: Budesonide

BDP: Beclomethasone dipropionate

ANOVA: Analysis of variance

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In a relative potency study that compared the systemic activity of inhaled BUD with prednisone in terms of their effects on the 8 AM serum cortisol level and blood eosinophil count, we found that 26 $\mu\text{g}/\text{kg}/\text{day}$ (1.84 mg of BUD per day for a 70 kg adult) had a level of systemic activity equivalent to about 15 mg of prednisone per day administered as a single morning dose.² Because prednisone doses >15 mg/day are known to be associated with a relatively high incidence of clinically important systemic adverse effects, including osteoporosis, whereas lower doses are not,³⁻¹² we inferred that this dose of 26 $\mu\text{g}/\text{kg}/\text{day}$ of BUD may demarcate a clinically meaningful threshold for different levels of risk of adverse effects on bone induced by BUD.²

However, a study designed to examine this hy-

pothesis found that BUD doses bracketing this cutoff (0.6 and 2.4 mg/day) did not, in fact, demonstrate any discernible adverse effect with either dose on calcium, phosphate metabolism, serum parathormone, serum vitamin D levels, or urinary cyclic adenosine monophosphate, even though the larger dose partially inhibited endogenous cortisol production.¹³ Two limitations of the study were the period of treatment that was only 2 weeks and the fact that bone turnover was not measured.

Bone turnover comprises the linked processes of bone formation and resorption. Circulating levels of a protein secreted by osteoblasts, which is variously called bone Gla protein, BGP, or osteocalcin, provide an index of bone formation.¹⁴ Serum levels of osteocalcin vary diurnally, peaking late at night or in the early morning.¹⁵ Bone resorption is reflected by changes in the urinary output of calcium and hydroxyproline. The latter is a breakdown derivative of the osteoid matrix.^{16, 17}

We therefore undertook to study the effects on these indices of bone turnover of 1 month of BUD treatment and to determine whether any inhibitor effect observed may be reduced by administering all the BUD dose in the morning rather than diurnally, as is customarily done.

The rationale for such a trial lay in studies that have demonstrated a similarly cyclic diurnal system, the hypothalamic-pituitary-adrenal axis, to be generally less sensitive to inhibition by low or intermediate doses of various glucocorticoids administered systemically or orally during the hours 8 AM to 4 PM, and more sensitive to the same doses administered later in the day.¹⁸⁻²¹ Also, a previous comparison of morning versus diurnal dosing of BUD had demonstrated the morning schedule significantly reduced the unwanted systemic activity of 1.6 mg of BUD per day as measured by changes in the 8 AM serum cortisol levels, while most of the antiasthmatic efficacy of the drug was retained.²²

METHODS

The study protocol was approved by the institutional Review Board on Human Research at the University of Western Ontario and accorded with the Helsinki Declaration of 1975. Forty-eight nonsmoking, healthy subjects (24 male and 24 female adults) who had normal pulmonary function were treated with placebo or inhaled BUD. They had no metabolic disorders, were not using any drug known to affect renal or skeletal metabolism, and had not used inhaled or oral steroids previously. Their demographic characteristics at entry into the study are presented in Table I.

The test drug, BUD, is a nonhalogenated corticosteroid²³ with high affinity for the glucocorticoid receptor,²⁴ high topical anti-inflammatory activity,^{23, 25} a large volume of

distribution,²⁶ and low bioavailability.²⁷ It is not metabolized in the lung or serum²⁸ and is biotransformed more rapidly than BDP after absorption.^{25, 27} BUD has demonstrated less systemic glucocorticoid activity than BDP when the drugs were compared in patients with asthma at doses >0.8 mg/day,²⁹ and it is at least as effective as BDP.³⁰⁻³⁶ BUD is available in a formulation that delivers 200 μ g of active drug with each activation of the pressurized metered-dose inhaler. This formulation makes it practical to administer intermediate doses (1 to 2 mg/day) or large doses (>2 mg/day). BUD was compared in this study with a placebo metered-dose inhaler that contained the same propellants without the active drug.

With a balanced crossover design, stratified by sex to allow for male-female differences in osteocalcin production, the test subjects were randomly assigned to receive either an intermediate dose of BUD, 1.2 mg/day ($N = 20$), or a large dose of BUD, 2.4 mg/day ($N = 20$), or placebo ($N = 8$). The active drug was inhaled twice daily, that is, at 8 AM and noon (AM schedule) or 8 AM and 8 PM (AM-PM schedule). After 4 weeks of treatment, followed by a 2-week washout, each subject crossed over to the alternative dosing schedule for an additional month. Placebo inhalations were administered at 8 AM and noon or 8 PM to ensure that subjects and investigators were blind as to scheduling, dose, and whether the active drug or placebo was in use.

The placebo and BUD were inhaled from a 750 ml Nebuhaler (AB Draco, Lund, Sweden) with the same technique across all phases of the study, that is, inhalation from residual volume at 25 L/min, followed by a 10-second breath hold. This standard procedure was used to minimize inter- and intrasubject variability in delivery of the drug to the lung and its subsequent systemic absorption.

The test subjects visited the clinic every 14 days between 6:30 and 8:30 AM after a 12-hour fast. Collection of the specimens for hydroxyproline assay after an overnight fast ensures the hydroxyproline is specifically of skeletal, rather than dietary origin.¹⁶ At each visit and at the same time of day, we collected a 24-hour urine specimen for measurement of creatinine, calcium, phosphate, and urinary free cortisol; a freshly voided specimen for measurement of fasting creatinine, calcium, and hydroxyproline; and blood for measurement of plasma cortisol and serum osteocalcin. Specimens were stored at -20°C and batch assayed at completion of the study.

Osteocalcin was assayed by RIA (IncStar Corp., Stillwater, Minn.): intra-assay coefficient of variation, 5.3%; interassay coefficient of variation, 4.5%; normal range in young adults, 0.3 to 1.2 nmol/L. Hydroxyproline was measured by a colorimetric method¹⁷: interassay coefficient of variation, 7.9%; intra-assay coefficient of variation, 1.8%; normal range in young adults, 2.6 to 40.9 μ mol/mmol of creatinine. Plasma cortisol was measured by high-performance liquid chromatography³⁷: intra-assay coefficient of variation, 1.3%; normal range, 150 to 640 nmol/L. Urinary free cortisol was assayed by gas chromatograph mass spectrometry: intra-assay coefficient of variation, 5.2%; normal range, 40 to 200 nmol/day.

At every clinic visit the oropharynx was examined for

TABLE I. Characteristics of test subjects at entry to study

Schedule sequence BUD dose (mg/day)	AM → AM		PM	AM	PM → AM	
	0	1.2	2.4	0	1.2	2.4
M	2	5	5	2	5	5
F	2	5	5	2	5	5
	Mean	Mean	Mean	Mean	Mean	Mean
	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)
Age (yr)	34.25 (16.82)	33.10 (11.56)	32.70 (10.45)	28.00 (3.92)	35.10 (9.40)	28.10 (2.60)
Weight (kg)	67.33 (12.00)	72.71 (14.67)	69.75 (13.43)	67.80 (9.91)	75.19 (15.28)	68.21 (11.24)
Urinary free cortisol (nmol/day)	65.50 (40.15)	93.14 (32.36)	94.39 (29.29)	95.45 (35.42)	64.53 (34.63)	82.71 (29.79)
Plasma cortisol (nmol/L)	641.3 (251.0)	584.7 (313.8)	573.6 (297.8)	793.8 (280.6)	460.6 (324.0)	654.7 (309.7)
Serum osteocalcin (nmol/L)	0.643 (0.160)	0.740 (0.281)	0.624 (0.375)	0.710 (0.273)	0.499 (0.142)	0.594 (0.269)
24-hr Urinary Cr (mol/L)	0.017 (0.019)	0.012 (0.010)	0.008 (0.005)	0.018 (0.011)	0.021 (0.024)	0.013 (0.010)
24-hr Urinary calcium (mmol/mmol Cr)	0.307 (0.130)	0.276 (0.081)	0.229 (0.123)	0.238 (0.122)	0.202 (0.135)	0.236 (0.187)
8 AM Urinary calcium (mmol/mmol)	0.181 (0.041)	0.165 (0.130)	0.117 (0.108)	0.110 (0.067)	0.148 (0.127)	0.101 (0.076)
Urinary hydroxyproline (μmol/mmol Cr)	17.33 (5.99)	19.22 (4.82)	20.75 (5.79)	16.36 (2.34)	19.38 (8.53)	22.67 (7.57)
24-hr Urinary phosphate (mmol/mmol Cr)	2.228 (0.862)	2.245 (0.691)	2.292 (0.371)	2.042 (0.295)	2.135 (0.615)	2.145 (0.520)

CR, Creatinine.

thrush and cultured for *Candida*. Colony counts after 48 hours of incubation at 30° C were log transformed for analysis. All adverse symptoms experienced during the study were recorded in a current symptom diary and tabulated for analysis. The drug canisters were weighed before and after each treatment period to provide an objective measure of compliance.

The group size of 10 subjects was determined before the study to yield a power of 90% for detecting a difference of 50% in the change in osteocalcin level with AM dosing as compared to AM-PM dosing. The small placebo-treated group was included to facilitate blinding of the study and to serve as a reference for analysis of between-patient effects of drug and dose. Changes from baseline after 2 and 4 weeks of treatment were analyzed by Student's paired *t* tests. Within-subject comparisons of the two dosing schedules and preliminary tests for differential carryover effects associated with the two sequences of drug presentation were performed with Student's *t* tests based on within-subject contrasts.³⁸ Schedule by dose interactions were tested by two-way ANOVA for repeated measures.

RESULTS

Use of the test drugs, calculated from the changes in canister weight, averaged $96.92\% \pm 1.28$ (SD) during the entire study. There were no appreciable differences in mean BUD use between the AM and AM-PM schedules (96.97% versus 97.2% , respectively) or between the 1.2 and 2.4 mg doses (97.67% versus 96.4% , respectively). These data were complete except for urinary free-cortisol values from one subject in whom an unidentifiable interfering substance in the urine precluded accurate assay. Since this subject's response profiles for the remaining data did not differ substantially from profiles of the other subjects, they were included in the analysis.

The effects of the intermediate and high-dose BUD treatments are presented for each response index in Table II. Both the 1.2 and 2.4 mg of BUD doses reduced the 24-hour urinary free-cortisol output relative to baseline ($p < 0.001$) but only the large dose

TABLE II. Mean change ($\pm$ SEM) from baseline after 4 weeks averaged during the two treatment periods (N = 20 in each dose group)

Row No.	BUD dose/day	
	1.2 mg	2.4 mg
1 Urinary free cortisol (nmol/day)	$-32.4 \pm (4.6)$ <0.001*	$-49.6 \pm (8.1)$ <0.001
2 Plasma cortisol (nmol/L)	$-81.6 \pm (39.8)$ 0.054	$-177.0 \pm (48.7)$ 0.002
3 Serum osteocalcin (nmol/L)	$-0.134 \pm (0.026)$ <0.001	$-0.161 \pm (0.034)$ <0.001
4 24-hr Urinary calcium (mmol/mmol Cr)	$-0.011 \pm (0.023)$ 0.638	$0.033 \pm (0.014)$ 0.029
5 8 AM Urinary calcium (mmol/mmol Cr)	$-0.003 \pm (0.013)$ 0.820	$-0.013 \pm (0.009)$ 0.165
6 Urinary hydroxyproline (μ mol/mmol Cr)	$-1.74 \pm (1.16)$ 0.150	$-1.94 \pm (0.88)$ 0.040
7 24-hr Urinary phosphate (mmol/mmol Cr)	$0.041 \pm (0.103)$ 0.695	$0.099 \pm (0.106)$ 0.362
8 Log <i>Candida</i> (colony counts)	$0.170 \pm (0.089)$ 0.071	$0.806 \pm (247)$ 0.004

Cr, Creatinine.

*The figures listed below the mean for each index are *p* values from Student's paired *t* tests.

demonstrated strong evidence of a fall in the AM plasma cortisol level ($p = 0.002$). Both doses reduced the AM serum osteocalcin level relative to baseline ($p < 0.001$); -19.6% and -24.3% for the intermediate and large doses, respectively. The urinary creatinine output per 24 hours did not change from baseline with either BUD dose (data not presented). The 24-hour urinary output of calcium, adjusted for creatinine, increased during high-dose BUD treatment ($p = 0.029$). There was no accompanying hypercalciuria in the 8 AM fasting specimen ($p = 0.165$). The urinary output of hydroxyproline fell with both doses ($p = 0.04$ with the larger dose). Neither dose affected the urinary phosphate output per 24 hours.

Most of the effect on osteocalcin occurred within the first 2 weeks of treatment (Fig. 1, *top*). Similarly, the drop in hydroxyproline output occurred in the first 2 weeks. There was no trend thereafter toward a rise in hydroxyproline output with accumulative weeks of treatment (Fig. 1, *bottom*).

Preliminary analyses found no significant carryover from the initial treatment period into the washout or second treatment period. Thus, these data from both treatment periods could be combined for testing for differences related to the two dosing schedules.

The influence of the dosing schedule on the effects of BUD treatment is summarized in Table III. The

mean levels of serum osteocalcin and plasma cortisol were each significantly higher on AM treatment than on the AM-PM schedule ($p = 0.01$). The individual plasma cortisol values of every subject remained within the normal range of the assay (mean $\pm$ 2 SD) on AM-PM dosing with 2.4 mg/day. All but one value were normal on AM dosing (data not presented). The mean urinary output of hydroxyproline, calcium, and phosphate, and the 24-hour urinary free cortisol did not differ significantly with respect to the dosing schedule (Table III).

The relative advantage of the morning-dose schedule was independent of BUD dosage, as evidenced by the absence of significant dose times schedule interactions in ANOVA for osteocalcin ($p = 0.87$) and plasma cortisol ($p = 0.61$). This independence of BUD dosage is illustrated in Figs. 2 and 3. On average, the osteocalcin level was 12.5% higher on the morning-dose schedule than on diurnal dosing.

Adverse oropharyngeal symptoms and/or headache were reported by 39 of the 48 test subjects at one or more of the six scheduled visits (data not presented). There was no significant difference between the BUD- and the placebo-treated groups with respect to the incidence of these complaints ($p = 0.42$, 0.25, and 0.52 for sore throat, huskiness, and headache, respectively, by χ^2). Oropharyngeal candidiasis in-

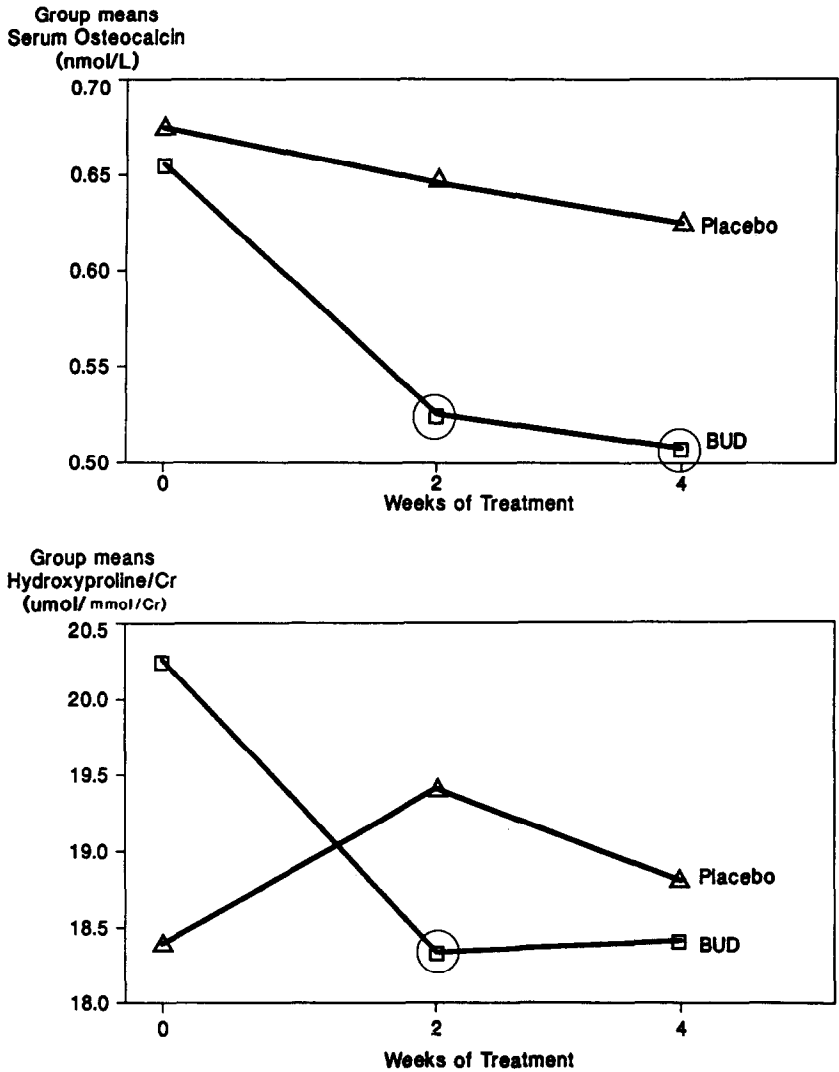


FIG. 1. Effect of duration of treatment on serum osteocalcin (**top**) and urinary hydroxyproline output (**bottom**). Group means are illustrated for BUD (□) and placebo (Δ) treatments. *Encircled symbols* differ significantly from the pretreatment mean ($p = <0.05$ by Student's paired t test).

TABLE III. Comparison of effects of BUD dosing schedules means ($\pm$ SD)

	AM plus PM	AM	p Value for difference
Urinary free cortisol (nmol/day)	42.7 $\pm$ 51.7	42.4 $\pm$ 29.0	0.96
Plasma cortisol (nmol/L)	392.4 $\pm$ 210.8	483.4 $\pm$ 204.5	0.01
Serum osteocalcin (nmol/L)	0.48 $\pm$ 0.20	0.54 $\pm$ 0.25	0.01
24-hr Urinary calcium (mmol/mmol Cr)	0.252 $\pm$ 0.143	0.242 $\pm$ 0.147	0.48
8 AM Urinary calcium (mmol/mmol Cr)	0.133 $\pm$ 0.098	0.137 $\pm$ 0.100	0.82
Urinary hydroxyproline (μ mol/mmol Cr)	18.8 $\pm$ 5.8	18.0 $\pm$ 6.3	0.42
24-hr Urinary phosphate (mmol/mmol Cr)	2.30 $\pm$ 0.50	2.25 $\pm$ 0.47	0.48
Log <i>Candida</i> (colony counts)	0.82 $\pm$ 1.76	0.59 $\pm$ 1.21	0.48

Cr, Creatinine.

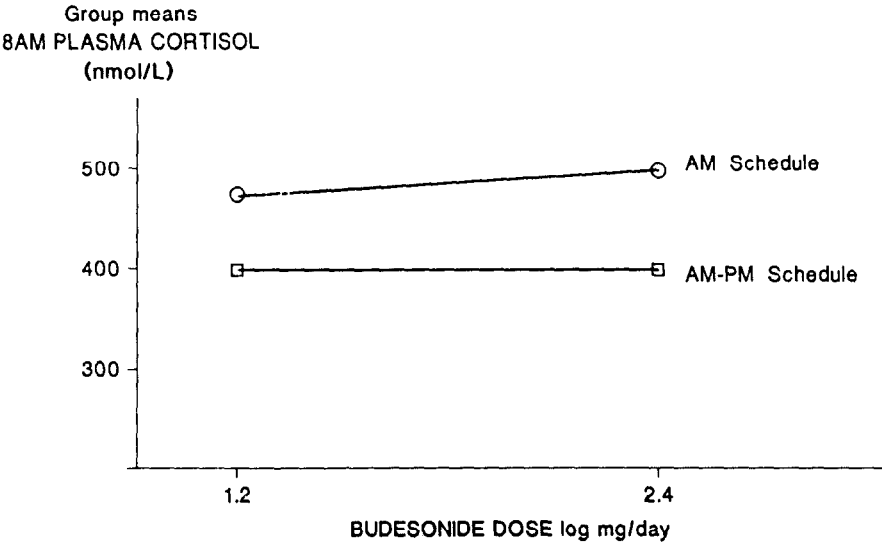


FIG. 2. Group mean plasma cortisol levels compared on different schedules of BUD treatment. AM cortisol levels were higher on the morning dosing schedule ($p = 0.01$, ANOVA).

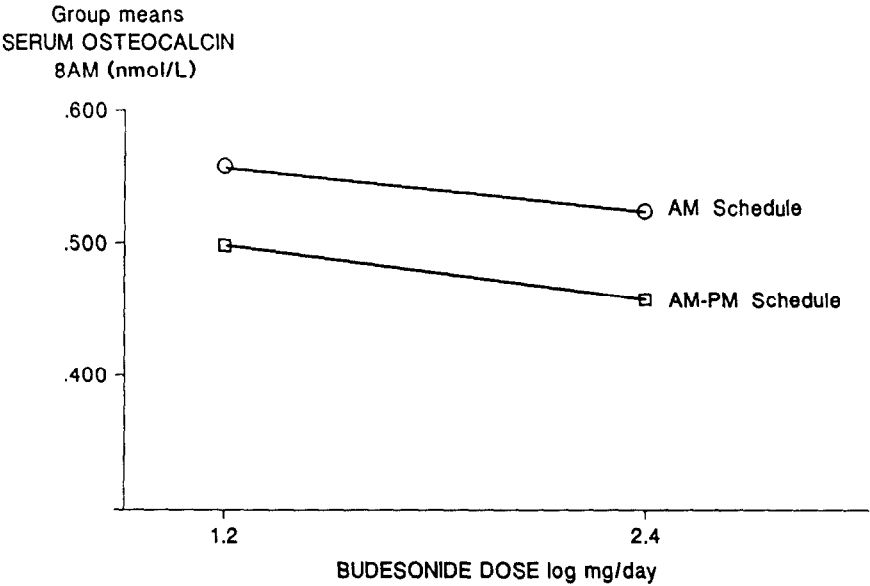


FIG. 3. Group mean serum osteocalcin levels are compared on different schedules of BUD treatment. AM dosing reduced the inhibitory effect on osteocalcin of AM-PM dosing with BUD ($p = 0.01$, ANOVA).

creased with both doses of BUD ($p = 0.004$ with the larger dose, Table III). Clinical thrush did not occur.

DISCUSSION

These data reveal that BUD, which is systemically absorbed after inhalation, can adversely affect skeletal metabolism. The inhibitory effect on bone formation, reflected by the changes in osteocalcin production,

was not restricted to large dosage (≥ 2 mg of BUD per day) but occurred also at intermediate dosage, that is, 1.2 mg of BUD per day. The latter dose was free of any discernible effect on the AM plasma cortisol levels, although it significantly inhibited the 24-hour urinary cortisol output (Table II).

BUD doses lower than the doses tested in this study have been demonstrated to be free of any inhibitory

effect on osteocalcin production.³⁹ There are no similar published data for any of the other inhaled steroids used to treat asthma. The possibility that currently used doses of a particular inhaled steroid might adversely affect bone turnover cannot be excluded on the basis of its failure to suppress the 8 AM plasma cortisol level. This can be observed from the disparity between the sensitivities of osteocalcin and plasma cortisol to the systemic action of 1.2 mg of BUD per day, as illustrated in Table II. In contrast, if a dose of inhaled steroid is sufficiently active, systemically, to reduce the 8 AM plasma cortisol level, it may reasonably be assumed to inhibit bone turnover as well (compare rows 2 versus 3, Table II).

The magnitude of the inhibitory effect of BUD on serum osteocalcin production was significantly less when the drug was administered with an AM dosing schedule rather than diurnally (Table III; Fig. 3). It is not possible to determine from these data alone whether this difference signifies a clinically important advantage or not. It would have been desirable to supplement these data with a measure of the impact of each dosing regimen on the production of osteocalcin during a full 24 hours. Because this was not feasible technically, we studied the effects of the dosing schedule of BUD on another diurnally cyclic system, namely, endogenous cortisol production.

As in the case of osteocalcin, AM dosing was associated with a slight, but statistically significant, mitigation of the inhibitory effect of BUD on the AM plasma cortisol level (rows 2 and 3, Table III). This confirms the results of a previous comparison of morning versus diurnal treatment with BUD.²² However, the apparent advantage of morning dosing was not substantiated when the adrenocortical response integrated during 24 hours was examined in the current study (row 4, Table III). This observation is consistent with earlier studies that found that the clinically manifest signs of long-term steroid excess consequent to long-term prednisone therapy occur as frequently when the drug is administered as a single morning dose as when doses are divided throughout the day, when the same daily dosages are compared.^{40, 41} This has been observed with low⁴¹ as well as large⁴⁰ dosages of prednisone and does not substantiate the implied benefits of AM scheduling as determined from acute dosing studies.¹⁸⁻²¹ The weight of evidence suggests that it is unlikely that a clinically useful reduction in the unwanted systemic glucocorticoid activities of high-dose BUD, including inhibition of bone turnover, can be achieved by resorting to an AM dose schedule.

Although an increase in the 24-hour urinary output of calcium was noted in this study during high-dose

BUD treatment (Table II), the weight of evidence suggests that this was not the result of an increase in bone resorption in response to the BUD. First, the absence of an increase in hydroxyproline output, the most specific index of bone resorption among the three indices measured, demonstrated that increased bone resorption did not occur. In fact, the observed changes suggest the reverse might have been the case. Second, hypercalciuria was not demonstrated in the 8 AM fasting urine specimen as would have been expected with increased bone resorption. Third, hypercalciuria typically occurs during systemic glucocorticoid treatment, probably as a direct result of the action of the drug on the renal tubular reabsorption of calcium.^{42, 43} Finally, other studies have found no evidence of increased bone resorption in test subjects treated with BUD with doses as large or larger than doses used here and treatment durations ranging from 1 to 4 weeks.^{39, 44-46} However, these negative findings do not exclude the possibility of an increase in bone resorption after longer periods of BUD treatment.

Clinical implications

The demonstration in this study of an inhibitory effect of inhaled BUD on skeletal metabolism is clinically important because of current trends toward the use of more concentrated formulations and larger daily doses of inhaled steroid in the treatment of asthma.⁴⁷⁻⁴⁹ Concentrated formulations of flunisolide and triamcinolone acetonide have been available for some years in the United States, and their use is increasing. In Canada, BUD, 0.2 mg per puff, and BDP, 0.25 mg per puff, have recently been approved for clinical use. This makes large dosing with these drugs easily feasible. These concentrated formulations have been widely used in Europe for more than 5 years and are reported to have largely supplanted the more dilute formulations that were originally introduced for clinical use in Europe and the United States.

With the methods used in this study, it is not possible to state with certainty the extent to which the inhibition of osteocalcin production that we observed after short-term BUD treatment may imply a clinically important risk with the long-term use of intermediate or large doses of this drug. However, the fact that these dosages are being used at this time in clinical practice⁵⁰ indicates an immediate need for some estimate of the likelihood of bone complications accruing after prolonged usage.

Direct comparisons of graded doses of prednisone versus BUD under controlled conditions that used changes in the serum osteocalcin level⁵¹ or nonosseous response indices² to quantify the systemic activity of both drugs found the systemic activity of BUD, 1.0

mg/day, to be equivalent to ~9 mg of prednisone per day. By applying this ratio to these data in this study, it may be estimated that the effect of 2.4 mg of BUD per day on skeletal metabolism is likely to be clinically important, since it is systemically equivalent to ~22 mg/day of prednisone, a dose that is known to be associated with osteoporosis and fractures after long-term use. In contrast, the 1.2 mg of BUD dose would be systemically equivalent to ~11 mg/day of prednisone, which is a dose known to be associated with a relatively low incidence of bone complications. The reliability of these estimates of risk needs to be tested directly by controlled prospective studies of changes in bone density in patients with asthma treated with inhaled steroid drugs at various dose levels.

Notwithstanding the inhibitory effect of BUD treatment on bone turnover that was observed in this study, other studies suggest that the risk of clinically important bone complications is likely to be considerably lower with inhaled BUD at any particular dose level than with therapeutically equivalent doses of oral prednisone or prednisolone.^{2, 39}

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