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Changes in carbohydrate and lipid metabolism in children with asthma inhaling budesonide

Markku Turpeinen, MD, Ritva Sorva, MD, and
Kaisu Juntunen-Backman, MD Helsinki, Finland

*In a longitudinal study, antiasthmatic and metabolic effects of budesonide inhalations in initially high (800 $\mu\text{g}/\text{m}^2/\text{day}$ for 1 month) and subsequently lower (400 $\mu\text{g}/\text{m}^2/\text{day}$ for 4 months) dosage were evaluated in nine children with asthma, aged 5 to 10 years. The FEV₁ increased significantly after high dosage (median, 96.5% versus 105.5%; $p = 0.0339$). After lower dosage, FEV₁ was still higher than at the baseline (106% versus 96.5%; $p = 0.0339$). Clinically, no additional β_2 -agonist was needed after 2 weeks of treatment. Serum high-density lipoprotein cholesterol increased significantly by 22% after high dosage (medians, 1.18 versus 1.44 mmol/L). A significant decline to 1.31 mmol/L was observed when the dose was reduced (overall, $p = 0.0319$). The treatment had no significant effect on serum total cholesterol, on serum triglycerides, on the ratio of high-density lipoprotein to total cholesterol, on the body mass index, or on glucose tolerance. The high dosage increased significantly the ratio of serum insulin to blood glucose, calculated from the areas under the incremental 2-hour curves in the glucose tolerance test (medians, 17.3 versus 23.2 mU/mmol). After lower dosage, the ratio declined significantly to 13.5 mU/mmol (overall, $p = 0.0164$). No significant changes were observed in plasma cortisol in the 2-hour adrenocorticotrophic hormone test. The antiasthmatic effect of budesonide inhalations in a dose of 800 $\mu\text{g}/\text{m}^2/\text{day}$ for 1 month was accompanied by detectable changes in lipid and carbohydrate metabolism. These metabolic changes were reversible, and the antiasthmatic effect could be maintained by a dose of 400 $\mu\text{g}/\text{m}^2$ for 4 months without significant systemic effects. This dose is safe and efficient in the maintenance treatment of childhood asthma. (*J ALLERGY CLIN IMMUNOL* 1991;88:384-9.)*

Key words: Asthma, children, glucocorticoids-topical, pituitary-adrenal function tests, carbohydrate metabolism, lipid metabolism

From the Department of Allergic Diseases, University Central Hospital, Helsinki, Finland.

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Reprint requests: Markku Turpeinen, MD, Department of Allergic Diseases, University Central Hospital, Meilahdentie 2, 00250 Helsinki, Finland.

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Inhaled glucocorticoids are now an integral part of the management of asthma. The safety of these agents depends on the dose and on the ratio of topical to systemic potency.¹ Large doses may cause adrenal and growth suppression in children.¹ Disturbances in carbohydrate and lipid metabolism, without adrenal suppression, have been observed in adults inhaling beclomethasone in a dose of 1000 $\mu\text{g}/\text{day}$.² In children, little is known of the effects on carbohydrate and lipid metabolism.

Budesonide is known for a favorable ratio of topical to systemic activity.¹ We have evaluated the efficiency and safety of budesonide inhalations in initially large and, subsequently, smaller dosage. We report the effects on pulmonary function, on HPA axis, and on carbohydrate and lipid metabolism in children with asthma.

PATIENTS AND METHODS

Patients

Nine children, two girls and seven boys, with perennial asthma³ were studied. Their ages ranged from 5 to 10 years (mean, 7.4 years), and the duration of their asthma was from 1 to 8 years (mean, 3.8 years). Their asthma was unstable despite daily treatment. Five children were taking inhaled sodium cromoglycate and slow-release oral theophylline, two were taking cromoglycate, and two other children were taking theophylline. All the children used, in addition, inhaled β_2 -agonists regularly three times daily, but extra doses were needed more than once a week. No subject had taken any glucocorticoid previously. The study protocol was approved by the ethical committee of the department. All the parents and the children themselves, when they were old enough, gave their informed consent.

Study design

Sodium cromoglycate was stopped, but oral theophylline and inhaled β_2 -agonists were continued at the same dosage. Each child was studied on three occasions: before the treatment with an aerosol preparation of budesonide, after 1 month, and after 5 months of treatment. During the first treatment period of 4 weeks, the daily dose of budesonide was 800 $\mu\text{g}/\text{m}^2$ (range, 600 to 800 μg) divided into morning and evening doses. During the next 3 weeks, the dose was reduced to the daily maintenance of 400 $\mu\text{g}/\text{m}^2$ (range, 300 to 400 μg) divided into two doses for the following 13 weeks. Before the study, the children were taught the inhalation technique. Budesonide was inhaled from a metered-dose inhaler with a valved spacer device (Nebuhaler, Draco AB, Lund, Sweden). The children used a standard diary card to record additional use of β_2 -stimulant. At each examination, children were admitted to the ward at 8 AM after a 10-hour overnight fast. All therapy was stopped for 12 hours before the tests.

Assessment

Pulmonary function was studied with a pneumotachograph (Vitalograph Compact, Vitalograph, Ltd., Buck-

Abbreviations used

ACTH:	Adrenocorticotrophic hormone
HDL:	High-density lipoprotein
HPA:	Hypothalamic-pituitary-adrenocortical
CV:	Coefficient of variation
BMI:	Body mass index

ingham, England). The blood samples for determination of blood glucose, plasma cortisol, serum insulin, triglyceride, cholesterol, and HDL cholesterol were taken through an intravenous plastic cannula inserted under local anesthesia (a cream containing lidocaine and prilocaine). The children were administered 1.75 gm/kg of glucose orally in a concentration of 0.25 gm/ml. Blood samples for glucose and insulin determination were obtained before and 30 and 120 minutes after oral glucose. Thereafter, synthetic tetracosactide (S-Cortophin, N.V., Organon, Oss, The Netherlands) was administered as an intravenous bolus injection of 0.25 mg/1.72 m² within 2 minutes. The blood sample for cortisol determination was obtained 120 minutes after the injection. This 2-hour plasma cortisol concentration was used as an index of the cortisol secretion reserve.⁴ The lower limit of normal was 700 nmol/L for the 2-hour cortisol and 162 nmol/L for the basal morning value. These limits represent the geometric 2.5th percentile of the values for 22 children with asthma (aged 3 to 16 years; mean, 7.9 years) examined by our laboratory. These children had never used any glucocorticoid.

Blood glucose was measured by a glucose dehydrogenase method.⁵ The day-to-day CV was 2.4%.

Serum cholesterol concentrations were determined with an enzymatic CHOD-PAP kit (Boehringer Mannheim). The CV of the determination was 2.4%.

Serum HDL cholesterol was determined enzymatically on samples of the supernatant after precipitation of other lipoprotein particles with dextran sulfate and MgCl_2 . The CV of HDL cholesterol was 2.6%.

Serum triglyceride concentrations were determined with enzymatic GPO-PAP kit (Boehringer Mannheim). The CV of the determination was 3.1%.

Serum insulin was measured by RIA (Phadaseph insulin RIA, Pharmacia Diagnostics AB, Uppsala, Sweden). The sensitivity of the assay was <2.5 $\mu\text{g}/\text{ml}$. Cross-reactivity with C peptide was <0.1%.

Plasma cortisol levels were determined with cortisol (¹²⁵I) RIA kit (Farnos Diagnostica, Turku, Finland). The cortisol antiserum used in the assay has a negligible cross-reactivity with other endogenous corticosteroids and cortisol metabolites. The sensitivity of the assay was 3 to 5 nmol/L.

BMI was calculated as weight (kilogram)/height (square meter).

Statistical analysis

These data were not normally distributed. Therefore, the results are presented for each individual and as medians and ranges. Statistical comparisons were performed with Friedman's nonparametric analysis of variance.⁶ The areas under

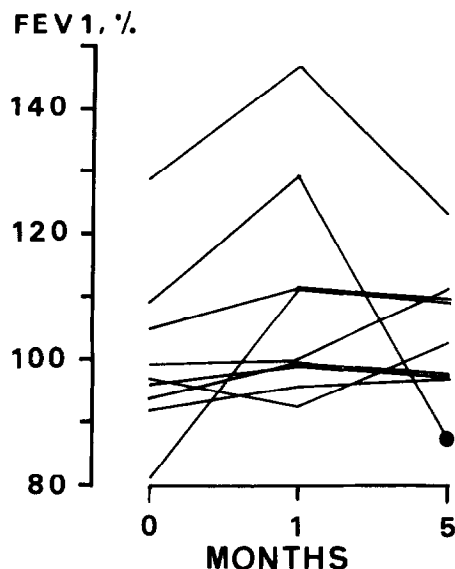


FIG. 1. FEV₁ as a percentage of predicted, before and after 1 month of high and, subsequently, 4 months of lower dosage of budesonide inhalations; respiratory infection at 5 months (●); significant differences between the values for baseline and 1 month ($p = 0.0339$) and between values for baseline and 5 months ($p = 0.0339$).

the incremental blood glucose and serum insulin curves were calculated by the trapezoidal rule.⁷

RESULTS

The pretreatment ratio of FEV₁ to FVC ranged from 63% to 99% (median, 75%). After 4 weeks of high-dose therapy with budesonide, the median FEV₁ percent predicted increased from 96.5% to 105.5% ($p = 0.0339$; Fig. 1). The 1- and 5-month values did not differ (medians, 105.5% versus 106%). The 5-month values were significantly ($p = 0.0399$) higher than the pretreatment values. One child was excluded from the statistical analysis because of a respiratory infection at 5 months (Fig. 1). After 2 weeks of therapy with budesonide, no additional β_2 -agonist was needed apart from temporary use for 2 to 3 days in two children during acute respiratory infections.

After large dosage treatment, a substantial rise in serum cholesterol was found in four children, but statistically significant changes were not observed between the groups (Fig. 2). The respective medians were 4.3, 4.2, and 4.4 mmol/L. All values were normal for Finnish children of this age group.⁸

After high-dose therapy, serum HDL cholesterol increased by 22% (respective medians, 1.18 versus 1.44 mmol/L) (Fig. 2). After lower dosage, it was reduced by 9% to 1.31 mmol/L (overall, $p = 0.0319$ for the whole study period). The baseline and 5-month

values did not differ. There were no significant changes between the ratios of serum HDL to total cholesterol (median, 0.29) nor in serum triglycerides (medians: 0.5, 0.6, and 0.6 mmol/L) during treatment (Table I). Serum HDL-cholesterol values, the ratios of serum HDL to total cholesterol, and serum triglyceride values were all within the limits of normal.⁸

No significant changes were observed in the fasting blood glucose (medians, 4.5, 4.5, and 4.7 mmol/L; Table I). All the individual values were normal (<6.4 mmol/L).⁹ The fasting serum insulin did not change during treatment (medians, 6, 7, and 6; Table I). Also, all the individual values were normal.¹⁰ Neither blood glucose nor serum insulin concentrations in the glucose tolerance test were affected by budesonide (Table I). Impaired glucose tolerance (2-hour blood glucose, 6.7 to 10 mmol/L)⁹ was found in one child before and after 5 months of therapy; in another child, after 1 and 5 months of therapy; in a third child, before treatment only. Neither the areas under the incremental 2-hour blood glucose curves (respective medians: 3.8, 4.3, and 4.4 mmol/L/hr) nor the areas under the incremental 2-hour serum insulin curves (medians: 65, 92, and 62 mU/L/hr) were significantly affected by treatment. However, the ratio of serum insulin to blood glucose, calculated from the areas under the incremental 2-hour curves, increased by 34% after high-dose therapy (17.3 versus 23.2 mU/mmole). After lower dosage, the ratio declined to 13.5 mU/mmole. Both the rise and the decline of this ratio were significant (overall, $p = 0.0164$ for the whole study period; Fig. 3). The baseline and 5-month values did not differ.

Neither the basal nor the 2-hour plasma cortisol levels in the ACTH test were significantly affected by treatment. The median basal morning values were 306 (before treatment), 314 (after high dosage), and 310 nmol/L (after lower dosage). The respective 2-hour values were 937, 893, and 894 nmol/L (Fig. 4). After high dosage, a mildly subnormal basal plasma cortisol (145 nmol/L; normally, >162 nmol/L) was transiently observed in one child. A mildly impaired response to ACTH (plasma 2-hour cortisol, 600 nmol/L, normally >700 nmol/L) was found in another child after high dosage only (Fig. 4).

There were no significant differences in the BMI between the pre- and posttreatment occasions (medians: 16.4, 16.3, and 16.1 kg/m²) (Table I).

DISCUSSION

These data confirm the previous findings that inhaled budesonide improves pulmonary function in childhood asthma.¹¹ Clinically, the antiasthmatic ef-

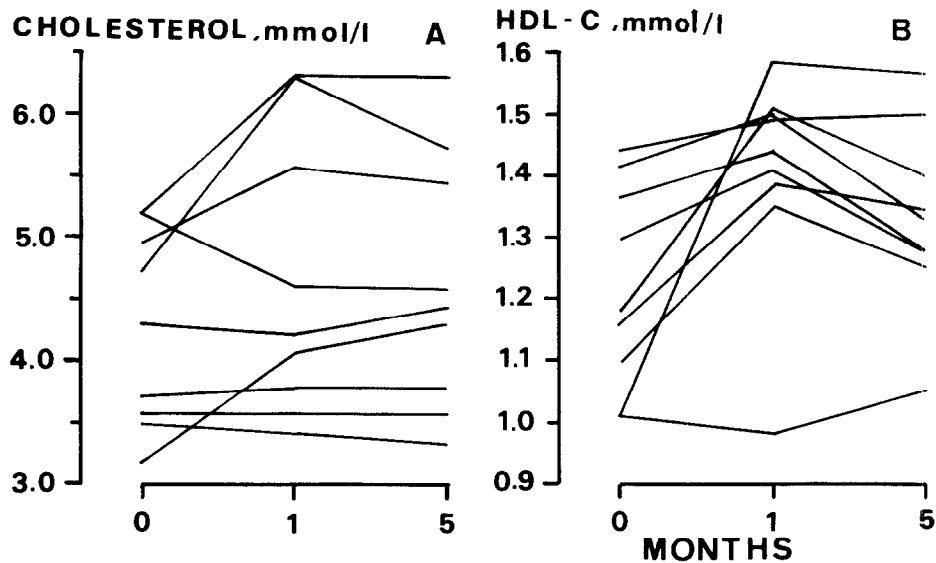


FIG. 2. A, Serum total cholesterol. B, HDL-cholesterol (*HDL-C*) before and after 1 month of high and 4 months of lower doses of budesonide. Significant changes in HDL-cholesterol between the values for baseline and 1 month and between the values for 1 and 5 months (overall, $p = 0.0319$).

TABLE I. Metabolic characteristics (medians and ranges) before and after 1 month of high and 4 months of lower dosage of budesonide inhalations in nine children with asthma

	Before treatment	After 1 month of high dosage	After 4 months of lower dosage
Fasting blood glucose (mmol/L)	4.5 (3.9 - 4.9)	4.5 (4.1 - 4.9)	4.7 (3.9 - 4.9)
Blood glucose (mmol/L) after oral glucose			
At 30 min	7.2 (5.9 - 9.8)	7.5 (5.6 - 9.6)	7.4 (5.2 - 9.3)
At 120 min	5.8 (5.3 - 7.1)	4.8 (3.7 - 7.1)	5.3 (4.7 - 9.3)
Fasting serum insulin (mU/L)	6 (4 - 10)	7 (2 - 10)	6 (4 - 14)
Serum insulin (mU/L) after oral glucose			
At 30 min	52 (24 - 98)	75 (26 - 189)	51 (20 - 95)
At 120 min	29 (18 - 57)	23 (5 - 76)	27 (13 - 48)
Ratio of serum HDL to total cholesterol	0.29 (0.19 - 0.39)	0.29 (0.21 - 0.39)	0.29 (0.22 - 0.40)
Plasma triglyceride (mmol/L)	0.5 (0.4 - 1.2)	0.6 (0.3 - 1.2)	0.6 (0.4 - 1.1)
BMI (kg/m ²)	16.4 (14.3 - 20.2)	16.3 (14.2 - 19.4)	16.1 (13.9 - 21.0)

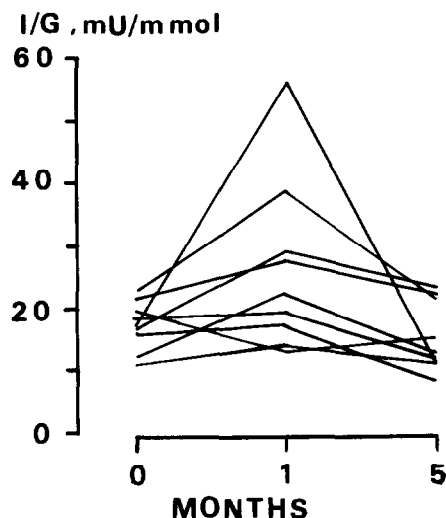


FIG. 3. The incremental areas of serum insulin concentrations in the oral glucose tolerance test, adjusted for the incremental areas of blood glucose (I/G), before and after 1 month of high and 4 months of lower doses of budesonide. Significant changes between the values for baseline and 1 month and between the values of 1 and 5 months (overall, $p = 0.0164$).

fect was detectable in all the children during 2 weeks of high-dose therapy and could be maintained by lower dosage. However, the antiasthmatic response was accompanied by systemic metabolic effects.

Insulin levels, adjusted for blood glucose, increased significantly in the glucose-tolerance test after high-dose therapy. This finding indicates that the glucocorticoid induced insulin resistance.¹² The treatment had no major effect on glucose tolerance. The metabolic influence of inhaled high-dose budesonide accords with that of inhaled beclomethasone dipropionate (1000 $\mu\text{g}/\text{day}$) in healthy adults² but was considerably less than the metabolic disturbance observed in Cushing's syndrome¹³ and in children taking oral glucocorticoids.¹⁴ After low-dose therapy, insulin secretion returned to the pretreatment level. In adults with asthma, the treatment with inhaled beclomethasone in a dose of 400 $\mu\text{g}/\text{day}$ had no significant effect on blood glucose and plasma insulin levels.¹⁵

Serum HDL cholesterol increased by 22% after 4 weeks of high-dose therapy. This is considerably less than the increases of 68% and 34%, respectively, after 4 weeks of oral prednisone in a dose of 30 to 80 mg/day ¹⁶ and 15 mg/day .¹⁷ The budesonide-induced rise in HDL cholesterol equals that observed after 4 weeks of therapy with inhaled beclomethasone (1000 $\mu\text{g}/\text{day}$) in healthy adults.² In that study, plasma total cholesterol increased by 11%. In the present study, a substantial rise in serum total cholesterol was found

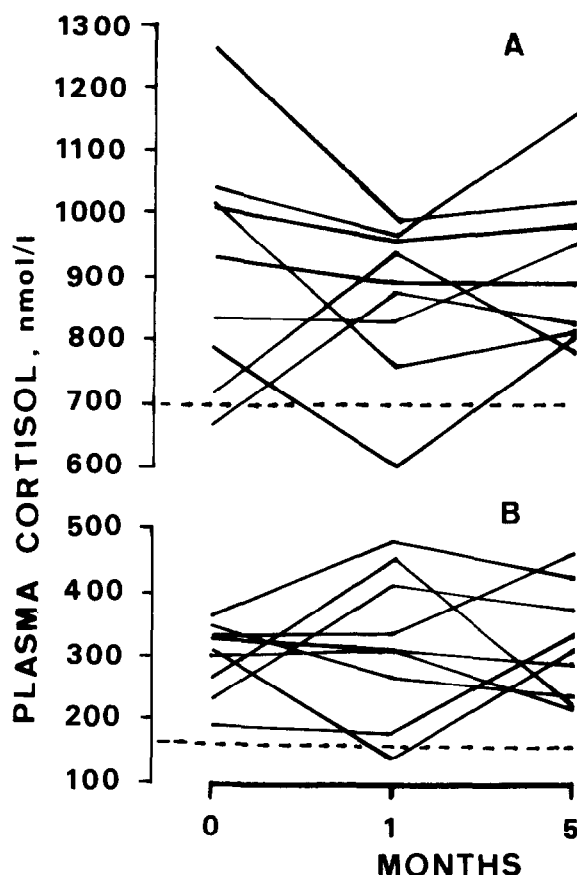


FIG. 4. Plasma cortisol concentrations. **A**, Two-hour levels after ACTH stimulation and **B**, basal morning levels before and after 1 month of high and 4 months of lower dosage of budesonide inhalations; lower limit of the normal basal plasma cortisol level (---) (162 nmol/L); lower limit of the normal response (---) (2-hour plasma cortisol, 700 nmol/L).

in four children. The increase in serum total cholesterol might carry an increased risk of cardiovascular disease.¹⁸ However, there were no significant changes in the ratio of HDL to total cholesterol, suggesting that the risk of cardiovascular disease would not be increased.¹⁹ The actions of glucocorticoids on glucose and lipid metabolism appear to be independent, but the basic mechanisms underlying the increase in HDL cholesterol by glucocorticoids are still unclear.²⁰ When the dose was lowered, serum HDL-cholesterol levels were reduced significantly and returned to a level that was not different from the baseline.

Budesonide inhalations had no significant effect on the HPA axis. A slightly suppressed basal plasma cortisol level in one child and a mildly subnormal 2-hour plasma cortisol level in another child was observed after high dosage only. These changes might be discovered in sensitive individuals receiving the high-

dose regimen. However, the clinical significance of these mild changes is uncertain. The possible suppressive effect of lower doses of inhaled glucocorticoids is detected by more sensitive methods, for example, by measuring cortisol secretion during the night.²¹

The antiasthmatic effect of budesonide inhalations in a dose of 800 µg/m²/day was accompanied by detectable changes in carbohydrate and lipid metabolism. The clinical significance of these changes in the long-term treatment is not known. The treatment had no significant effect on glucose tolerance or on the HPA axis. The antiasthmatic response could be maintained without significant systemic effects when the dose was reduced to 400 µg/m²/day. This finding is consistent with the finding that budesonide in a dose of 200 µg/day to preschool-age children with asthma was efficient without adverse systemic effects.²² Budesonide inhalations in a dose of 400 µg/m²/day are safe and efficient in the maintenance therapy of childhood asthma.

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