

Serum eosinophil cationic protein during treatment of asthma in children

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Background: Serum eosinophil cationic protein (ECP) is suggested to reflect the degree of bronchial inflammation and hyperactivity in patients with asthma. We measured serum ECP levels before and 1 and 5 months after treatment with inhaled budesonide ($n = 10$) or sodium cromoglycate (SCG) ($n = 7$) in children with asthma.

Methods: The daily dose of budesonide was $800 \mu\text{g}/\text{m}^2$ during the first month and $400 \mu\text{g}/\text{m}^2$ during the next 4 months. ECP levels were determined by radioimmunoassay.

Results: ECP decreased during the 5 months of treatment ($p = 0.020$ for treatment groups combined; $p = 0.049$ for the budesonide group; $p = \text{NS}$ for the SCG group). The higher the serum ECP level at entry, the more it decreased during treatment, both in the budesonide group ($r = -0.697$, $p < 0.05$) and in the SCG group ($r = -0.893$, $p < 0.05$). No correlation was found between the ECP level and the ratio of forced expiratory volume in 1 second to forced vital capacity ($\text{FEV}_{1\%}$) or between changes in these. However, basal pulmonary function was reduced in 8 of 16 subjects only, and $\text{FEV}_{1\%}$ did not change significantly in either group. Thus the absence of a correlation is understandable.

Conclusions: The clinical value of the sensitive decrease in serum ECP remains to be established. (*J ALLERGY CLIN IMMUNOL* 1993;92:34-8.)

Key words: Asthma, children, glucocorticoids, budesonide, sodium cromoglycate, eosinophil cationic protein

Eosinophil-mediated damage to the respiratory epithelium is a major pathogenetic mechanism in asthma.^{1, 2} Activated eosinophils secrete several granule proteins, one of which is eosinophil cationic protein (ECP),³ which can injure pneumocytes.⁴ In asthma, ECP levels are increased in the bronchoalveolar fluid; the level correlates with the severity of the disease.⁵ Serum ECP levels are also increased in asthma,^{6, 7} and they have been suggested to reflect the degree of allergic inflammation in the lungs and thus the degree of bronchial hyperactivity.⁸ The serum ECP level could be used as a marker for clinical monitoring of the disease activity.

To evaluate the effect of treatment of asthma on serum ECP levels, we measured serum ECP

Abbreviations used

ECP: Eosinophil cationic protein
 $\text{FEV}_{1\%}$: Ratio of forced expiratory volume in
1 second to forced vital capacity
SCG: Sodium cromoglycate

levels before and 1 and 5 months after treatment with inhaled budesonide or sodium cromoglycate (SCG) in 17 children with asthma and compared the results with those of pulmonary function tests.

PATIENTS AND METHODS

Patients

The children were 17 consecutive outpatients with asthma at the Department of Allergic Diseases of Helsinki University Central Hospital. They were first started on a regimen of inhaled budesonide ($n = 10$) or SCG ($n = 7$) (no previous use of steroids in any form). The treatment groups were not randomized. The choice of treatment was made on an individual basis, depending on the clinical judgment of one of the authors. Both drugs were administered as aerosols with a valved spacer device (Nebuhaler, Draco AB, Lund, Sweden). The daily dose of budesonide was $800 \mu\text{g}/\text{m}^2$ for the first month and $400 \mu\text{g}/\text{m}^2$ for the next 4 months, both divided into morning and evening doses. SCG was

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TABLE I. Individual data on serum ECP and pulmonary function (FEV_{1%}) before (basal) and after 1 and 5 months of treatment with inhaled SCG or BUD

	Age (yr)	ECP (μg/L)/FEV1%		
		Basal	At 1 month	At 5 months
SCG group	5.9	11.3/78	15.6/78	5.7/87
	7.3	43.0/86	21.5/86	10.0/78
	8.2	7.6/83	5.0/80	6.2/81
	8.7	23.5/91	11.8/95	12.5/84
	9.9	18.4/81	8.9/85	8.9/76
	9.9	9.6/77	10.9/79	15.6/68
	11.7	10.7/91	8.8/93	14.9/86
	Median	8.7	11.3/83	10.9/85
Budesonide group	5.3	11.4/—	—	10.2 —
	6.5	13.1/73	15.9/75	9.9/79
	7.0	42.9/81	32.0/87	11.4/93
	7.1	6.7/89	11.4/87	7.6/88
	7.2	12.1/68	—	7.8/87
	8.9	15.8/87	22.3/75	15.5/90
	9.0	17.3/86	—	9.7/74
	9.4	10.3/75	12.6/80	9.6/78
	11.0	23.9/73	38.7/86	10.8/82
	12.2	13.0/86	7.1/92	14.7/92
	Median	8.1	13.1/81	15.9/86
All patients		13.0/82	12.2/86‡	10.1*/87†
				10.0§/83

**p* = 0.049 between basal and 5-month ECP levels in the budesonide group.

†*p* = 0.098 between basal and 5-month FEV_{1%} levels in the budesonide group.

‡*p* = 0.096 between basal and 1-month FEV_{1%} in both treatment groups combined.

§*p* = 0.020 between basal and 5-month ECP levels in both treatment groups combined.

given in three daily doses of 10 mg each for 5 months. The patients were permitted to use inhaled β-adrenergic agonists as needed. The median ages were 8.1 years (range, 5.3 to 12.2 years) for the budesonide group and 8.7 years (range, 5.9 to 11.7 years) for the SCG group. There were nine boys and one girl in the budesonide group and four boys and three girls in the SCG group.

Twelve children were atopic (i.e., had more than one positive skin prick test result for common allergens), and five were nonatopic (i.e., had negative skin prick test and RAST results for common allergens and normal serum IgE levels).

Methods

Venous blood was drawn in the morning after a 12-hour fast before (*n* = 17) and after treatment for 1 month (*n* = 14) and 5 months (*n* = 17). The sera were stored deep-frozen (−20° C), and pre- and posttreatment samples were determined simultaneously.

Serum ECP was determined by radioimmunosorbent assay with an ECP RIA kit (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions. All of the samples were determined in the same assay. The intraassay coefficient of variation of was 4.1%.

Pulmonary function, ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_{1%}), was

assessed by pneumotachograph (Vitalograph Compact, Vitalograph Ltd, Buckingham, England) in 16 children at entry, at 1 month, and at 5 months. One child was not able to use the pneumotachograph correctly.

The patients and their parents gave their informed consent. The study protocol was approved by the Ethical Committee of the Department of Allergic Diseases of Helsinki University Central Hospital.

Statistics

The distribution of serum ECP was not Gaussian, and therefore the results are expressed as medians and ranges, and nonparametric statistical analysis was used. The parameters at entry were compared with the parameters at 1 month and at 5 months by Wilcoxon's signed-rank test. The correlations were calculated with Spearman's rank correlation test.

RESULTS

ECP

Serum ECP levels at entry and after 1 and 5 months of treatment are given in Table I. ECP decreased during the 5 months of treatment (*p* = 0.020 for the two treatment groups combined). The decrease was also significant in the

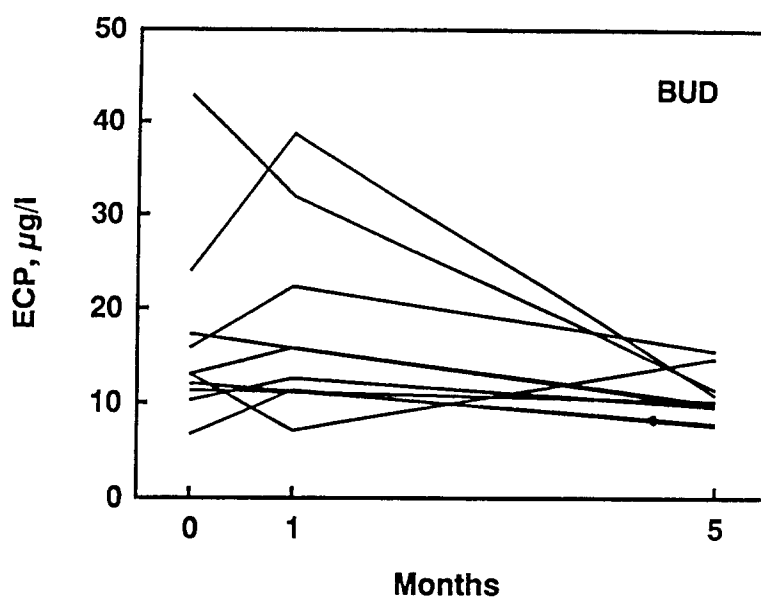


FIG. 1. Serum ECP at entry and after 1 and 5 months of treatment with inhaled budesonide in 10 children with asthma. The change during 5 months was significant ($p < 0.05$).

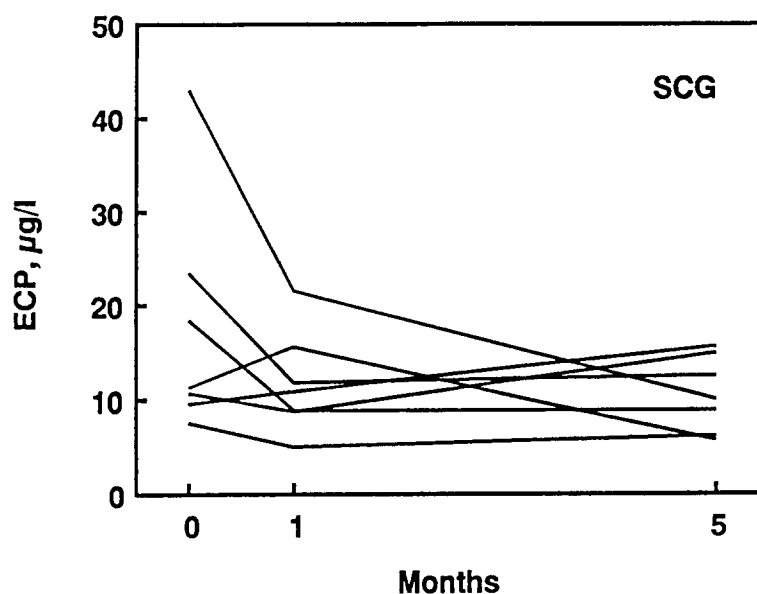


FIG. 2. Serum ECP at entry and after 1 and 5 months of treatment with inhaled SCG in seven children with asthma.

budesonide group (Fig. 1), but not in the SCG group (Fig. 2).

At entry, ECP levels were high ($> 16 \mu\text{g/L}$) in six patients (four atopic, two nonatopic), of whom three were treated with budesonide and three with SCG. At 1 month, ECP was still high in two of the six patients, but at 5 months all six, as well as all other 11 patients, had ECP levels lower than $16 \mu\text{g/L}$.

The change in ECP level during the 5 months correlated significantly with the level at entry ($n = 17$, $r = -0.799$, $p < 0.001$); the higher the

serum ECP level at entry, the more it decreased during treatment. This was true both in the budesonide group ($n = 10$, $r = -0.697$, $p < 0.05$) and in the SCG group ($n = 7$, $r = -0.893$, $p < 0.05$). At 1 month, this relationship was not significant ($n = 14$, $r = -0.385$ for the two groups combined).

Pulmonary function

$\text{FEV}_{1\%}$ did not change significantly during treatment in either group (Table I) but tended to be higher than at entry at 1 month when the two

groups were combined ($p < 0.10$) and at 5 months in the budesonide group ($p < 0.10$).

Serum ECP levels were not associated with FEV_{1%} ($r = 0.012$ at entry, $r = -0.252$ at 1 month, and $r = 0.071$ at 5 months). Neither were the respective changes significantly related. The median (range) basal FEV_{1%} in the patients with ECP values greater than 16 $\mu\text{g/L}$ was 84% (range, 73% to 91%) ($n = 6$) and in the other patients ($n = 10$) 81% (range, 68% to 91%) (NS).

DISCUSSION

Elevated serum ECP seems to be a feature of inflammatory conditions, such as asthma,⁶ atopic dermatitis,^{9, 10} various other skin diseases,¹¹ rheumatoid arthritis,¹² and ankylosing spondylitis.¹³ ECP levels are increased in jejunal fluid of patients with celiac disease¹⁴ and in nasal fluids in patients with hay fever.¹⁵ ECP levels are also increased during infections: nasopharyngeal mucus ECP levels were increased in patients with respiratory syncytial virus bronchiolitis.¹⁶ Thus in inflammatory conditions, increased secretion of ECP seems to be a nonspecific reaction. Correspondingly, ECP levels are reduced by antiinflammatory treatment, such as systemic glucocorticoid treatment in patients with rheumatic disease,¹² or sulfasalazine treatment in patients with spondylitis.¹³ Also, topical glucocorticoid treatment inhibits the development of the late asthmatic reaction and the increase in serum ECP¹⁷; it also inhibits the increase in ECP in nasal lavage fluid.¹⁸⁻²² During treatment of asthma with theophylline or antiallergic drugs, serum ECP decreased.²³

In the present study, serum ECP levels were high ($>16.0 \mu\text{g/L}$)²⁴ in 6 of 16 children with asthma, of whom three were atopic and three were nonatopic. A previous study has shown that the levels are higher in those patients with asthma who have a late reaction in bronchial allergen challenge.¹⁷ In the present study, serum ECP levels decreased during treatment. The decrease was significant in the budesonide group but not in the SCG group. However, ECP levels fell within the normal range²⁴ in all six children with high ECP levels at entry, irrespective of whether medication was budesonide or SCG. Furthermore, the higher the serum ECP level at entry, the more it decreased during treatment in both the budesonide and SCG groups. The decline in serum ECP levels suggests a decline in inflammatory activity in these patients.

In the present study, no correlation was found between the ECP level and pulmonary function or between the changes in them. This fact appears to

argue against ECP as a clinical marker of asthma. However, the basal pulmonary function was reduced (FEV_{1%} $< 85\%$) in 8 of 16 children only, and in fact, FEV_{1%} did not change significantly. The absence of a correlation is thus understandable, and ECP could be a more sensitive variable than basal pulmonary function. No relationship was found between serum ECP and clinical variables in 30 adults with asthma of varying severity.⁷ However, in adults with severe labile asthma and pronounced eosinophilia before treatment, an inverse relationship between serum ECP level and pulmonary function has been reported after treatment.²⁵ Similarly, the results of provocation tests, exercise,⁸ and histamine challenges²⁶ seem to be better related to serum ECP than is basal pulmonary function.

In conclusion, a decrease in serum ECP was observed during treatment of asthma. The decrease was significant in the children who were treated with inhaled budesonide. The high levels of ECP found in six patients normalized during treatment with either budesonide or SCG. Serum ECP was not correlated with FEV_{1%}, nor were the respective changes interrelated. The clinical value of ECP levels and the decreases in them remain to be established.

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