

Safety Profile of Frequent Short Courses of Oral Glucocorticoids in Acute Pediatric Asthma: Impact on Bone Metabolism, Bone Density, and Adrenal Function

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ABSTRACT. *Objective.* Our study was designed to establish in children with asthma the safety profile of repeated short courses of oral glucocorticoids on bone mineralization and metabolism and adrenal function.

Methods. This cross-sectional study compared the bone density, bone metabolism, and adrenal function of children who were and were not exposed to bursts of oral glucocorticoids. Children were considered exposed when, in the preceding year, they received ≥ 2 courses of oral glucocorticoids and were prescribed the same therapy for the index exacerbation. Children were considered unexposed when they had no exposure to oral glucocorticoids and were not prescribed any for the index exacerbation. Indices of bone metabolism were measured during the subsequent month. Cortisol responses to adrenocorticotropic hormone stimulation and bone density were assessed 30 days after the index exacerbation.

Results. Eighty-three children (48 exposed, 35 unexposed) aged 2 to 17 years were enrolled. The median exposure level was 4 courses (range: 3–11) in the preceding year. Among exposed children, a transient decrease in serum osteocalcin was observed at the end of the 5-day course with a return to baseline by 30 days; no change was observed in urine pyridinoline cross-links. Mean bone density z score was similar in the exposed (-0.61 ± 1.0 [standard deviation]) and unexposed (-0.67 ± 0.9) groups. No cases of abnormal response to adrenocorticotropic hormone suggestive of adrenal insufficiency were documented in the exposed (95% confidence interval: 0%–7%) or unexposed (0%–10%) groups.

Conclusions. Repeated short courses of oral glucocorticoids in the treatment of asthma seem to be reasonably safe; this practice was not associated with any lasting perturbation in bone metabolism, bone mineralization, or adrenal function. *Pediatrics* 2003;111:376–383; *oral glucocorticoids, bone metabolism, bone mineral density, pyridinoline crosslinks, osteocalcin, adrenal function, child, acute asthma.*

ABBREVIATIONS. DHEAS, dehydroepiandrosterone sulfate; SD, standard deviation; CI, confidence interval; PTH, parathyroid hormone.

Airway inflammation is now recognized as a major element in the pathogenesis of asthma, and recent consensus statements advocate aggressive anti-inflammatory treatment.^{1–3} In acute pediatric asthma exacerbations, anti-inflammatory treatment usually entails a short course of high-dose oral glucocorticoids. Although the efficacy of this practice has been documented,⁴ few efforts have been made to assess its safety. Many parents and physicians are uncomfortable with or resistant to repeated use of oral glucocorticoids. Parents seldom discuss their worries about potential side effects of steroids with treating physicians, yet their fear is an important reason for noncompliance⁵ and may partially explain the underuse of anti-inflammatory drugs in pediatric asthma.⁶

Osteopenia and adrenal suppression are among the dreaded adverse effects of repeated high-dose steroid therapy. Indeed, chronic systemic glucocorticoids exert direct inhibitory effects on the osteoblast and possibly on the osteoclast function.⁷ A 5-day course of oral glucocorticoids has been associated with marked decrease in osteoblastic activity.⁸ It is unclear whether repeated short courses of oral glucocorticoids lead to a lasting suppression of osteoblastic activity and/or stimulation of osteoclastic activity, which causes osteopenia. A single course of systemic glucocorticoids can result in significant, albeit transient (<15 days), blunting of adrenal function.^{9,10} The 10% to 20% prevalence of adrenal dysfunction reported by Dolan et al¹¹ in children who received repeated (≥ 3) bursts of oral steroids in the preceding year has caused some alarm. However, the inconsistent timing of adrenal testing may have led to an overestimation of adrenal dysfunction in patients tested shortly after a burst.

The objectives of this study were to evaluate in children with asthma the effect of repeated bursts of oral glucocorticoids on bone mineralization, bone metabolism, and adrenal function. Specifically, we wanted to assess whether repeated bursts of oral glucocorticoids carried any cumulative effect on bone mineral density and how a 5-day burst of oral glucocorticoids affected bone metabolism and adrenal function 1 month after a burst.

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Received for publication Apr 25, 2002; accepted Sep 5, 2002.

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METHODS

Design

We conducted a cross-sectional study with a 1-month follow-up of children who presented with an acute asthma exacerbation to the emergency department of The Montreal Children's Hospital during a 15-month period. The protocol was reviewed and approved by the Institutional Review Board, and informed consent was obtained from parents or guardians. Children were invited to participate in 1, 2, or 3 subprojects: the assessment of bone metabolism, the assessment of bone density, and the assessment of adrenal function.

Subjects

Patients were eligible when they had experienced repeated (≥ 3) wheezing episodes and presented with an acute asthma exacerbation in accordance with the American Thoracic Society's criteria.¹² Children were considered to have been exposed when they had received at least 2 5-day courses of high-dose (1–2 mg/kg/d) prednisone-equivalent systemic glucocorticoids in the preceding year and were prescribed a new burst for the index exacerbation. Unexposed children had not received any systemic glucocorticoids in the preceding year or for the index exacerbation. Exclusion criteria included the following: 1) a clinical diagnosis of pneumonia; 2) any chronic disease, such as bronchopulmonary dysplasia, cystic fibrosis, or endocrine or bone disease; 3) intake of medications that could interfere with vitamin D metabolism (eg, anticonvulsants); and 4) treatment of the index exacerbation with high doses of inhaled glucocorticoids (≥ 1000 $\mu\text{g}/\text{d}$ beclomethasone or equivalent). Some exclusion criteria, intended to maximize comparability of asthma severity between the exposed and unexposed groups, were eliminated a few months into the study because they excluded most patients: 1) infrequent asthma (< 3 exacerbations requiring an unscheduled medical visit in the preceding 12 months), 2) intake of inhaled glucocorticoids in the preceding 6 months, 3) treatment of index exacerbation requiring < 2 nebulizations of β_2 -agonists in the emergency department, and 4) hospital admission.

Treatment Protocol

Children received hourly inhalations of 0.15 mg/kg of a 5% albuterol solution until the desired bronchodilation was achieved. Ipratropium bromide was added if indicated. The decision to administer a short course of systemic glucocorticoids was made by the treating physician. When administered, the burst consisted of oral prednisone at 1 to 2 mg/kg/d (maximum: 50 mg) in 1 or 2 divided doses for a 5-day period.

Measurements

On presentation at the emergency department, medical history, anti-asthmatic medications, and demographic variables were recorded. Adolescents were asked to indicate their sexual development using pictures of Tanner stages.^{13,14} Eligible children interested in participating were followed during their stay in the emergency department to determine final eligibility status. Total respiratory resistance was measured by the forced oscillation technique on the Custo Vit R (Custo Med, Munich, Germany) at baseline and disposition, in accordance with a previously described protocol.¹⁵ Only reproducible measurements were recorded (ie, a coefficient of variation on 3 repeated measurements of ≤ 0.15).¹⁵ The mean of the 3 technically valid baseline respiratory resistance measurements was expressed in percentage of predicted for height.¹⁶ All biochemical samples and imaging procedures, detailed below, were interpreted by the endocrinologist (C.P.) or the bone metabolism expert (G.C.), both blinded to exposure status.

Exposure to Glucocorticoids

Parental report and medical record review provided information about glucocorticoids exposure during the preceding year. Confirmation was documented within 72 hours of recruitment by pharmacy records of all (oral, inhaled, nasal, and topical) glucocorticoid preparations dispensed in the preceding 2 years. This information was updated 30 days later. Compliance with glucocorticoids prescribed for the index exacerbation was assessed by parental report and, for children aged ≥ 6 years, by serum dehy-

droepiandrosterone sulfate (DHEAS) levels sampled on day 4 or 5 of the burst (within 12 hours of the previous dose). A topical anesthetic cream (EMLA; Astra Pharma Inc, Mississauga, Ontario, Canada) was applied to puncture sites 45 to 60 minutes before blood sampling to reduce discomfort. Serum DHEAS was measured by radioimmunoassay according to the protocol of Buster and Abraham.¹⁷ DHEAS values < 2 $\mu\text{mol}/\text{L}$ (< 4 $\mu\text{mol}/\text{L}$ in pubertal children) were considered "suppressed," values ≥ 2.5 $\mu\text{mol}/\text{L}$ (≥ 4 $\mu\text{mol}/\text{L}$ in pubertal children) were considered "normal," and values in between were considered "possibly suppressed."¹⁸

Bone Metabolism

Serum osteocalcin, calcium, phosphorus, and alkaline phosphatase levels; urine calcium/creatinine ratio; renal threshold phosphate concentration¹⁹; and urine pyridinoline cross-links were measured at the index visit (day 1), on the last day of the burst (day 4 or 5), and 4 weeks after the index visit (day 30). Serum was separated and kept frozen at -20°C until analyzed. All assays were performed twice by a technician blinded to exposure status. Osteocalcin was measured by immunoradiometric assay using a commercial kit (N-tact Osteo SP; INCSTAR Corp, Stillwater, MI) with a within-assay coefficient of variability of 5.4%. Urine pyridinoline cross-links (ie, type 1 collagen cross-linked N-telopeptides) were measured by a commercial enzyme-linked immunosorbent assay kit (Osteomark; Ostex International Inc, Seattle, WA) with a within-assay coefficient of variability of 7.6% and a detection limit of 20 nmol.²⁰ The pyridinoline cross-links normalized to creatinine were expressed as picomoles of bone type 1 collagen per micromole of creatinine.

Bone Density

For the bone density subproject, bone age and bone mineral density of the lumbar spine (L1–L4) were obtained 1 month after the last burst using the Hologic dual radiograph absorptiometer (QDR 4500A; Hologic, Inc, Bedford, MA). Bone mineral density values, standardized for age, gender, and race, were reported as z scores (unpublished US reference values, Hologic, Inc). In patients with abnormal baseline calcium-phosphorus balance, the level of 25-dihydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ measured by radioimmunoassay and radioreceptor assay, respectively (INCSTAR Corp), and/or the level of carboxyl-terminal PTH were documented.

Adrenal Function

For the adrenal function subproject, adrenal reserve was examined 1 month after the exacerbation using basal cortisol (sampled between 7:00 and 8:00 AM) and cortisol response to adrenocorticotrophic hormone (ACTH) stimulation. Serum cortisol was measured twice by radioimmunoassay (ACTIVE Cortisol; Diagnostic Systems Laboratories Inc, Webster, TX) with an intra-assay coefficient of variation of 5.3% to 11.1%. Samples were obtained at baseline and at 30 and 60 minutes after an intravenous injection of synthetic Cortrosyn (125 μg if < 6 years; 250 μg otherwise). Basal levels were considered depressed when < 138 nmol/L, which corresponds to 1 standard deviation (SD) below the mean in normal children.²¹ A stimulated cortisol level was considered depressed when below 400 nmol/L.²²

Statistics

Sample size was based on 80% power to detect a group difference of 0.66 of an SD in the peak cortisol response to ACTH stimulation and in bone density at an α (2-tailed) of 0.05. Although 30 children per group was sufficient, the number of exposed patients was increased to 40 to ensure that if the prevalence of adverse outcome was 0, then the upper level of the confidence interval (CI) would be no more than 7.5%.²³ The prevalence of abnormal findings is presented with the 95% CI.

Changes in osteocalcin and pyridinoline cross-links were examined over time using the repeated-measures regression models, adjusting for potential confounders (including demographic and anthropometric measures); cumulative dose of oral (mg and number of bursts), inhaled (μg), topical (μg), and nasal (μg) glucocorticoids; indices of acute and chronic asthma severity; sampling time; and fasting status. Differences in proportions and risks are presented with the 95% CI.²⁴ Linear and nonlinear regression

models were used to examine the possible dose-response relationship between adverse outcomes and exposure.²⁵ Results are displayed as median (D₁, D₃; ie, the value of the 25th and the 75th percentiles). *P* < .05 indicated statistical significance.

RESULTS

During a 15-month period, 1145 children were approached; 160 were not screened because of the absence of a guardian (*n* = 44), inadequate language skills (*n* = 48), impending respiratory failure (*n* = 61), or refusal to answer questions (*n* = 7). A detailed account of the selection process for the 985 patients who received preliminary screening is provided in Fig 1. Briefly, 439 children did not meet the eligibility criteria. Of the 546 provisionally eligible patients, 244 (45%) expressed interest in participating, 83 of whom became ineligible because of the treatment received in the emergency department. Of the 161 patients (83 exposed, 78 unexposed) who met the final eligibility criteria, 70% agreed to participate. Children who chose not to participate were comparable to participants in age, gender, race, age at first wheezing, number of previous admissions for asthma, maintenance inhaled steroids, and initial oxygen saturation; however, they were less frequently hospitalized (6% vs 20%) for the index exacerbation than their counterparts.

A total of 113 children (64 exposed, 49 unexposed)

were enrolled. Ten patients became or were subsequently found to be ineligible when exposure status was invalidated by pharmacy reports or unexposed children were subsequently treated with systemic glucocorticoids. Twenty patients (10 exposed, 10 unexposed) dropped out of the study. The description of the 83 children (48 exposed, 35 unexposed) who completed 1 or more of the 3 subprojects is presented in Table 1.

Exposure to Glucocorticoids

As expected, children who were repeatedly exposed to systemic glucocorticoids experienced more asthma exacerbations requiring medical attention, were more frequently treated with inhaled glucocorticoids in the preceding year, and presented with a more severe index exacerbation than their counterparts. In the 44 (exposed and unexposed) children on maintenance therapy, the median daily dose of inhaled glucocorticoids in the preceding year was 115 μg (range: 27–1132) of chlorofluorocarbon-propelled beclomethasone equivalent. Exposed children received a median of 4 bursts (range: 3–11) in the preceding year at a mean interval of 3 (1–5) months.

Bursts of glucocorticoids generally consisted of oral prednisone administered in a once-daily (70%) or twice-daily (30%) dose of 1.3 mg/kg/d (D₁, D₃;

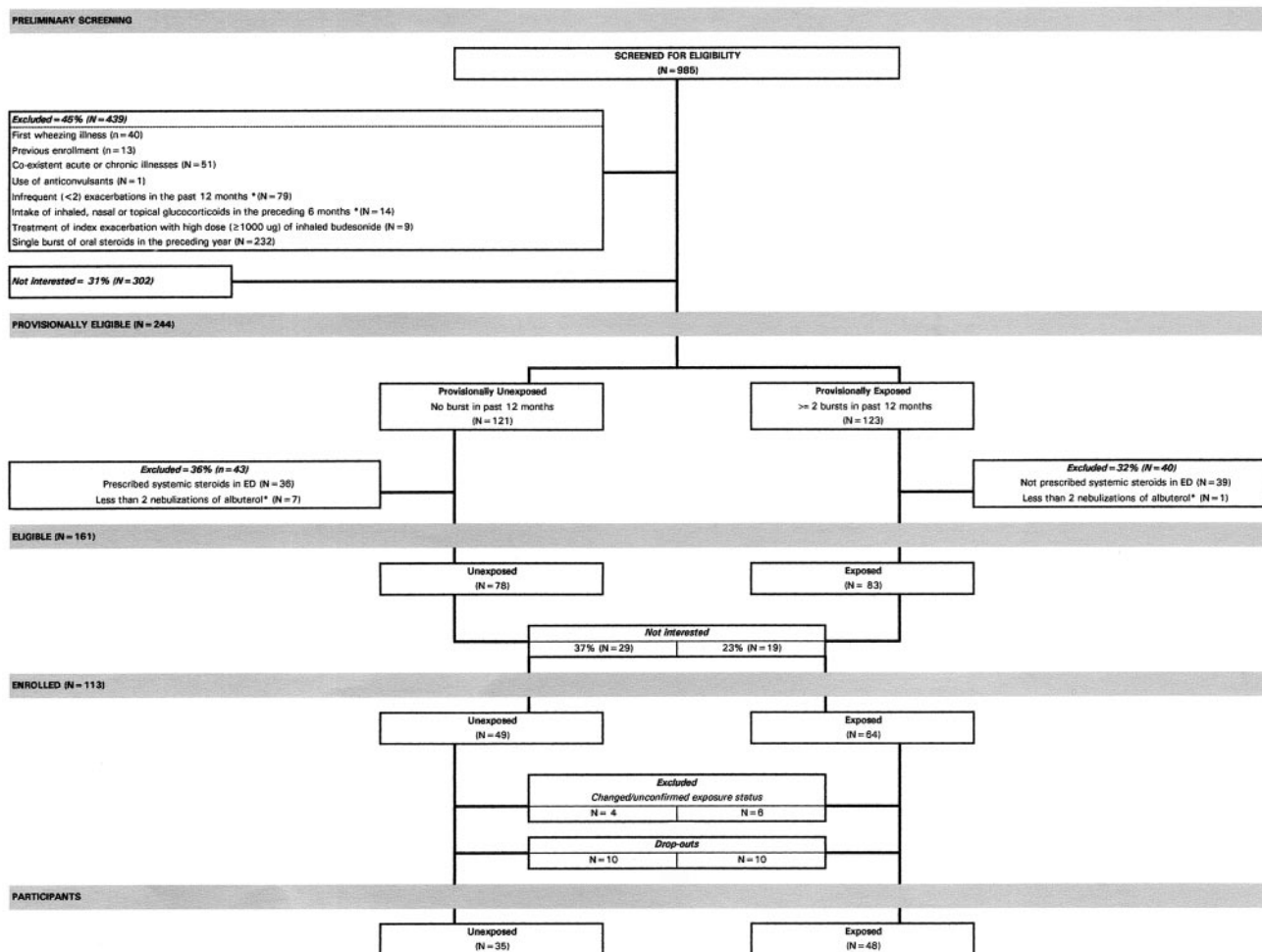


Fig 1. Flow diagram of enrolled participants.

TABLE 1. Description of Participants

	Exposed (N = 48)	Unexposed (N = 35)	P Value
Demographics			
Age	6 (4, 10)	11 (6, 13)	.02
Gender (% male)	50%	40%	NS
Race (%)			
White	77%	83%	NS
Black	10%	3%	
Other	10%	14%	
Bone age	6 (4, 11)	11 (5, 14)	.02
Standardized weight†	0.7 (-0.1, 1.3)	1.0 (0.1, 1.8)	NS
Standardized height‡	1.0 (0.0, 1.8)	1.8 (0.8, 2.3)	NS
Tanner stage	1 (1, 3)	2 (1, 3)	.01
Medical history			
ED visits in past year	4 (3, 5)	1 (0, 2)	.0001
No. of hospital admissions since birth	2 (1, 6)	0 (0, 2)	.008
Severity of index exacerbation			
Low oxygen saturation (<95%)	46%	20%	.03
Predicted respiratory resistance (%)	114 (92, 152)	120 (96, 166)	NS
B2-agonist nebulizations	4 (3, 5)	2 (1, 2)	.001
Hospital admission (%)	31%	0%	.002
Oral glucocorticoids "bursts"			
No. in past year	4 (3, 5)	0 (0,0)	.001*
Delay in days between bursts (median)	87 (43, 145)		
Other glucocorticoids in past year			
Inhaled	71%	29%	.001
Topical	6%	6%	NS
Nasal	15%	6%	NS

ED indicates emergency department.

Values are displayed as median (D₁, D₃: interquartile range) or percentages.

* Expected difference by study design.

† Presented as standardized deviation values based on references values.

‡ Height (SD score).

1.1, 1.9) for a median 5 days.^{4,5} Parents of the 48 exposed children reported good compliance with no doses missed (0, 1) and pharmacy records confirmed dispensing the prescription in all cases. Measures of DHEAS in the 19 exposed children ≥ 6 years confirmed compliance with prescribed steroids; 18 (95%) children had "suppressed" and 1 had "possibly suppressed" levels.

Bone Metabolism

In 63 (80%) of 83 children, the baseline measurements of calcium, phosphorus, and alkaline phosphatase were within the normal range. Two children had marginal or transient anomalies suggestive of seasonal variation in vitamin D₃; 1 child had an isolated low alkaline phosphatase level, and the other had an isolated and transient low serum calcium. The remaining 18 children had 1 or more mild anomalies in serum calcium, phosphorus, or alkaline phosphatase. Serum parathyroid hormone (PTH) measurements in these 18 children and serum 25 D₃ and 1-25 D₃ assays in all 20 children with baseline anomalies confirmed the normality of vitamin D₃ and PTH status in all cases.

Baseline serum osteocalcin was 30% lower (95% CI: 25–34) in the 32 exposed children than in the 35 unexposed children. In the absence of published pediatric reference values using the same immunoradiometric assay, firm assessment of the normality of these baseline values could not be made; however, the values of exposed children all were within the reference range of a small sample (N = 30) of normal children (F. Glorieux, personal communication, 2000).

A complete set of osteocalcin values at baseline, day 5, and day 30 were available in 16 exposed and 25 unexposed children. Clearly, the exposure status (P = .008) and the sampling day (interaction of sampling day \times exposure; P = .004) had significant influence on the osteocalcin levels (Fig 2). In exposed children, there was a 41% decrease (95% CI: 19–57) in

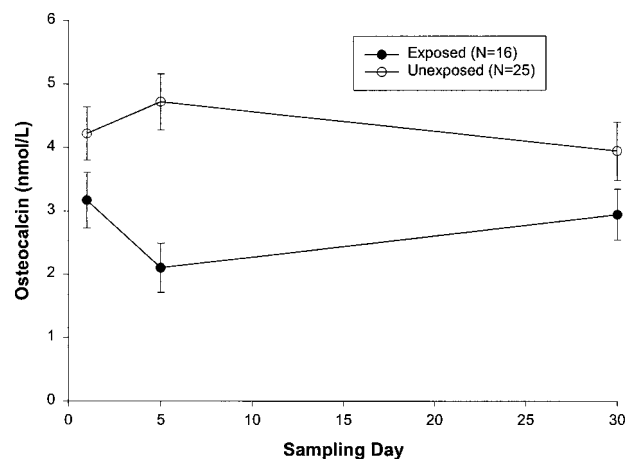


Fig 2. Profile of serum osteocalcin over time at 0 (index visit), 5, and 30 days in the 16 children who had complete data and were repeatedly exposed (●) and in the 25 children unexposed to short courses of high-dose glucocorticoids in the preceding year (○). In exposed children, the 5-day course of glucocorticoids (1.0–2 mg/kg/d; maximum: 50 mg) was administered between days 0 and 5. The error bars represent the standard error of the mean. After adjusting for the baseline group difference in serum osteocalcin levels (P < .02), a statistically significant group difference was observed at 5 days (P < .004) but not at 30 days (P = .93).

osteocalcin level between the first and last day of the burst, with a return to baseline by day 30, at a level comparable to that of the control group. No such changes were observed in the unexposed group. Adjustment for potential confounders gave similar results.

In contrast, no significant group differences in urine pyridinoline were observed in the 71 children (37 exposed, 34 unexposed) who provided samples at baseline. The strongest predictor of baseline cross-link values was bone age ($r^2 = 0.22$). Adjustment for bone age and other possible confounders also failed to reveal any baseline group difference. Only 3 children (2 exposed, 1 unexposed) had abnormal baseline values, all of which were elevated (≥ 2 SD above the mean for age) despite a sampling time earlier than the evening peak of pyridinoline excretion.^{20,26} The 3 elevated values were observed in adolescents, an age group with intense bone remodeling.²⁷

Complete sets of urine pyridinoline levels were gathered for 35 exposed and 30 unexposed children. The day of sampling ($P = .003$) influenced pyridinoline values, but exposure status did not (Fig 3). Most of the group differences occurred between day 1 and day 5 ($P = .04$); unexposed children experienced a 51% increase (95% CI: 25–82) in pyridinoline, with a return to comparable group values at 30 days. The pyridinoline profile over time was unaffected by the adjustment for potential confounders.

Bone Density

Bone density measurements were obtained in 81 children (47 exposed, 34 unexposed). The mean z scores were similar in the exposed (-0.61 ± 1.0 SD) and unexposed (-0.67 ± 0.9) groups, both being significantly lower than expected for age, gender,

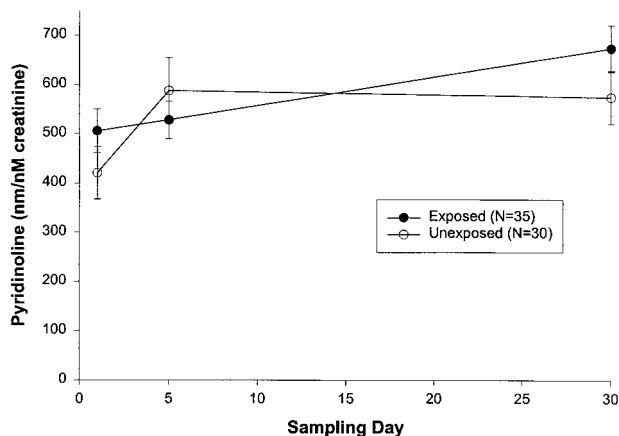


Fig 3. Profile of urine pyridinoline type 1 collagen cross-linked N-telopeptides over time in the 35 children who had complete data and were repeatedly exposed (●) and the 30 children unexposed (○) to short courses of high-dose glucocorticoids. Samples were collected on spot urine at enrollment on the index visit (time 0) and on the second urine of the day on days 4 or 5 and 30. In exposed children, the 5-day course of glucocorticoids (1.0–2 mg/kg/d; maximum: 50 mg) was administered between days 0 and 5. The error bars represent the standard error of the mean. No group differences were observed at any point in time. The profile of pyridinoline cross-links was significantly affected by the day of measurement in unexposed subjects, with a significant difference apparent only between 0 and 5 days ($P < .05$).

and race. The prevalence of osteopenia, defined as a z score < 2 SD below the predicted mean, was also similar in both groups (Table 2). Although several potential confounders were examined, including bone age and cumulative dose of oral, inhaled, nasal, and topical corticosteroids during the preceding 2 years, we were unable to explain satisfactorily the significantly lower-than-expected bone density observed in both groups. Comprehensive evaluation of osteopenia in the Department of Genetics (F.G.) was obtained in 6 of the 8 children with osteopenia; the remaining 2 children failed to attend the appointments despite repeated rescheduling. Final diagnoses included inadequate calcium and/or vitamin D intake attributable to past or ongoing milk intolerance/allergy ($n = 2$), transient osteopenia of puberty ($n = 2$), and no apparent explanation ($n = 2$). All received specific medical advice regarding calcium intake and vitamin D supplementation.

Adrenal Function

ACTH testing was obtained in 74 children (43 exposed, 31 unexposed). The mean delay between the index exacerbation and ACTH stimulation test was similar in both groups (37 ± 11 days). Basal cortisol (304 ± 167 vs 308 ± 107 nmol/L) and peak cortisol response to ACTH (754 ± 184 vs 726 ± 198 nmol/L) were comparable in the exposed and the unexposed groups. Although 5 children (3 exposed, 2 unexposed) had basal cortisol levels below 1 SD, none had a suppressed response to ACTH stimulation warranting stress coverage with steroids (Table 2). Multivariate analyses failed to identify cumulative exposure to any steroid preparation, acute or chronic asthma severity, or delay since last burst as predictors of basal cortisol or stimulated cortisol. No dose-response relationship was identified between the cumulative exposure to oral, inhaled, nasal, and/or topical steroids and adrenal function.

DISCUSSION

This report represents the first study to examine concurrently the effect of repeated short courses of high-dose systemic glucocorticoids on the bone metabolism, bone density, and adrenal function of children with asthma. Among the 83 children enrolled during an acute asthma exacerbation, a new burst of oral glucocorticoids was associated with a transient decrease in plasma osteocalcin during the 5-day burst but no significant change in urine pyridinoline cross-links during the subsequent month. There was no cumulative effect on bone density among children with repeated (range: 3–11) bursts during the preceding 12 months as compared with unexposed children. There was also no evidence of impaired adrenal reserve 1 month after the index exacerbation. Moreover, greater-than-expected height and weight suggest no significant impact of episodic short courses of systemic steroids on growth.

The children in the exposed group experienced significant morbidity, with a median of 2 hospital admissions and 4 emergency department visits for acute asthma exacerbations in the preceding year. Although three quarters of exposed children were on

TABLE 2. Prevalence of Adverse Outcomes 30 Days After the Index Exacerbation

	Exposed		Unexposed		Risk Difference
	N	% (95% CI)	N	% (95% CI)	% (95% CI)
Osteopenia*	4/47	9% (2, 20)	4/34	11% (3, 28)	-3 (-25, 15)
Adrenal suppression					
Low basal cortisol†	3/43	7% (1, 19)	2/31	7% (1, 21)	0% (-19, 12)
Low peak cortisol‡	0/43	0% (0, 7)	0/31	0% (0, 10)	—

* Z score < -2.

† Basal cortisol <138 nmol/L.

‡ Peak cortisol <400 nmol/L.

maintenance steroids, the actual daily dose dispensed by pharmacists in the preceding year was relatively low.

Osteocalcin, the most abundant noncollagenous protein of bone, is probably 1 of the markers of choice for bone formation.²⁸ The 41% reduction from baseline decrease in serum osteocalcin levels, observed immediately after the administration of oral glucocorticoids, was transient, with a return to baseline values within 30 days. A reduction of similar magnitude has been observed in adults.^{8,29} Because chronic low osteocalcin levels have been associated with bone mass reduction³⁰ and low trabecular bone mass linked with an increased incidence of vertebral fractures,³¹ the return to baseline values is reassuring. In contrast, no group difference in pyridinoline levels was evident, suggesting that a new short course of systemic steroids had no impact on bone resorption. The absence of prolonged or cumulative impact on bone metabolism suggests that the administration of repeated bursts of oral glucocorticoids in children is not an important risk factor for osteopenia and thus is unlikely to be associated with an increased risk of fracture. Moreover, the comparable bone density in exposed and unexposed children provides no evidence to suggest a negative cumulative effect of repeated courses of systemic glucocorticoids on bone mineralization. However, the lower-than-expected bone density (negative mean z score) in both groups was disconcerting. Cumulative exposure of oral, inhaled, nasal, and/or topical corticosteroid during the preceding 2 years showed no correlation to the bone density z score. This is consistent with the literature, in which a low dose of maintenance inhaled steroids (<400 $\mu\text{g}/\text{d}$ beclomethasone equivalent) as used by our participants has not been associated with decreased bone mineral density.³² Delayed bone maturation, associated with poorly controlled asthma, was also ruled out as a cause for spurious osteopenia in our participants, who were generally heavier and taller than expected, with a close concordance between chronological and bone ages. Perhaps inadequate protein, calcium, and vitamin D intake³³; inadequate physical activity³⁴; or asthma per se³⁵ adversely affected the bone density of recruited patients.³⁶

Previous studies have confirmed that a single course of high-dose glucocorticoids may be associated with transient suppression of the hypothalamo-pituitary-adrenal axis during treatment, with complete recovery within 10 days of stopping treatment.^{9,37} Our data support similar recovery in

children receiving repeated short courses of systemic steroids. Moreover, the absence of a dose-response relationship between the cumulative exposure to oral, inhaled, nasal, and/or topical steroids and adrenal function is reassuring. The only previously published report on the effect of repeated bursts of glucocorticoids on adrenal function¹¹ had raised alarms. Of the 10 children who received 3 to 7 bursts of oral glucocorticoids with 300 $\mu\text{g}/\text{d}$ inhaled steroids in the preceding year, 4 (20%) patients had subnormal cortisol response to hypoglycemia and 2 (10%) had a suppressed response to ACTH stimulation. The timing of adrenal testing, patient selection, or chance may explain the discrepancy of our findings and those of Dolan et al.¹¹ In the study by Dolan et al, children were tested between 16 days and 4 months after a burst. We systematically tested children 1 month after the burst, reasoning that a suppressed adrenal response observed after this period would indicate more than a transient dysfunction. Sensitivity of the stimulation test is unlikely to be at stake: the short tetracosactin test that we and Dolan et al used is reported to be much safer and as sensitive as the insulin hypoglycemic test.³⁸ Maintenance inhaled steroids used at low doses, as seen in our children and the report by Dolan et al,¹¹ have not been shown to be associated with impaired adrenal function,^{22,32} except in occasional case reports.³⁹ The power of our study also must be considered in the interpretation of data; the prevalence of adrenal suppression in children repeatedly exposed to oral steroids may still be as high as 7%.

Recruiting in the emergency department allowed for the simultaneous assessment of the effect of an acute asthma exacerbation and a new burst of systemic steroids in acutely ill patients with asthma. Considerable time and effort were invested to minimize the burden on participants (home visits and anesthetic patch before blood sampling); however, because of the demanding protocol, only 70% of eligible patients were enrolled. The promise of learning bone density and adrenal function results probably enhanced the attractiveness of the study. It is therefore conceivable that a selection bias occurred, in that parents who perceived their child to be at higher risk of adverse outcomes were more likely to participate; "worry about adverse effects of steroids" was the most frequent reason given by parents for participating. Such a selection bias likely would lead to an overestimation of the prevalence of adverse outcomes. There were no group differences among the 161 eligible children with regard to demograph-

ics, asthma history, use of maintenance inhaled steroids, and oxygen saturation; however, nonparticipants were less frequently hospitalized for the index exacerbation than their counterparts, possibly because the additional time required for study enrollment deterred more parents of children who were ready for discharge.

The cross-sectional design and the definition of exposure allowed baseline group differences, particularly in asthma chronicity and severity. A randomized, controlled trial, which would have favored a balanced distribution of such confounders between groups, was ethically precluded because of the proven efficacy of glucocorticoids in moderately to severely ill children with asthma. A trial restricted to children with mild exacerbations would not have given us access to children with the desired exposure to oral glucocorticoids and thus was not feasible. Although it cannot be excluded, the cross-sectional design is unlikely to have introduced significant bias because no indicators of asthma severity or chronicity seemed to be important predictors of adverse outcomes in multivariate analyses.

Although our results are reassuring, the sample size precludes total reassurance. In particular, children who received successive bursts of oral glucocorticoids over a short interval may be a particular risk and should be screened for adrenal suppression. Furthermore, the safety of repeated bursts of oral glucocorticoids cannot be assumed until other areas of concern, such as growth⁴⁰ and immunity,⁴¹ have been studied adequately.

Repeated short courses of high-dose oral glucocorticoids, administered to treat acute asthma exacerbations, are associated with transient perturbation of the bone deposition but not with a higher risk of osteopenia and adrenal suppression 30 days after the last burst. Although the sample size precludes total reassurance, it is hoped that these results may alleviate some concerns about the safety of repeated short courses of systemic glucocorticoids and improve physicians adherence and parents' compliance to this highly effective treatment. Preferably, however, children with repeated exacerbations should receive adequate prophylactic therapy.

ACKNOWLEDGMENTS

This work was supported by a grant 6605-4341-401 from the National Health Research and Development Program of Canada. Astra Pharma Inc graciously provided the EMLA cream and patches.

We are indebted to the many patients; the emergency physicians; the 2 research nurses (Mary Cooke and Francine Proulx); the nurses of the Clinical Investigation Unit; Charlotte Branchaud, PhD, Associate Director of the Clinical Endocrinology Laboratory of The Montreal Children's Hospital, for ensuring quality control of all cortisol assays; the Genetic Laboratory of the Shriners' Hospital for diligent measurements of bone metabolism markers; the Radiology Department of Shriners' Hospital for measuring bone mineral density and bone age; and the Biochemistry Department of St-Luc Hospital for providing the PTH measurements, whose precious collaboration made this study possible. We thank Michele Gibbon for diligent data entry, M. Hong Yang for statistical assistance, Dr Geoffrey Dougherty for constructive comments, and Judy Fuoco and Colette Maillé for manuscript preparation.

Francine Ducharme is the guarantor of this article. With the

assistance of all co-authors, she conceived the protocol, obtained funding, trained and supervised research nurses and assistants, supervised the analyses, interpreted the results with the co-authors; and wrote the article. Francis Glorieux supervised all measurements of bone metabolism markers in the Generic Laboratory of the Shriners' Hospital. Gilles Chabot specifically interpreted all bone metabolism markers, PTH, and vitamin D when indicated and provided follow-up for children with abnormal results. Constantin Polychronakos specifically supervised the ACTH testing and provided interpretation of results and follow-up for children with abnormal results.

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GUNS DON'T KILL PEOPLE???

“Among children and youth less than age 15, the firearm homicide rate in the United States was 16 times the average for other industrialized countries, the firearm suicide rate was 11 times higher, and the unintentional firearm was 9 times higher.”

Fingerhut LA, Christoffel KK. Firearm-related death and injury among children and adolescents. *Future Child*. 2002;12(Summer/Fall):24–37

Submitted by Student